CCDSI
Clinical Cardio & Diabetic Society of India

Quarterly eBulletin on Diabetes

April

2021

शुक्लां ब्रह्मविचारसारपरमांद्यां जगद्व्यापनीं
वीणा पुस्तक धारिणीमभयदां
जाड्यांधकारपहाम्।
हस्ते स्फाटिक मालिकां विदधतीं पद्मासने
संस्थिताम्
वन्दे तां परमेश्वरीं भगवतीं बुद्धिप्रदां शारदाम्।।

CLINICAL CARDIO – DIABETIC SOCIETY OF INDIA

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From the desk of

Founder President CCDSI

I would like to congratulate Dr. Madhukar Rai Editor and Dr. N.K Singh Associate Editor of eBulletin on Diabetes for timely publishing the 2nd quarterly eBulletin of CCDSI on Diabetes.

I would also congratulate and give credit to Dr. D.P Khaitan , President CCDSI for his Vision to publish quarterly eBulletin on Cardiology, Diabetes, Hypertension and Kidney Diseases. The 1st quarterly eBulletin on Cardiology was published on December 2020. The 3rd quarterly eBulletin on Hypertension will be published on June 2021. The last and 4th eBulletin on Kidney Diseases will be published in September/October 2021 and will be released during CCDSICON 21 at Puri, Odisha.

Last but not the least I would like to thank the learned members and authors for contributing articles timely for publication of eBulletin on Diabetes.

Clinical CardioDiabetic Society of India (CCDSI) was established on 30th November, 2016 at meeting of API, CSI and RSSDI members from Bihar inview of increasing numbers of Cardiodiabetic cases. It's aim is to update clinicians on newer developments in diagnosis and managements in fields of Cardiology, Diabetes, Hypertension ,Nephrology and Metabolic Diseases by holding regular CMEs, Screening Camps, Annual conferences.

The idea to form CCDSI came when we had a CME on CardioDiabetic diseases at Port Blair in September 2016.

CCDSI had its 1st National Conference at Sundar Ban in September 2017, 2nd at Mount Abu in October 2018, 3rd at Chennai in September 2019.

4th National conference was Scheduled from 9 to 11 October 2020 at Bhuneshwar but due to Covid19 pandemic It was held as virtual conference on 10 & 11 October through webinar. 5th National Conference of CCDSI (CCDSICON 21) will be held at Puri, Odisha in September/ October 2021.

Dr D P Khaitan President CCDSI has regularly arranged webinar once a month since November 2020 after taking charge as President of CCDSI on 10th October 2020. Dr Khaitan also decided to publish Quarterly eBulletin on Cardiology, Diabetes, Hypertension and Nephrology.

Dr Ajay Kumar Sinha , Editor with Dr Dinanath, Associate Editor of 1st eBulletin on Cardiology released the eBulletin on 27th December 2020 during GB meeting of CCDSI

CCDSI at it's General Body meeting on 27th December 2020 also took unanimous decision to form Indian College of Cardiodiabetolgy and Metabolic Diseases (ICCMD). Faculty council of ICCMD will has following members :

1) Chairman: Dr D P Khaitan, President CCDSI
2) Dean : Dr R Rajasekar , Immediate Past President, CCDSI
3) Course Advisor: Dr A N Rai , Founder President, CCDSI.
4) secretary : Mritunjay Kumar Singh
5) Treasurer: Dr R S P Singh

Faculty Council Members

1) Dr Jayant Panda
2) Dr A K Virmani
3) Dr Ajay Kumar Sinha
4) Dr R K Jha
5) Dr Akash Singh

Permanent Invitee:

Dr RAJAY NARAIN , MRCP(U.K.) , Consultant Cardiologist
St George's University Hospital, London, Director, Global Health Alliance, UK and Director, U.K. Cardiovascular Diabetes Innovation Network today.

Aims and Objective

1) It will be academic wing of CCDSI and will select and award Fellowship in Indian College of Clinical Cardiodiabetolgy to Founder and life members.

Eligibility

i) Founder or Life members of CCDSI with minimum 5 years duration and good academic credentials
ii) Senior members of allied associations like API, CSI, HSI, RSSDI and Nephrology.

2) ICCMD will start following Certificate courses in Partnership with London Institute of Health Sciences (LIHS), London and UK Cardiovascular Diabetes Innovation Network (UKCDIN)

i) Postgraduate Certificate Course in Diabetes
ii) Postgraduate Certificate Course in Clinical Cardiology.
iii) Postgraduate Certificate course in Echocardiography

3) Award of Scholarships for Basic Research in Diabetes , Cardiology, Hypertension and Nephrology

4) To have Academic Collaboration with International Institutions

5) To appoint Honorary International Faculties

Dr. A.N Rai

From the desk of

Imm. Past President CCDSI

It is my privilege to send a write up in eBulletin on Diabetes Updates. I am thankful to Prof. Dr. A. N. Rai, Founder President , Dr. D. P. Khaitan--President and Dr. Mritunjay Kr Singh-- Secretary—CCDSI for the kind motivation of release of periodic eBulletin. Thus , they moulded the eBulletin at par excellence to quench academic appetite. I eulogize Editor Prof Dr Madhukar Rai and Associate Editor - Dr N K Singh for bringing out this nice Academic eBulletin.

With best wishes,

Dr.R.RAJASEKAR
MD.,FICP., FACP(USA)
FRCP(Glasgow,Ireland,London and Edinburgh)
SENIOR CONSULTANT PHYSICIAN & DIABETOLOGIST
Chairman, RR.Charitable And Educational Trust, Heart and Diabetes Therapy Centre,
Diabetes Training Centre For Doctors,
Kumbakonam.Tamil Nadu.

From the desk of

President CCDSI

It is indeed a great pleasure to have quarterly eBulletin on diabetes. I congratulate with thanks to the scholarly team of Editorial Board with Prof. Dr. Madhukar Rai and Dr. N.K Singh who have made their sincere efforts to get this eBulletin published in time with so excellent academic articles. I also extend my warm regards to all the esteemed faculties who have contributed their articles for the purpose.

I take this opportunity to express my regards to our Founder President Prof. Dr. A.N Rai who has been always guiding us with his farsighted vision. I also extend my regards to our Imm. Past President Dr. R. Rajasekar for his constant endeavours in uplifting our knowledge through his par excellence academic write up.

There is no word to express my feeling about our dynamic National Secretary Dr. Mritunjay Kumar Singh for his excellent working throughout and his efforts related to this eBulletin .
I would always remain thankful to all the members of our society.

Dr. D.P Khaitan

From the desk of

Secretary CCDSI

It is indeed a great pleasure to know that CCDSI is coming up with a diabetic update, second in a series of quarterly update.

I congratulate and acknowledge the effort of editorial team comprising Prof. Dr Madhukar Rai and Dr N K Singh - it will be a useful guide for our day to day practice. I also express my regards to our Founder President Prof. Dr. A.N Rai and gratitude to President Dr D P Khaitan for their guidance and support during publication of this update.

CCDSI at its GB meeting with Faculty Council of ICCMD on 24th January unanimously approved the following recommendations of Dr. Rajay Narain, Consultant Cardiologist, St. George's University Hospital , London and International Advisor, ICCMD.

1) It was approved that ICCMD should have partnership with UK Cardiovascular and Diabetes Innovation Network (UKCDIN) and London Institute of Health Sciences, London for following Postgraduate Certificate Courses.

a) Postgraduate Certificate Course in Diabetes
   Course Director
   Dr Akash Singh
   Dr Anuradha Kapoor
   Dr Kamaldeep Chawla
   National Faculties for the Diabetes Course
   Dr Jayant Panda : Senior President elect of CCDSI and professor and head medicine, medical college Cuttack
   Dr. Anil Kumar Virmani : Physician & Cardio-Diabetologist, Jamshedpur, Jharkhand
   Dr. Hem Shanker Sharma, Physician and Diabetologist, Bhagalpur/Bihar
   Dr. N.K. Singh : Diabetologist and Physician, Jharkand
   Dr. Sudhir Chandra Jha : Associate Professor Medicine/Darbhanga Medical College, Bihar
   Prof (Dr) L Sreenivasamurthy, Physician and Diabetologist
   Dr. Bijay Patni, Consultant Physician and Diabetologist/Kolkatta
b) Postgraduate Certificate Course in Clinical Cardiology
c) Postgraduate Certificate Course in Echocardiography
   Duration of Certificate Couses 6 Months.
   Fee of Certificate Courses
   Indian Students – 500 Dollars (Rs. 35000.00)
   International Students – 1000 Dollars
   Minimum Eligibility Criteria – MBBS or Equivalent Qualifications

2) Approved the Appointment of the following Honorary International Faculties :

a) Dr Mimi Chen FRCP
   Consultant Diabetologist & Lead for Diabetes
   St. Georges University Hospital, London

Diabetes Champion of United Kingdom

b) Dr Deerek Connolly FRCP
   Lead Interventional Consultant Cardiologist
   City, Sandwell & Midland Metropolitan Hospital,
   Birmingham, UK
c) Dr Alexandru Mischie MD, FESC
   Head of Interventional Cardiology
   Centre Hospitalier Montucon,
   France

d) Dr Sandeep Basavarajaiah, FRCP
   Consultant Cardiologist
   Birmingham Heartlands Hospital
   Birmingham, UK

e) Ms Rhona Riley
   Associate Prof & Head Cardiac Physiology
   University of Leeds, UK

3) Approval to open account of Indian College of Cardiodiabetology and Metabolic Disease (ICCMD) on each of the 3 social platform, Twitter, Instagram and Facebook. Following faculty members were requested to take responsibility to operate it
   Dr Ajay Kumar Sinha : Twitter
   Dr Akash Singh : Instagram
   Dr Mritunjay Kumar Singh : Facebook

Long live CCDSI
Jai Hind
Dr Mritunjay kumar singh
Secretary, CCDSI
HQ, Gaya

From the desk of

Editor

It gives me immense pleasure to publish this eBulletin on diabetes .. It is an effort to give glimpses on important aspects of diabetes.

Diabetes being a silent killer has emerged as a global pandemic. In USA, where around 29 million (9.3%) population has diabetes, it was estimated that total cost of diabetes care in 2012 was $ 245 billion. India has an estimated diabetic population of more than 70 million. Moreover, given the high genetic predisposition for developing diabetes among Indian population, growing obesity in middle class children and adolescent due exposure to fast food and less physical activity, poor town planning etc. is threatening India into the dubious distinction of diabetes capital of the world and its economic and social consequences.

This is the time when a concerted effort is needed not only in diagnosing and treating the disease but also in its prevention. A nation with poor resources and lack of social security, the health care policy makers have to seriously dwell on the idea of hitting it at all levels to prevent this burgeoning epidemic.

I am thankful to Dr D.P Khaitan, President CCDSI for choosing the very second issue on Diabetes and entrusting me with the responsibility of editing the manuscript. I am indeed grateful to the dynamic founder of CCDSI Prof A N Rai, whose academic appetite is still undaunted in spites his very busy involvement in patient welfare, for his constant guidance. Thanks to my co editor Dr N K Singh and all the contributing authors.

Long live CCDSI and Jai Hind

Dr. Madhukar Rai

From the desk of

Editor

BENEDICT'S REAGENT TO ERA OF PERSONALISED MEDICINE IN DIABETES

Dr N. K Singh, MD, FICP, Editor: www.cmeindia.in Diabetologist physician, Dhanbad.Chairman RSSDI-Jharkhand and CCDSI-BJ

Understanding metabolic karma is need of hour

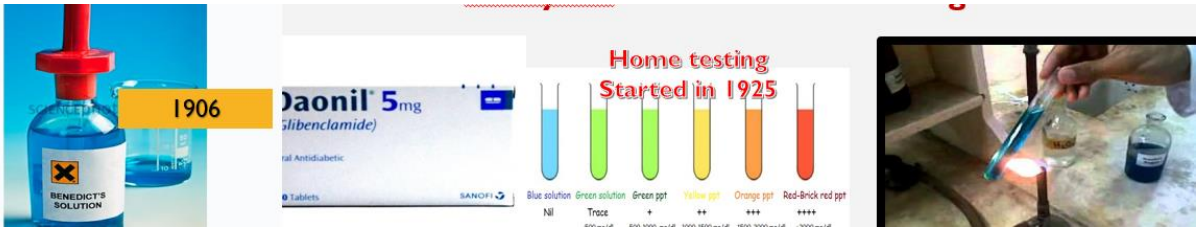
We must remember that actions and intentions have consequences. If we do efforts today, it can have long term gains. Our mistakes today can have effects for years to come. What it may be, hyperglycaemic variability, postprandial hyperglycemia, complications without elevated Hb1ac or vascular complications in prediabetes, our metabolic karma is involved. Live to modify it.

Make a Mission to Move

I met PhilSoutherland at EASD on15th Sept 2014 after his oration on Exercise motivation. First time witnessed that over 7 thousand delegates gave him standing ovation for 5 minutes when he finished his talk. I met him later and came to know that he developed diabetes at age 7 months. He was predicted to live up to 20 years but won the Race Across America event four times and hold the record for the fastest trans-continental crossing for the Race Across America. He founded Team Type1 and today he is hope of millions. In 2014 he was 35years old. In 2021, he bypassed all predictions and very energetic. Many of guideline in Type 1 diabetes and exercise comes after research by his team. His book -NOT DEAD YET is the best seller. He tells “Exercise is the billion-dollar drug that never gets prescribed”

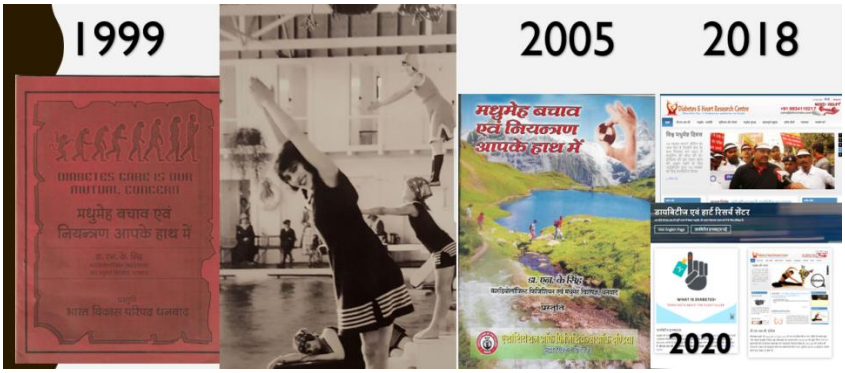
I witness the Saga of Four decades

My Father posted at Jamshedpur in 1977 had severe mental stress after that and that led to Diabetes [??}He was seen by Late Dr Bhola Mahato who prescribed Daonil 5mg-Gold standard SU that time.That was my first exposure to this disease .Benedict's Test method was shown to family. No other education was given. **After sometime he got transferred to Chhatarpur Thana in Palamau, (that time in Bihar) as officer in-charge. I remember a day, after extreme restlessness, sweating and abnormal mentation. He became unconscious. As usual PHC doctor gave steroid inj. infused Dextrose and saline. He regained consciousness and after removing dextrose became repeatedly unconscious for 4 to 5 days. No one was telling what was happening. My uncle later came to get him checked at Mumbai. It was a big thing when Mumbai doctors diagnosed the condition as Hypoglycemia. Daonil was changed to DBI-TD [Phenformin, widely available that time]. This was very important as after that no hypoglycaemia occurred**



How I got interested in Diabetes

After doing MD in 1988, I devoted most of my time in HIV medicine. I presented national talks in APICONS but my father illness kept me in agony and I started to devote my interest to diabetes. I wrote many awareness books and my first talk in APICON -Hyderabad 2016 was science and art of diabetes prevention.



Changing concepts, evolving science

At ADA 2017 San Diego, California, Dr Nissan's (he man who destroyed the empire of Rosiglitazone by his meta-analysis on heart failure issues) words still keep ringing in my ears- "After 60 year of stagnation, we are now witnessing the dawning of a new era of enlightment in pharmacological management of type 2 diabetes allowing choice of therapies based on actual clinical outcomes (risks and benefits) rather than a surrogate biochemical marker (glucose levels)

He roared that how guidelines are far lagging behind the evidences and emphasized to say good bye to glucocentric mindset.

The opportunity ahead

We live in the midst of a revolution of big data across all domains of the human experience. We practice medicine and conduct research within an unprecedented whirlwind of data, spanning from populations to the individual.

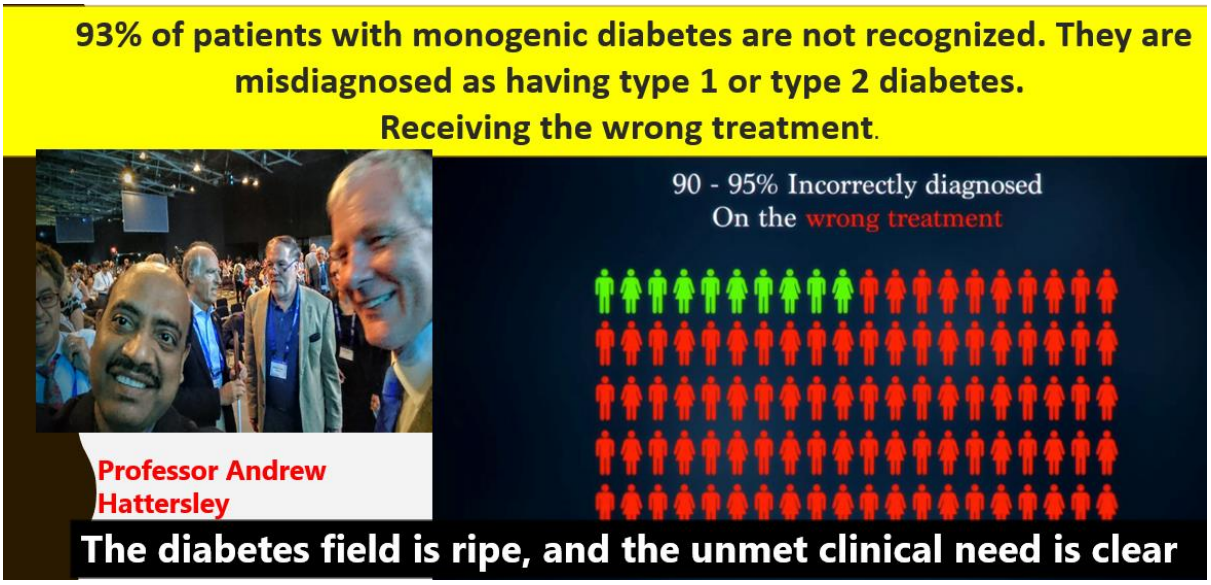
Failure is big but future is great.

Despite extensive epidemiological and physiological characterization, we have fallen short in cataloging risk factors, identifying triggering events, elucidating pathophysiological pathways, outlining prognostic course, selecting effective therapies, and **predicting complications.**

Specific patients continue to represent diagnostic challenges, and our approach to therapy continues to be based on population average.

Traditional classification into type 1 and type 2 diabetes has proven useful in differentiating distinct pathophysiological mechanisms with clear therapeutic implications, it remains insufficient in explaining the wide variety of clinical manifestations of this disease. We see lean members of specific ethnic groups with antibody-negative, nonketotic diabetes; we treat patients with childhood-onset, antibody-positive diabetes who become insulin resistant as they age; We do not fully understand why some patients progress rapidly to microvascular and/or macrovascular complications or require aggressive escalation of therapy; We cannot predict the rate of β-cell failure, the degree of weight loss required to normalize glycemia, or the type of medication best suited for a given patient.

Precision Medicine in Diabetes is the Answer



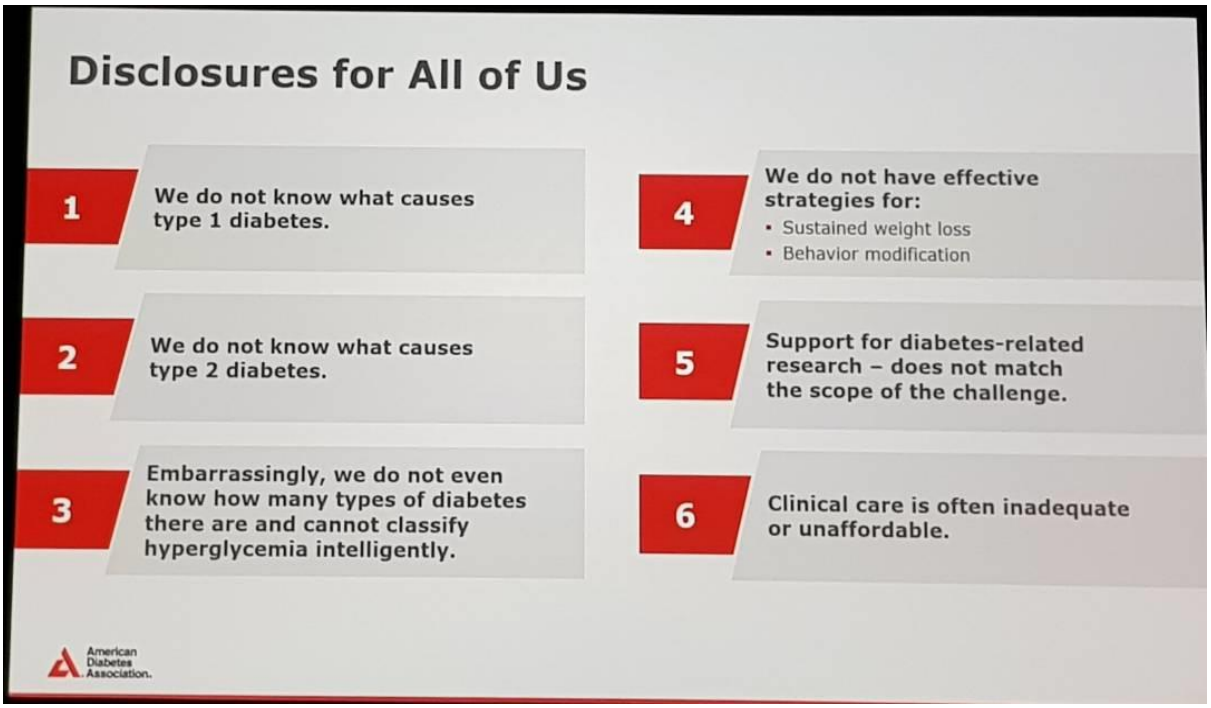
It is a new concept for diabetologist, it is now possible to test all genes involved in monogenic diabetes in a single gene panel test, both quickly and efficiently. This gene panel testing approach identifies approximately an additional 25% of monogenic patients with less common causes compared with selected testing of common genetic subtypes. It removes the need to define the likely genetic etiology/subgroups prior to testing.

Within a decade it may be possible to map the genome within 5 to 10 minutes. Precision **diabetes based on genetic testing is a new concept for diabetologists. Genetics is not a part of routine clinical training. Traditionally, the speciality of diabetes emphasis is based on treatment rather than diagnosis.**

Type 2 diabetes is a polygenic condition in which environment, as well as genetic predisposition, play a big role. In this case, an approach concentrating on newer technologies may not be optimum and certainly examining simple clinical criteria like BMI, sex and age should be carried out before rushing to molecular technologies.

Final Message

Four years back ADA President showed this slide .Think over it again and again



Contents

Page

1. **Updates in Diabetes** ……..……...**01**
   Dr. R. Rajasekar

2. **Clinical Practice Influencing Developments in Diabetes over last four decades**..……..…**06**
   Dr. Madhukar Rai

3. **Prediabetes and CV Risk**……..…**08**
   Dr. N.K Singh

4. **Medical Nutrition Therapy of Diabetes**……..……**11**
   Dr. Deepak Das & Smita Gupta

5. **Diabetes diagnosis and management : an Endocrinologist's Perspective**.....……..…**15**
   Prof N.K Agrawal

6. **Management of Type I Diabetes : Beyond Insulin**…….....…….……**17**
   Dr. Meena Chhabra

7. **Diabetes and Pregnancy : Window of opportunity for diabetes prevention in India**…….**22**
   Dr. Anand Shankar

8. **An Inevitable Transition for Good Glycaemia : Orals to Insulin**….……....**27**
   Dr. Madhukar Rai

9. **Practical approach to deal with hyperglycemia within the hospital**…….……..…….....**32**
   Dr. Madhukar Rai

10 . **Update Sotaglifilozin**……...**39**
   Dr. Bijay Patni

11. **Obesity, family history of diabetes , and consanguineous marriages are risk factors among urban population in South Indian city of Bengaluru**..…….…….…..…..**42**
   Dr. Aravinda Jagadeesha

12. **Management of Diabetic foot in Physician's office**…….……**45**
   Dr. R.K Modi

13. **Diabetes and Cancer**…….....……**47**
   Dr. Akash Kumar N Singh & Dr. Anuradha Kapoor

14. **Diabetes & Kidney**…….....**56**
   Dr. Raj Kamal Choudhary

15. **Top 10 Papers at EASD**…….……..…..**58**
   Dr. N.K Singh

UPDATES IN DIABETES

UPDATES IN DIABETES

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Diabetes is a chronic metabolic disorder characterized by hyperglycemia – caused by insulin deficiency often combined with insulin resistance. There is an exponential peak in the detection of diabetes worldwide. If the current scenario persists, around 642 million people worldwide and around 87 million people in India will have diabetes.

PATHOPHYSIOLOGY OF DIABETES:

There is an increasing need to control blood sugar both in the fasting and postprandial state for an efficient control of hyperglycemia. There are multiple , complex mechanisms leading to hyperglycemia. These mechanisms are the cornerstone behind the occurrence of diabetes. The control can be done by using drugs with different mechanism of actions.

1. Increased hepatic gluconeogenesis
2. Decreased renal glucose excretion
3. Decreased peripheral glucose uptake
4. Increased pancreatic glucagon secretion
5. Decreased pancreatic insulin secretion
6. Decreased incretin effect

AGENTS CURRENTLY USED IN DM MANAGEMENT:

S. no	Class	Agent	Mechanism of action	Site of action	HbA1c reduction	Adverse effects
1.	Sulfonylureas	Glimepride Glipizide Gliclazide Glyburide	Stimulation of insulin release	B cells	1-2	Hypoglycemia, Weight gain
2.	Glinides	Meglitinide Nateglinide	Stimulation of insulin release	B cells	1-2	Hypoglycemia, Weight gain
3.	Biguanides	Metformin	Inhibition of hepatic gluconeogenesis	Liver	1-2	GI effects B12 deficiency
4.	Alpha glucosidase inhibitors	Acarbose Miglitol Voglibose	Inhibition of intestinal absorption of glucose	Jejunum	0.5-1	Bloating
5.	Thiazolidinediones	Pioglitazone	Reduces peripheral insulin resistance	Muscles Adipocytes	1-1.5	Weight gain Edema

WHY NEWER DRUGS NEEDED?

Because of the limitation of the existing drugs as well as the side effects of the medications, there is a high need of new drugs in managing diabetes. As it is a chronic disease, the drug which has better efficacy with limited side effects and prevents the progression of disease is the need of the hour,

INCRETIN MIMICS:

Incretins are insulinotropic hormone secreted by the specialized neuroendocrine cells in the mucosa of small intestine which stimulates insulin release. Eg.GLP-1,GIP.The release of insulin is glucose dependant, so hypoglycemia risk is low. Because of its extremely short half - life, it is rapidly metabolized by DPP4 .

GLP-1 ANALOGUE:

1. Short acting: Exenatide, Lixisenatide
2. Long acting : Liraglutide, Albiglutide, Dulaglutide, Semaglutide

Exenatide: 5-10 ug BD , sc . HBA1C reduction 1%. Weight loss present.

Liraglutide: First non insulin drug for type 2 diabetes in children.It is effective in reducing body weight, decreasing visceral fat, lowering systolic blood pressure and improves lipid profile.

Dose: 0.6 mg – 1.8 mg OD .It has only few GI side effects ,effective for long term use.

Semaglutide : First oral GLP-1 analogue .It is not used as a first line drug.

Dose: 3 mg oral OD for 30 days .Dose can be increased to 7 ,14 mg for every 30 days. It should be taken 30 minutes before first food with no more than 4 ounces of plain water. There is an increased risk of medullary carcinoma of thyroid on chronic use.

Albiglutide : Recombinant human serum albumin-GLP-1 hybrid protein. Its half life is 1 week.

DPPP-4 INHIBITORS:

These drugs acts mainly by inhibiting the degradation of GIP,GLP-1,thereby leading to increased incretin release and subsequently insulin secretion and glucagon inhibition. It is contraindicated in pregnancy ,lactation as well as in diabetic ketoacidosis. The drugs in this group are as follows.

1. ***Sitagliptin*** – 100 mg
2. ***Vildagliptin***– 50 m
3. ***Linagliptin*** – 5 mg
4. ***Saxagliptin*** – 5 mg
5. ***Alogliptin*** – 25 mg

The dose of saxaglitin has to be reduced,when used in combination with CYP3A4 inhibiting drugs.

SGLT2 INHIBITORS: (Sodium Glucose Transporter)

SGLT are transmembrane proteins specialized in the co transport of sodium and glucose across different cell types.They contribute to renal glucose reabsorption. These drugs acts by enhancing renal glucose excretion and consequently lower plasma glucose levels.These drugs has a better glycemic control with better cardiovascular protection. The drugs in this class is as follows.

1. ***Dapagliflozin*** : 5 ,10 mg
2. ***Canagliflozin***:100,300 mg
3. ***Empagliflozin***:10,25 mg
4. ***Remigliflozin*** : stopped in phase ii trials
5. ***Sergliflozin*** : Promising role in obese diabetics, but stopped in phase ii trials
6. ***Ertugliflozin*** :This shows 0.5% reduction in HbA1c and effective in weight reduction and blood pressure control. It decreased recurrent heart failure hospitalizations.
7. ***Ipragliflozin*** : It has insulin dependant action ,safe and well tolerated.I t may reverse beta cell dysfunction and insulin resistance. It is in phase 3 trial.

AMYLIN MIMETICS:

Amylin is a glucoregulatory polypeptide which acts centrally by its central action. It induces satiety and slows gastric emptying. They suppress pancreatic glucagon secretion .The analogues of amylin can be used in the treatment of both type 1 and typ2 diabetes as an adjunct to meal time insulin.

Pramlintide: They suppress glucagon secretion and attenuate hepatic glucose production with concomitant reduction in weight and insulin use. They acts via amylin receptors present in the hindbrain. They showed

0.1 -0.67% reduction in HbA1c and 3.6 – 4.8 mmol/l reduction in 2 hr PPG.Transient nausea and hypoglycemia were the most common side effects

Dose: Type 1 DM : 15 µg – 60 µg

Type 2 DM : 60 µg – 120 µg

DUAL PPAR GAMMA(Peroxisome Prolifertaor Activated Receptors) AGONIST:

These drugs improve insulin sensitivity , reduce atherogenic triglycerides and raises the cardio protective HDL levels. The drugs in this class are as follows.

1. ***Aleglitazar***
2. ***Muraglitazar*** – Improves TG, HDL, Apo B and non HDL levels.

Dose: 5 mg/day. Discontinued because of adverse cardiac outcomes.

3. ***Ragaglitazar*** **-** discontinued
4. ***Naveglitazar*** – discontinued
5. ***Tesaglitazar*** - 100 % bioavailability , stopped due to adverse renal outcomes

DOPAMINE AGONIST :

Bromocriptine: D2 receptor agonist. They modify the autonomic responses maintaining euglycemia. It reduces HbA1c by 0.5 – 1.2%.

Dose: 1.6 - 4.8 mg . It should be taken along with food in the morning(within 2 hrs of waking). It is not recommended for typ1 DM as well as in DKA.

BILE ACID BINDING RESIN:

Bile acids binds to and remove blood glucose from enterohepatic circulation.

Colesevelam : Only approved drug for typ2 DM. It is available as oral solution or in the form of tablets. It is used as an adjunct to diet and exercise.

Dose: 3 tabs BD before lunch and dinner/ 6 tabs before largest meal.

GLUCOKINASE ACTIVATORS:

It increases glucose metabolism. It increases insulin concentration by stimulating beta cells and thereby reduces glucose concentration. Eg.Piragliatin

PDEI's: There are several PDE'S in beta cells. The inhibition of this enzyme leads to degradation of CAMP and insulin release. It may be a possible intervention in DM.

BETA 3 AGONISTS: It stimulates insulin release and improves glycemic control in obese diabetic rodents. Its efficacy in humans is still under trial.

11 beta hydroxysteroid dehydrogenase type 1 inhibition:

Increased levels of glucocorticoids in the blood leads to truncal obesity, insulin resistance and hyperglycemia. These are glucocorticoid antagonists and antagonize the effects in preventing insulin resistance.

ANTI CD3 MONOCLONAL ANTIBODY :

Otelexizumab: It is a humanized anti CD-3 monoclonal antibody. It is evaluated in the treatment of type 1 diabetics as it is immune mediated. It acts by blocking the functions of effector T cells ,mistakenly destroying the beta cells.

TEPLIZUMAB: This drugs delays the diagnsis of type 1DM by 2 years. There is a striking reversal in C–Peptide levels in the 6 months following treatment, after which c-peptide levels seems to be stabilized. It acts by stabilizing the beta cell function. Eventhough its efficacy is still under trial, living 3 yrs without diabetes is a meaningful outcome.

H3 RECEPTOR AGONIST: H3 receptors are present in presynaptic membranes of histamine neurons. Eg. Proxyfan – central agonist. It improves glucose excursion by increasing plasma insulin levels.

VITAMINS AND MINERALS:

Vitamin D3 – Helps in insulin production, secretion and action. Most of the diabetics are deficient in vitamin D3.The supplementation with vitamin D3 helps in glycemic control.

Zn, Li, Se, Mb, Hg, Ca – Insulin like antidiabetic effects.

Alpha lipoic acid : It has antioxidant property and increase the insulin sensitivity. It is useful in diabetic neuropathy.

Isoferulic acid : It increases the expression of GLUT- 4 , leading to impaired gluconeogenesis.

ACEI's: Because of increased bradykinin, it modestly increases the insulin sensitivity.

NEWER INSULINS :

Insulin play a major role in control of blood sugars in patients not tolerating oral drugs or not controlled with multiple oral medications. Insulin has a wide variety of improvement in the recent past. There are short acting, intermediate acting and long acting insulins. Due to advancements in the field of pharmaceuticals, now there are ultra short and ultra long acting insulins with better glycemic control and low risk of hypoglycemia.

1. ***CONCENTRATED INSULIN:***

The increased requirement of dose of insulin leads to the development of concentrated insulins. They supply the required dose with minimal quantity. So far 7 types of concentrated insulin are available in the market.

GLARGINE U-300(ultra long acting):

It is 3 fold more concentrated than the conventional 100 U glargine. It reduces nearly half of the surface area of subcutaneous depot as well as reduction of $1/3^{rd}$ volume of the required dose because of its high concentration. It is a peakless insulin with slow but more constant rate of absorption, thereby reducing the incidence of hypoglycemia.

DETEMIR:

It is subcutaneous and it binds to albumin. It has a smooth action similar to glargine with less hypoglycemia risk.

DEGLUDEC U 200:

Its safety is well documented with even a lower risk of hypoglycemia compared to glargine. Nearly 160 U of insulin can be delivered via a single injection.

REGULAR INSULIN U 500:

It has both short acting prandial activity and long acting basal activity. The onset of action is less than 20 minutes. It has a greater duration of action and long time to maximal effect when compared to U-100 insulin. It is contraindicated in patients with hypoglycemia unawareness ,old age and patients with cognitive/psychiatric impairement. The total daily dose is reduced by 20% using this preparation. It is indicated in patients with severe insulin resistance and refractory diabetes.

ONCE WEEKLY INSULIN : This type of insulin reduces hurdles in patients who are afraid of injections, hesitant to start insulin or handling devices. The main disadvantage is that ,dosage cannot be modified according to life disruptions. It is still under trial.

2. ***FIASP (Fast acting insulin aspart):***

It is a combination of insulin aspart with vitamin B3 and arginine. Vitamin B3 helps in increasing the speed of initial absorption and arginine aids in stabilizing the formulation. It can be used as subcutaneous or intravenous .

3. ***INSULIN PENS:***
4. ***INSULIN JETS:***
5. ***CSII (Continuous subcutaneous insulin infusion)***

This helps in the constant basal infusion of insulin. Only rapid acting insulin can be used. It is more physiological even during exercise.

6. **SMART INSULIN:**

It is a pharmaceutical preparation with an inbuilt sensor mechanism to assess ambient glycaemia. It is a promising area of innovation in the management of diabetes. It ensures the release of insulin based upon this formulation. It avoids hypoglycemia dips as well as hyperglycemia peaks thereby ensuring adequate euglycemia.

It has 2 components, a glucose sensor and an insulin delivery device. When there is an exposure of high blood sugar, there will be enzymatic catalysis of insulin nanoparticles, which allows the release of insulin .Insulin release follows a non linear pattern. The duration of action lasts for upto 10 days in mice. It has both conventional as well as nano technology ligands and membranes.

7. ***AID(Automayted Insulin Delivery System)***
8. ***AHCC (Auomated Hybrid Closed Loop System)***
9. ***INSULIN INHALERS*** :It contains powdered insulin delivered via nebulizer. It has a more rapid absorption. It is inhaled at meal time or at th e begining of meal. It is contraindicated in chronic smokers, bronchial asthma and COPD patients.

Exubera – discontinued, Afreezza

10. Lyumjev (insulin lispro - aabc injection)

It is a novel formulation of isulin lispro. It is a rapid acting insulin .It speed the absorption of insulin into the blood stream and reduce A1c levels and also reduces postmeal spikes. It is contraindicated during episodes of hypoglycemia and in hypersensitivity to insulin lispro.

NEWER TARGETS:

The action of drugs at genetic level plays a new trend in the management of diabetes. But further large studies are needed to assess its efficacy in controlling hyperglycemia.

1. **UncOCN: (Undercarboxylated form of osteocalcin)**

The action on these receptors has a positive effect on metabolic syndrome. It also has a better improvement in beta cell function, insulin resistance and also in controling dyslipidemia.

2. **INDY gene :** The deletion of this gene mimics like the aspects of dietary restriction. Studies in mice showed its protective efficacy against adiposity.
3. **VEGF –B blocker**
4. **ABHD6 :** It is present in the ǎ/ β hydrolase domain 6. It helps in the breakdown of monoacylglycerol as well as it negatively controls insulin release. The inhibition of this domain plays a role in treating diabetes.
5. **FFAR 3**(beta cell short chain fatty acid receptor)

EMERGING THERAPIES:

1. ***LEPTIN THERAPY***: It regulates glucose metabolism via CNS. It controls both hepatic glucose production as well as glucose uptake.
2. ***MUCOADHESIVE DELIVERY (GLIPIZIDE):*** Mucoadhesive microspheres are produced by ionic gelation method like sodium alginate, ethyl cellulose, etc. It increases bio availability with reduced side effects.
3. ***GENE THERAPY***: It is used in type 1 DM. It has prohylactic role by preventing islet cell destruction and post disease role by replacement of insulin gene.
4. ***NANOTECHNOLOGY***
5. ***VACCINES (rhGAD65):*** Recominant human glutamic acid decarboxylase. It slows the destruction of insulin producing beta cells in preclinical studies by introducing "immune tolerance" It is currently in phase 3 trial.

CONCLUSION: The treatment of diabetes has undergone a tremendous advancements in the past few years. The role of different group of drugs with different mechanism of action and adverse effects place the physician in a huge dilemma. In order to overcome this ,the treatment is always tailored towards individual patient, blood sugar values and their associated comorbidities. As the science advances ,the treatment regimen also changes. Further studies are needed to elucidate the role of the emerging drugs in the treatment of diabetes.

CLINICAL PRACTICE INFLUENCING DEVELOPMENTS IN DIABETES OVER LAST FOUR DECADES

Clinical practice influencing developments in Diabetes over last four decades

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As a medical graduate when I joined medical school in 1980, the management of diabetes was in infancy. We were not aware of the natural history of Type2 Diabetes and there was uncertainty over whether diabetes could change the complications associated with it. The treatment was largely symptomatic and control the monitoring tools were scarce and cumbersome. The following are the key developments which I consider has influenced my clinical practice.

1. Self monitoring of blood glucose (SMBG) :

This was a very important tool in the management of diabetes. In 1965, Ames developed the first blood glucose test strip,the Dextrostix, using glucose oxidase. A large drop of blood was placed on the strip and, after 60 seconds, was washed away. The generated color was then compared to a chart on the bottle for a semi-quantitative assessment of blood glucose.

The first glucose meter was used in the 1970s with the Dextrostix, but its precision and accuracy were poor.By the mid-1970s, the concept of patients using blood glucose data at home was contemplated, and by 1980, the Dextrometer was launched; this meter used the Dextrostix along with a digital display. During the 1980s, meters and strips requiring less blood became available, all at a cheaper price. Self-monitoring of blood glucose (SMBG) became the standard of care, especially for patients with type 1diabetes. This advancement, along with A1C testing and insulin pump therapy, made possible the Diabetes Control and Complications Trial, which positively answered the long debate about the relationship between glucose control and diabetes complications.

Through the late 1980s, 1990s, and early 2000s, SMBG technology continued to improve. The blood removal step was eliminated, smaller amounts of blood were required, electrochemical strips were developed, wider ranges of hematocrit were permitted, and new enzymatic tests were used. Lancets also improved.

By 2010, SMBG was virtually painless and recommended for all patients receiving insulin and most who were not.The evolution of home glucose monitoring was furtherrevolutionized with the introduction of continuous glucose monitoring (CGM). In 1999, the U.S. Food and Drug Administration approved the first "professional" CGM, with which the patient was blinded to glucose data collected for 3 days, and then the information was downloaded in the health care provider's office for review. Until recently,all CGM devices required calibration with fingerstick blood glucose measurements.1

2. HbA1c:

Analysis of glycated hemoglobin (HbA1c) in blood provides evidence about an individual's average blood glucose levels during the previous two to three months, which is the predicted half-life of red blood cells (RBCs). The HbA1c is now recommended as a standard of care (SOC) for testing and monitoring diabetes, specifically the type 2 diabetes.

Historically, HbA1c was first isolated by Huisman et al. in 1958 and characterized by Bookchin and Gallop4 in 1968, as a glycoprotein. The elevated levels of HbA1c in diabetic patients were reported by Rahbar et al. in 1969. Bunn et al. identified the pathway leading to the formation of HbA1c in 1975. Using the HbA1c as a biomarker for monitoring the levels of glucose among diabetic patients was first proposed by Koenig et al in 1976. The HbA1c is now an accurate and easy-to-administer test with on-the-spot results availability and can be an effective tool in establishing the diagnosis of diabetes, especially in low- and middle-income countries and hard-to-reach populations.

Even though HbA1c has been endorsed for diagnosis of diabetes, in most of the countries worldwide, some testing strategies and cut-off ranges are still being debated. However, combination of FGT and HbA1c significantly enhances the diagnostic accuracy of these individual tests.

The prognostic potential of HbA1c lies in its unique ability of assessing retrospective glycaemia control in diabetic patients. As the epidemic of diabetes continues to grow worldwide, HbA1c test may continue to be implemented as part of the diagnostic and prognostic tool, leading to better patient care and successful clinical outcomes2.

These two test paved the way to large intervention trials: UKPDS and DCCT

3. UKPDS and DCCT:
These two trials proved beyond doubt that :
a) glycaemic contol can prevent microvascular complications
b) type 2 diabetes is a progressive disease and treatment need to be constantly modified in order to acheve glycemic control
c) macro vascular complications are not contolled merely by prevention of hyperglycaemia
d) strict blood sugar contol with insulin is difficult and it always comes with risk of hypoglycaemias specially with insulin and sulphonylureas.

4. STENO 2 :
With the advent of statins a mutlifactorial intervention trial with strict control of blood glucose, lipids and hypertension there was initiated. For the first time 50% reduction in macrovascular disease was found in tight control group. This paved the way for mutlifactorial intervention in type 2 diabetes

4. HOPE trial:
Studied the role of ACE inhibitors and found it to be nephro and cardioprotective leading to incorportarion of ACE inhibitors as first line anti hypertensive in diabetics.

4. ACCORD/VADT trials:
Proved that strict control of diabetes in patient with established atherosclerotic cardiovascular disease could be dangerous. This lead to individualisation of glycaemic control strategy.

2008 onward was an era mandatory Cardiovascular outcome trial (CVOT) with newer antidiabetic drugs following the controversy of Rosiglitazone.

5. Empareg tial:

SGLT 2 inhibitor class of drug in CVOT trial proved to offer cardio protection in patient with established ASVD. As a secondary outcome this drug offered neprho protection and prevented heart failure. Following this trial Heart failure also emerged as an important co morbidity.

6. GLP1 receptor agonist: specially Liraglutide and semaglutide were also found to offer Cardioprotection from ASVD.

These lead to emergence of these two class of drug as frontrunner in diabetic therapy in patients with high risk of ASCD or established ASVD while SGLT 2 inbibior also became first line contender in patients with CKD (upto class 3) and patients with Heart failure.

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PREDIABETES AND CV RISK

PREDIABETES and CV RISK

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Worldwide, more than 300 million people were estimated to have pre-diabetes. By 2025, it is estimated that approximately 500 million people will have prediabetes. Southeast Asia currently has the highest number of people with pre-diabetes. By 2025, it is estimated that Southeast Asia will continue to have the highest prevalence of pre-diabetes (13.5 percent), followed by Europe (10.9 percent).Prevalence of prediabetes around the world varies between 9.7 and 56.8%, and eventually most of the patients with prediabetes (70–80%) will develop T2D with high risk of vascular complications

Definition

Prediabetes is a state characterized by impaired fasting glucose or impaired glucose tolerance.
Prediabetes based on the American Diabetes Association criteria (ADA) is defined as:

i) Impaired fasting glucose (IFG): fasting glucose between 100 and 125 mg/dl;

ii) Impaired glucose tolerance (IGT): 2 h glucose 140–199 mg/dl; and iii) IFG + IGT. Most of the known physio pathological abnormalities characterizing T2D are already present in prediabetes although less severe

Pathophysiological Defects in Prediabetes

The known pathophysiological defects that underlie T2DM are being increasingly recognized in the prediabetic state. The natural progression of deglycation involves increasing insulin resistance and loss of pancreatic β-cell function. Significant defects in insulin action and secretion are consistently demonstrable in the prediabetic state of IGT.
Defects in the prediabetic state include:

- Increased lipolysis,
- Decreased endogenous levels of glucagon-like peptide 1 (GLP-1)
- Impaired postprandial suppression of glucagon secretion by the alpha-cells of the pancreas.
- Aberrant expression of proinflammatory cytokines adds to the toxic milieu of prediabetes.
- Emerging insights regarding the gut microbiome and its association with cardiometabolic disorders, such as obesity, diabetes, dyslipidaemia, etc., have relevance to prediabetes

- Epidemiologic evidence suggests that the relationship between diabetes and cardiovascular disease begins earlier in the progression from normal glucose tolerance to impaired glucose tolerance and impaired fasting glucose to diabetes, and is associated with resistance to the biologic activity of insulin.
- Over many years before the onset of type 2 diabetes, subjects exhibit excessive increases in postprandial plasma glucose levels (related to loss of first-phase insulin secretion), near normal fasting plasma glucose levels, and compensatory increases in fasting plasma insulin levels.
- The relative contribution of insulin resistance and impaired pancreatic -cell function may vary considerably among individuals during this phase of impaired glucose tolerance, but it is clear that both progress until overt hyperglycaemia is established.
- This long period of glucose dysregulation before the diagnosis of overt diabetes contributes to the initiation and progression of cardiovascular disease

Predictors of Glycaemic Progression to Prediabetes

An analysis of six prospective studies on progression from prediabetes to T2DM revealed the following features:

(1) Baseline fasting plasma glucose (FPG) and the 2-h OGTT glucose values were positively associated with diabetes risk;

(2) The rate of progression from prediabetes to T2DM was exponential among subjects in the top quartile of baseline FPG but increased linearly with increasing 2-h OGTT glucose levels;

(3) Incident diabetes occurred at higher rates in Hispanic, Mexican-Americans, Pima, and Nauruan populations than among other ethnicities such as Caucasians;

(4) increased BMI predicted T2DM risk in low risk populations but not in populations with the highest incidence of T2DM.

Macrovascular Complications of Prediabetes

1. CVD
2. Stroke
3. Peripheral vascular disease.

These disorders are established in patients with T2DM, but their initiation and progression are well recognized to occur during the prediabetes stage.

The traditional CVD risk factors (dyslipidaemia, obesity, hypertension) are quite prevalent among individuals with prediabetes.

Cardiovascular Disease:

- A recent meta-analysis based on 35 studies showed data for the association between myocardial infarction and congestive heart failure as well as coronary artery disease and atherosclerosis have all been reported in individuals with prediabetes.

Transient ischemic attack, stroke, and recurrent stroke.

- A recent study by Tanaka and colleagues demonstrated that both diabetes and prediabetes were associated with poor early prognosis 30 days after acute ischemic stroke.
- Subjects with prediabetes had an increased risk for carotid plaque and adverse functional cardiac parameters.
- In the IRIS trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, treatment with pioglitazone significantly decreased the risks of stroke, myocardial infarction or development of T2DM as compared with placebo treatment.

Peripheral Vascular Disease

- The development of diabetes is independently associated with mortality in PVD patients in some but not all studies.

Interactions among Prediabetes and CVD Risk Factors

- Epidemiologic studies have shown that prediabetes is a strong predictor of CVD.
- DECODE and Funagata Diabetes Study
- In the San Antonio Heart Study, there was evidence that the risk for CVD starts to increase long before the onset of clinical diabetes.
- Obesity and overweight, known risk factors for T2DM and prediabetes, have also been associated with CVD risk.

Preventing Progression from Prediabetes to T2DM

Prospective epidemiologic studies have reported an approximate 5% annual conversion rate to T2DM for both isolated IFG and isolated IGT.

- Lifestyle intervention has clearly been demonstrated to decrease progression to T2DM.

- The results of the DPP, Finnish Diabetes Prevention Study (FDPS), and other pertinent studies showed approximately 60% risk reduction for incident T2DM in the lifestyle arm compared to placebo. In both the DPP and FDPS, every 1 kg decrease in weight in the lifestyle arm was associated with 15%– 16% in future T2DM risk.
- Pioglitazone was found to decrease the risk of diabetes by ~70% in obese subjects with prediabetes in the ACT NOW study.
- STOP-NIDDM (25% risk reduction), Xendos (45% risk reduction), DREAM (62% risk reduction), CANOE (26% risk reduction) and the Valsartan arm of the NAVIGATOR trial (14% risk reduction).
- It must be noted, however, that in both the IDPP1 and the follow-up study IDPP2, pharmacologic intervention provided no additional benefit beyond lifestyle modification in subjects randomized to Lifestyle + Metformin or Lifestyle + Pioglitazone arms.
- Current guidelines from the ADA recommend lifestyle modifications as first line approach for diabetes prevention. Indications for possible use of metformin include women with a history of gestational diabetes and high-risk individuals unresponsive to optimal lifestyle modification.

New Paradigm suggested to treat IGT

- Begin treatment in individuals who exhibit impaired fasting glucose, impaired glucose tolerance, or both before the diagnosis of overt diabetes.
- As noted, these individuals are at high risk for both diabetes and cardiovascular morbidity and mortality, and the protracted progression from dysglycemia to overt diabetes offers a tempting target for intervention.
- Despite these clear and important risks, impaired glucose tolerance is not currently considered to be a disease in which aggressive treatment is recommended.
- However, the results of recent studies indicate targeting these high-risk subjects for treatment with aggressive lifestyle modification or pharmacotherapy can reduce the incidence of diabetes in this vulnerable population and has the potential to reduce cardiovascular risk.

Conclusion

- Physicians and healthcare providers should screen patients routinely for prediabetes and refer those with the condition for intensive lifestyle counselling.
- The goal is to achieve and maintain > 5% weight loss by caloric restriction and increased physical activity.
- Healthcare providers should endeavour to build strong ties within healthcare systems, communities, and payers, to increase the availability of evidence-based structured lifestyle programs.
- While it has long been known that diabetes confers significant cardiovascular risks, it is now becoming established that CVD risks precede diabetes and are evident in people with prediabetes.
- Identifying and intervening in the at-risk prediabetic populations requires education, increased awareness, care coordination and organization.
- Prediabetes carries an increased risk in cardiovascular disease
- Significant physiological, metabolic, and biochemical features are dysregulated in prediabetes
- Extensive Randomized Controlled Trials have demonstrated that lifestyle modification can decrease the rate of progression from prediabetes to diabetes.
- Early detection and intervention are vitally important for prevention of prediabetes progression to diabetes

Suggested Reading:

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MEDICAL NUTRITION THERAPY OF DIABETES

Medical Nutrition Therapy of Diabetics

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Introduction: Diabetes is one of the biggest global public health problems: the prevalence is estimated to increase from 425 million people in 2017 to 629 million by 2045, with linked health, social, and economic costs.1 Urgent solutions for slowing, or even reversing, this trend are needed, especially from investment in modifiable factors including diet, physical activity, and weight.

Medical nutrition therapy is an integral component of diabetes management and of diabetes selfmanagement education. Dietary factors are of paramount importance in the management and prevention of type 2 diabetes. Despite progress in formulating evidence based dietary guidance, controversy and confusion remain. Diet is a leading contributor to morbidity and mortality worldwide according to the Global Burden of Disease Study carried out in 188 countries.2 The importance of nutrition in the management and prevention of type 2 diabetes through its effect on weight and metabolic control is clear. However, nutrition is also one of the most controversial and difficult aspects of the management of type 2 diabetes.

The idea of being on a “diet” for a chronic lifelong condition like diabetes is enough to put many people off as knowing what to eat and maintaining an optimal eating pattern are challenging. Medical nutrition therapy was introduced to guide a systematic and evidence based approach to the management of diabetes through diet, and its effectiveness has been demonstrated,3 but difficulties remain. Although most diabetes guidelines recommend starting pharmacotherapy only after first making nutritional and physical activity lifestyle changes, this is not always followed in practice globally. Most physicians are not trained in nutrition interventions and this is a barrier to counseling patients.4 5 Moreover, talking to patients about nutrition is time consuming.

Goals of Medical Nutrition Therapy: 1) To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and to achieve and maintain body weight goals, attain individualized glycemic, blood pressure and lipid goals, delay or prevent the complications of diabetes. 2) To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes and existing barriers to change. 3) To maintain the pleasure of eating by providing non judgmental messages about food choices while limiting food choices only when indicated by scientific evidence. 4) To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients or single foods.

The simple rules of medical nutritional therapy is that it should be moderate in amount, with variety of natural foods in proportionate manners and the individual must adhere to the therapy. The dietary advice should be given after anthropometric assessment which helps in assessment of calorie consumption from which we can calculate the energy and macronutrient requirement.

In anthropometric assessment ideal weight for height is calculated and BMI is calculated which we try to keep under <23 kg/m2.

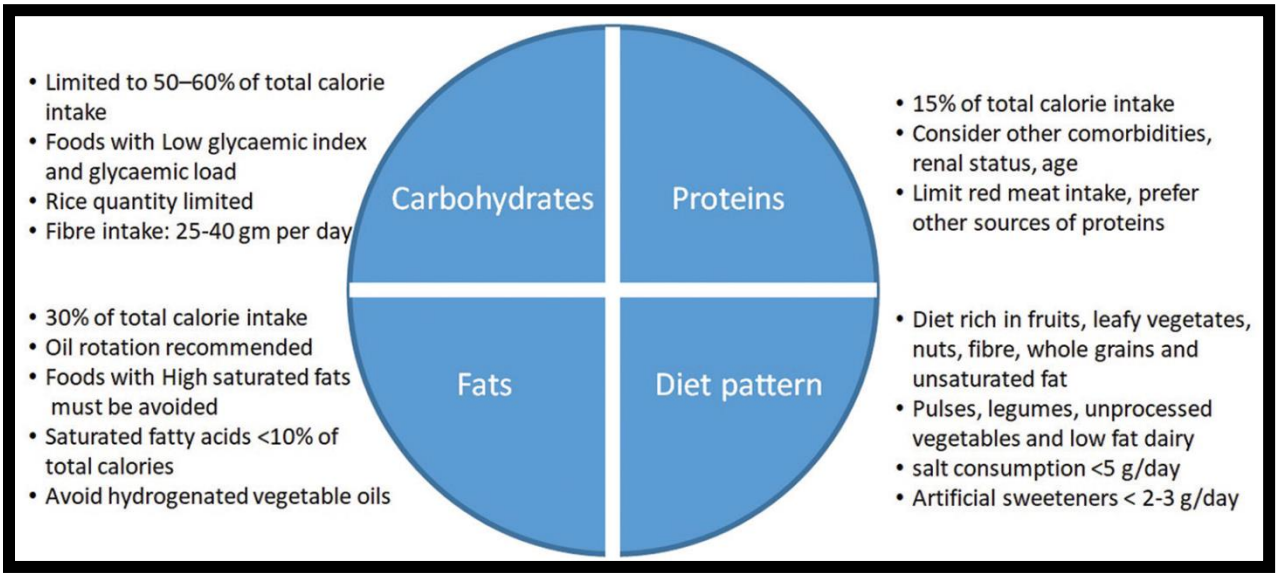
Calculation of Energy Requirement:

Energy Requirement (Kcal/Kg IBW/Day)			
Activity	**Obese**	**Normal**	**Underweight**
Sedentary	**20-25**	**30**	**35**
Moderate	**30**	**35**	**40**
Heavy	**35**	**40**	**45-50**

Minimum energy requirement for youth:

Age	Energy Requirements
1 yr	**1000 kcal for first year**
2-11 yr	**Add 100 kcal/yr to 1000 kcal up to 2000 kcal at age 10**
Girls 12-15	**2000 kcal + 50-100 kcal/yr after age 10**
Girls > 15 years	**Calculate as for an adult**
Boys 12-15	**2000 kcal plus 200 kcal/yr after age 10**
Boys > 15 years	**Sedentary: 30-35 kcal/kg, Moderate activity: 40 kcal/kg, Very physically active: 50 kcal/kg**

Recommendation for MNT in Type 2 Diabetes:



Carbohydrate and Fiber: Daily carbohydrate intake should be approximately 50 – 60% of total calorie intake (175 gm).Complex carbohydrate and its product are preferred over refined carbohydrate and its

product.Total dietary fibers in daily diet should be 25-40 gm/day. There should be minimum 5 servings of fruits and vegetables/day.Simple sugars should be avoided.Low GI food should be preferred.

Sugars: There is no recommendation for sugar.Artificial sweeteners can be used in moderation. FDA approved 5 artificial sweeteners: Saccharin, Aspartame, Acesulfame–K, Neotame and Sucralose.Stevia and some sugar alcohols have been approved by FDA under GRAS (Generally Recognized as Safe) status. We can use alternative to sweetened beverages like Skimmed buttermilk, Tender Coconut Water, Low Fat Milk, Green Tea.

Dairy: Dairy foods are encouraged for the prevention of type 2 diabetes, with more consistent evidence of the benefits of fermented dairy products, such as yoghurt. Similar to population level recommendations about limiting the intake of foods high in saturated fats and replacing them with foods rich in polyunsaturated fat, the current advice for diabetes also favours low fat dairy products but this is debated.

Proteins:protein intake should be based on body weight.1gm/kg/day considering the quality of protein in a usual Indian vegetarian diet.In conjugation with energy intake, protein intake should provide 10 – 15% of the total calories (53 gm) in sedentary to moderately active individuals.In Type 2 diabetes, ingested protein can increase insulin response without increasing plasma glucose concentrations. Therefore, protein should not be used to treat acute or prevent night time hypoglycemia.

Dietary fat: It is the major source of energy and aids your body in absorbing vitamins. It is important for proper growth, development and keeping you healthy. It provides tastes to the food and helps you feel full. Fat should not provide more than 15 – 30% of total energy (39 gm). There should be partial replacement of visible and invisible fat from animal foods with whole nuts such as pistachios and almonds.Saturated fatty acid should provide no more than 10% of total energy (for individuals having LDL > 100 mg/dl <7%).Essential PUFA (Linolenic acid) should provide 5 – 8% of total energy.Alpha Linolenic Acid (ALNA): 1 – 2% of total energy: optimal ratio of LA/ALA (5 – 10). Cis MUFA should provide 10 – 15% of total energy.Trans Fatty Acid < 1% of total energy.Cholesterol intake should be 200–300 mg/day.

Oils: Uncertainty continues about certain plant oils and tropical oils such as coconut or palm oil as evidence from prospective studies or randomised controlled trials on clinical events is sparse or non-existent. However, olive oil, particularly extra virgin olive oil, has been studied in greater detail with evidence of potential benefits for the prevention and management of type 2 diabetes29 and the prevention of cardiovascular disease within the context of a Mediterranean diet30 (see article in this series on dietary fats).31

Alcohol: In the fasting state, alcohol may cause hypoglycemia in persons using exogenous insulin or insulin secretagogues. Alcohol is a source of energy, but not converted to glucose; interferes with gluconeogensis. Excessive amounts of alcohol (three or more drinks per day) on a consistent basis, contributes to hyperglycemia.

Micronutrients: There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes (compared with the general population) thatdoes not have underlying deficiencies.Routine supplementation with antioxidants such as vitamins E and C and carotene is not advised because of lack of

evidence of efficacy and concern related to long term safety. Those who may need supplementation include those on extreme weight-reducing diets, strict vegetarians, the elderly, pregnant or lactating women, clients with malabsorption disorders, congestive heart failure (CHF) or myocardial infarction (MI).

MNT in Type 2 DM in youth: They are always advised to prevent themselves from excessive weight gain. They are always encouraged for healthy eating habits and increased activity. They are addressed for other health risk factors.

Basic strategies for Type 1 DM: For individuals with type 1 diabetes, insulin therapy should be integrated into an individual's dietary and physical activity pattern. Individuals using rapid-acting insulin by injection or an insulin pump should adjust the meal and snack insulin doses based on the carbohydrate content of the meals and snacks. For individuals using fixed daily insulin doses, carbohydrate intake on a day-today basis should be kept consistent with respect to time and amount. For planned exercise, insulin doses can be adjusted. For unplanned exercise, extra carbohydrate may be needed.

Expected outcome of MNT in diabetes: There should be decrease of 1% of HbA_1C in patients with newly diagnosed Type 1 diabetes,decrease of about 2% of HbA_1C in persons with newly diagnosed Type 2 diabetes, decrease of about 1% of HbA_1C in persons with Type 2 diabetes of 4 year duration and ↓ LDL-C by 15-25 mg/dL in 3-6 months.

Conclusion: T2DM patients require reinforcement of DM education including dietary management through stakeholders (health-care providers, health facilities, etc.) to encourage them to understand the disease management better, for more appropriate self-care and better quality of life. The overall purpose of treating T2DM is to help the patients from developing early end-organ complications which can be achieved through proper dietary management. The success of dietary management requires that the health professionals should have an orientation about the cultural beliefs, thoughts, family, and communal networks of the patients. As diabetes is a disease which continues for the lifetime, proper therapy methods with special emphasis on diet should be given by the healthcare providers in a way to control the disease, reduce the symptoms, and prevent the appearance of the complications. Active and effective dietary education may prevent the onset of diabetes and its complications.

DIABETES DIAGNOSIS AND MANAGEMENT : AN ENDOCRINOLOGIST'S PERSPECTIVE

Diabetes Diagnosis And Management: An Endocrinologist's Perspective

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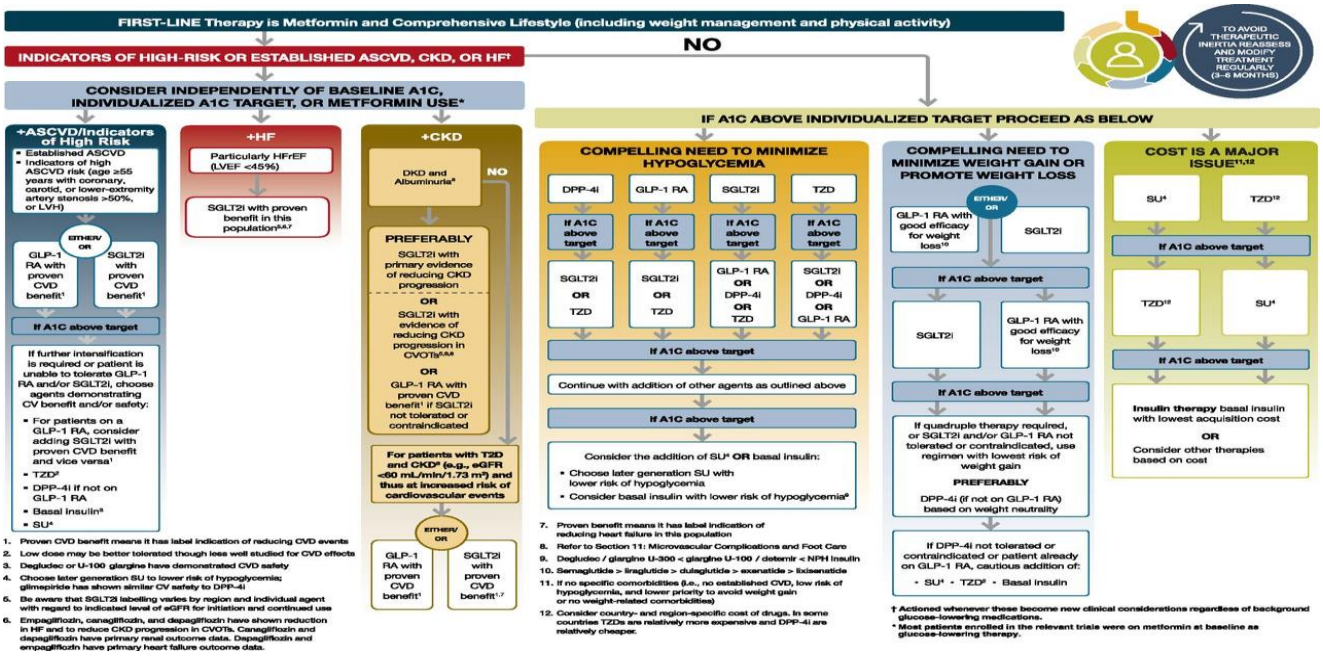
Diabetes as a disorder is of two types: diabetes mellitus and diabetes insipidus. Diabetes mellitus (DM) is a disorder of carbohydrate, protein and fat metabolism. The diagnostic criteria depend solely on levels of hyperglycemia; the spectrum varies from prediabetes to diabetes without or with complications. The disorder may be seen from birth to old age, due to various pathogenetic causes. The neonatal diabetes is a genetic disorder which may produce clinical disease temporarily or be permanent. The diabetes developing beyond neonatal period to young adult majority is autoimmune Type 1 DM (90%) and rest is idiopathic Type 1 DM (10%). The diabetes in young is a special entity and could result from beta cell failure, pancreatic damage, genetic mutations leading to maturity onset diabetes in young (MODY), flatbush diabetes and mitochondrial diabetes[1]. Beyond the age of 30-35 years, Indian population suffers type 2 diabetes occurring earlier than western population; although still some of them can be MODY misdiagnosed as type 2 DM. The pregnancy poses a special challenge to the clinician and is being dealt with separate diagnostic cut-offs and treatment protocols, as we will be dealing fetal wellbeing as well. The diabetes may be diagnosed when evaluating the patients before any planned intervention or before treatment of diabetes related complications. The gender differences have been variable in various disease stages.

The plasma glucose is the most accepted parameter. The gold standard for diagnosis for DM has been evolving from glucose tolerance test (GTT), to seeing only fasting hyperglycemia or by elevated glycosylated haemoglobin (Hb A1c) level. The spectrum of dysglycemia ranges from prediabetes [impaired fasting glucose (100-125 mg/dl), impaired glucose tolerance post GTT (140 to 199 mg/dl)] to diabetes (Fasting plasma glucose ≥126 mg/dl, post-glucose challenge ≥ 200 mg/dl). The A1c is also used nowadays for diagnosis: Prediabetes 5.7% to 6.4% and diabetes ≥6.5%. The fasting blood and urine sample can also be utilized for testing lipid levels, serum calcium, albumin, phosphate, alkaline phosphatase, ESR, complete hemogram, urinalysis (including ketone). The further evaluation of cardiac, vascular, neurological, renal, rheumatological, dermal complications are carried out as per indicated frequency. The macrovascular complications start developing in prediabetes stage while microvascular complications start from frank diabetes state.

The aim of diabetes treatment is maintaining glycemia (A1c <7%, Fasting 80-130 mg/dl; post-meal 2 hours 140-180 mg/dl) normal lipids and normotension. The management of neonatal, Type 1 DM, pancreatic DM and Type 2 DM with severe complications is insulin therapy. The diabetes developing beyond 3 years of age in a child may be tried to be treated with glibenclamide. The other forms of DM are first advised medical nutrition therapy with lifestyle modification, failing which, after 3 months we can start pharmacologic therapy.

The pharmacologic therapy consists of insulin based agents [secretogogues (sulphonylureas, meglitinides) and sensitizers (metformin, glitazones), glucagon based agents (GLP-1 receptor agonist GLP-1RA, DPP4 inhibitors) and hormone independent agents (SGLT2 inhibitors, alpha-glucosidase inhibitors, lipid absorption partial inhibitor orlistat and cetilistat). The antihypertensive agents and other cardiac, reno-protective drugs and neutraceutical agents for nerve health are used as indicated.

On being detected diabetic, the patients' are assessed for complications and possible compliance to diet and drugs to be prescribed here. The current severity of complications determines the intended intensity of glycemic control. The guidelines for choice of pharmacotherapy for diabetic patients are released from various associations based on cardiac complications and A1c levels. The obese and those with CAD benefit from GLP-1RA or SGLT2i whereas those without CAD can be prescribed according to the ADA algorithm.



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The intensive glycemic control within the range is prognostically beneficial and the combination multi-pharmaco-targeted therapy is very helpful in this. The delay in onset of microvascular complication and deceleration in macro-vascular complication is achieved with comprehensive glycemic, blood pressure and lipid control.

MANAGEMENT OF TYPE I DIABETES : BEYOND INSULIN

Management of Type I Diabetes: Beyond Insulin

Dr Meena Chhabra: Consultant Diabetologist New DelhiI ,Chairman RSSDI-Delhi

Issues related to accepting the disease and confirming the diagnosis

The emotional "GADBAD" following diagnosis of serious chronic disease

G - Guilt • A - Anger • D - Denial • B - Bargain • A - Anxiety • D – Depression

Type 1 DM – Tests to know the etiology & confirm diabetes

Antibodies • GADA, Islet cell, insulin, zinc transporter, tyrosine phosphate etc. • C – peptide, S. Insulin • Genetic testing – Only in monogenic diabetes • E.g. Neonatal and MOD

Management of Type 1 DM

Start Basal Bolus Insulin • Nutrition plan • Diabetes Self Management Education (DSME) • SMBG Insulin Injections • Teach urine ketone testing • Sick day management • Diabetologists, Pediatrician, Nutritionist, Psychologist (enrol in a multidisciplinary Diabetic clinic)

Nutrition in type 1 diabetes

Variables affecting blood sugar: • Dietary carbohydrate content • Fiber • Glycemic index • Protein, fat • Exercise /physical activity

• Insulin administered

Earlier approach: • fixed insulin regime, adjust meals and lifestyle to fit the insulin dose •

Current approach: • Adjust insulin to child's meal timings, carb intake & lifestyle

Key factors are:

✓ Understanding of determinants of blood sugar ✓ Dietary principles ✓ Monitoring ✓ Willingness to take multiple daily insulin injections

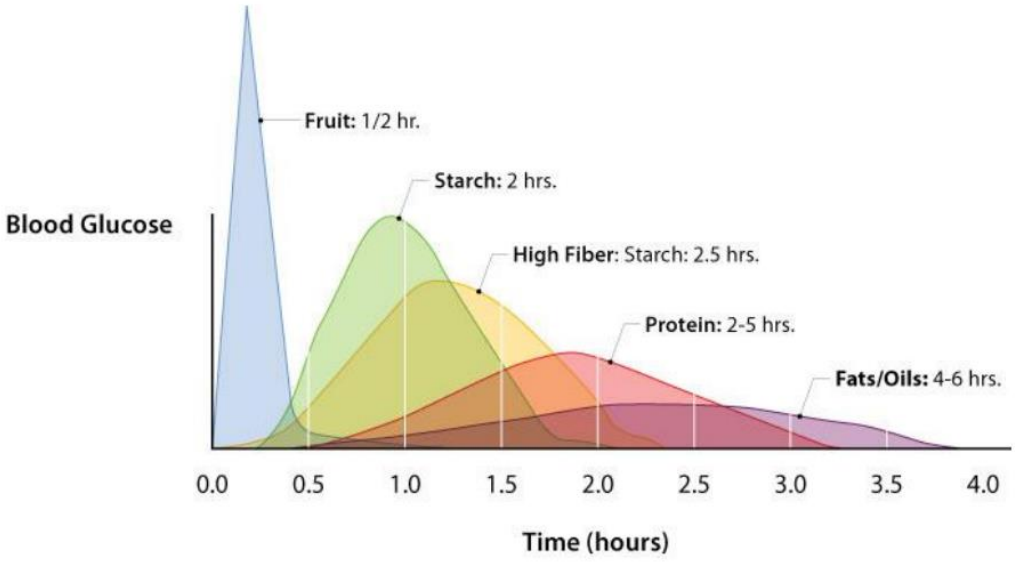
Healthy Nutrition for a T1DM Patient

'Diabetic diet' is essentially a healthy diet with same principles as for any other child/adolescent • Regularity of meal timings and eating routine important • 3 meals a day incorporating a wide variety of nutritious foods from all food groups will meet the child's requirements • Healthy, low carb snacks in between meals if required • Matching of insulin dose to carbohydrate intake

Type of carbohydrates:

Prefer whole grain breads, cereals, pulses, dairy products • Prefer low glycemic index over high glycemic index foods • Avoid processed foods low in fiber • Avoid sugary drinks • Avoid 'diabetic foods' rich in fats, artificial sweeteners, more expensive with no clear benefit

Straight to your blood stream



Exercise

Must be encouraged as part of daily activity: • Insulin sensitivity maintained • Reduces risk of hypertension/ overweight • Good peer relationship • Regular exercise easier to manage than occasional intense exercise • Recommended 60 minutes of cumulative activity per day • Allow for extra calories; for every 30 min of unaccustomed moderate exercise a 15 gm CHO snack should be consumed • Avoid exercise during periods of ketosis & high blood sugar >250 mg% • Sugar free fluids to avoid dehydration • Decrease in insulin in case of unaccustomed exercise • Monitor blood sugar before, during and after activity • Additional snack at bed time if blood sugar< 100 mg%

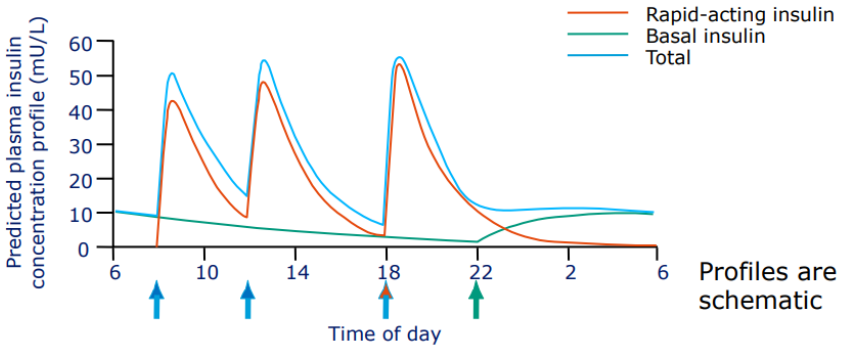
Treatment of Type 1 – Always insulin , No tablets

• Basal Bolus is the best • 3 boluses per day before every meal (regular / rapid acting analogue) • One basal such as Glargine or Degludec or 2 doses of NPH • Anecdotal Possibilities • Pronounced honeymoon phase • Type 2 that initially needed insulin injections • If type 1 is confirmed then insulin will be for ever**ype 1 DM .**

Insulin Therapy

Basal bolus insulin therapy

Attempts To Mimic The Physiological Insulin Profile



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Advantages with basal-bolus insulin regimen

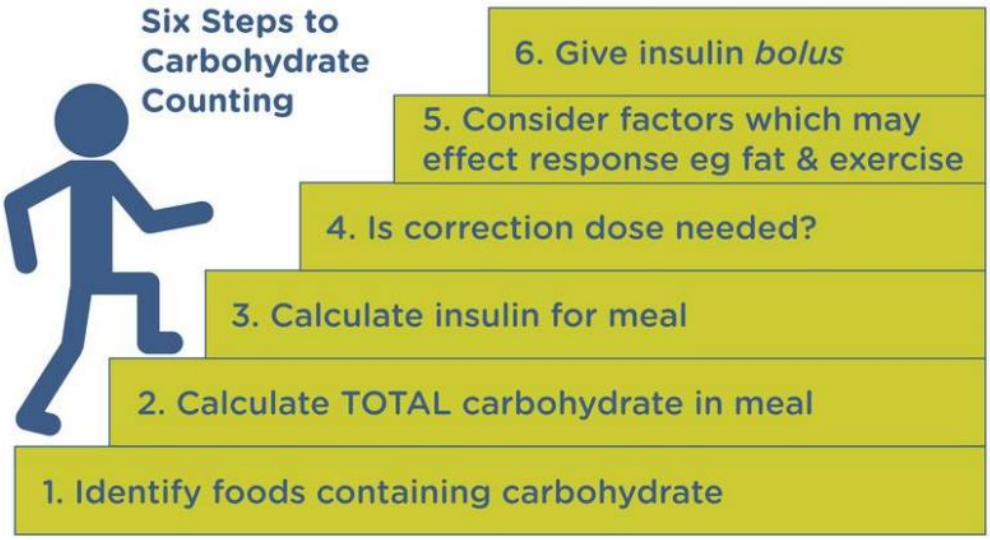
• This regimen is closest to physiological insulin profile • Offers greater flexibility over type of food and when it can be eaten • Suited to those who need optimal glucose control because of complications • Suited to those who are highly motivated • It offers greater flexibility for dose adjustments than other insulin regimen or premix analogue formulations, thereby allowing patients with irregular meal patterns or flexible lifestyles to reach glycaemic goals quickly, without increased risk of hypoglycaemia

Types of Insulin Plans with Carb Counting

There are 2 methods of insulin dosing using carbohydrate counting:

•Set Dose: follows a consistent carb meal plan with a consistent amount of insulin. 1. Usually there will be no insulin during lunch, possibly, only if blood sugars reach a designated level, s/he may get a correction shot of insulin.
•Basal/Bolus: uses a changing carb intake with an adjustable amount of insulin. 1. Receiving an insulin injection, or insulin through a pump for all carbohydrates that are eaten at lunch and possibly for snack times. With this plan, their insulin dose is determined by: 1. The amount of carbohydrates that they will consume 2. Their blood sugar prior to the meal

Steps to carb counting



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Optimal Blood Glucose in Type 1 DM

• Check CBS (capillary blood sugar) pre-meals and post meals initially to calculate and confirm ICR (Insulin Carb Ratio) & Bedtime • Subsequently pre-meals at least 3/d & bedtime
• Other tests TTGA IgA, IgA, FT4, TSH, Thyroid Antibodies,
• Visit to Clinic Initially Weekly, after stabilization monthly and subsequently 3-4 monthly • More Intensive education and frequent F/U for pump patients
• Target CBS before meals 90-130 mg/dl and bedtime/overnight 90-150mg/dl ADA 2017 • Target HbA1C < 7.5 % ADA 2017 < 7 ISPAD 2014

How Do I calculate Insulin Needed?

• 15 year old 50 kg child • Insulin – Carb Ratio = 500/Daily dose of insulin • E.g. Daily dose 50 , 500/50 = 10 gm ICR • 1 unit of insulin will cover 10 grams of carbs • Insulin Sensitivity Index • E.g. Daily dose 50 iu, 1800/50 = 36 ISI • 1 unit of insulin will reduce pre meal sugar by 36 mg%

Hypoglycemia: Management

• Mild-moderate hypoglycemia: patient conscious, accepting orally • Simple sugars like glucose (10-15 grams) /sucrose, candy, sugar containing juice given orally • Sweets containing fats eg ice-creams not preferred since fat delays sugar absorption • Repeat blood sugar after 10-15 min, if still low, repeat sugar administration. If >100 mg% give a snack like milk/biscuits/sandwich • Severe Hypoglycemia: patient unconscious • Injection glucagon (0.5 mg for children

Screening for Complications – ISPAD 2018

TABLE 1 Screening recommendations and risk factors for vascular complications

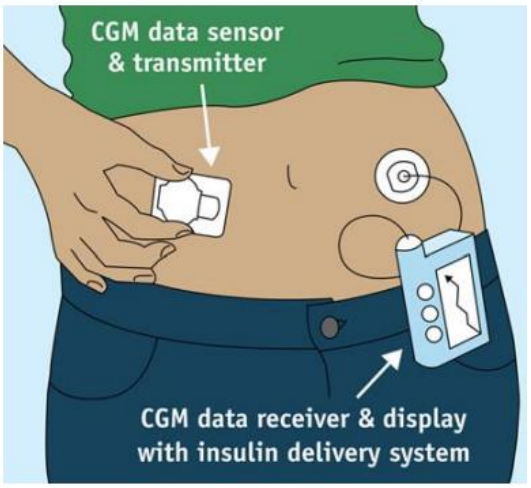
	When to commence screening?	Screening methods	Risk factors
Nephropathy	11 years with 2-5 years diabetes duration	Urinary albumin/creatinine ratio	Hyperglycaemia High BP Lipid abnormalities Smoking
Retinopathy	11 years with 2-5 years diabetes duration	Fundal photography or mydriatic ophthalmoscopy	Hyperglycemia High BP Lipid abnormalities Higher BMI
Neuropathy	11 years with 2-5 years diabetes duration	History Physical examination Clinical tests	Hyperglycemia Higher BMI Age Diabetes duration Genetics
Macrovascular disease	11 years with 2-5 years diabetes duration	Lipid profile every 2 years, BP annually	Hyperglycemia High BP Lipid abnormalities Higher BMI Smoking

A Closed Loop Insulin Pump

A tiny CGM sensor under the skin checks glucose. A transmitter sends data to a receiver. The CGM receiver may be part of an insulin pump, as shown here, or a separate device.

Useful for those who:

- are on intensive insulin therapy, also called tight blood sugar control
- have hypoglycemia unawareness
- often have high or low blood glucose



Empower your T1 Diabetic

It takes a village to raise a child Teach a man to fish and he will never starve. We doctors need to step down from our pedestals Empower the patients and their families

DIABETES AND PREGNANCY: WINDOW OF OPPORTUNITY FOR DIABETES PREVENTION IN INDIA

Diabetes and Pregnancy: Window of Opportunity for Diabetes Prevention in India

Dr. Anand Shankar
Consultant Diabetologist, Shankar Diabetes Care Centre, Patna, Bihar.

Introduction:

Gestational diabetes mellitus (GDM) is carbohydrate intolerance of varied severity that first recognized or begins during pregnancy [1]. In India the number of women who are pregnant and also have diabetes whether pre-existing (type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM)) or gestational are increasing day by day [2] and at any given time point women affected by GDM in India will cross 4 million [3]. Among 12-21% of Indian women GDM has been found, as reported in a recent meta-analysis [4]. Based on the two hour 75 g post glucose value ≥140 mg/dL, Seshiah et al in south India had conducted a recent community based study which confirms that GDM was detected among 17.8% of the women in urban, 13.8% in semi urban, and 9.9% women in rural areas [5] . It has been observed that diabetes in pregnancy is associated with a number of adverse outcomes including neonatal hypoglycaemia, pre-eclampsia, macrosomia and trauma.
Pregnant women with preexisting diabetes have the additional risks which include increased perinatal mortality and congenital defects.

Impact of Diabetes for Pregnant Women:

Women are more severely impacted by consequences of diabetes especially during pregnancy. The risk of pregnancy complications and maternal and perinatal morbidity and mortality significantly increases when they develop hyperglycaemia in pregnancy (HIP) like obstructed labour, infections, pre-mature delivery, hypertension and pre-eclampsia, postpartum haemorrhage, both large and small for gestational age (SGA) infants, stillbirths, hypoglycaemia, birth injuries and newborn deaths due to respiratory problems. Level of maternal hyperglycaemia are directly related to the risk and number of these complications [6]. Pregnancy may worsen pre- existing kidney disease and diabetic retinopathy and increases the risk of cardiovascular disease in much higher rate, which will further aggravate in presence of diabetes mellitus. In the HAPO study, GDM and obesity were independently predictive of fetal macrosomia, primary cesarean delivery, preeclampsia and neonatal adiposity [7]. The recurrence of GDM is as high as one third to two thirds in a subsequent pregnancy. Body mass index (BMI) and Waist circumference (WC) are the strongest two anthropometric measures which are associated with the development of T2DM in women with GDM [8].

To prevent the potential risk of shoulder dystocia and birth trauma in diabetic pregnancies the rate of cesarean delivery are increasing in numbers, among which elective cesarean are in higher proportion. Several finding suggested that gestational hyperglycemia can lead to hyperinulinaemia occurring during brain organisation in neonatal life and represent a teratogenic risk factor resulting in significantly increased susceptibility to diabetes, CV disease and obesity in later life [9]. There were several study which has already confirmed that after GDM frequency and rate of development of diabetes are highly depends to the severity of hyperglycemia present during GDM diagnosis and along with magnitude of impaired insulin secretion and further weight gain [10, 11]. Figure 1 depicts that a vicious cycle is created by GDM in which diabetes begets more diabetes [12].

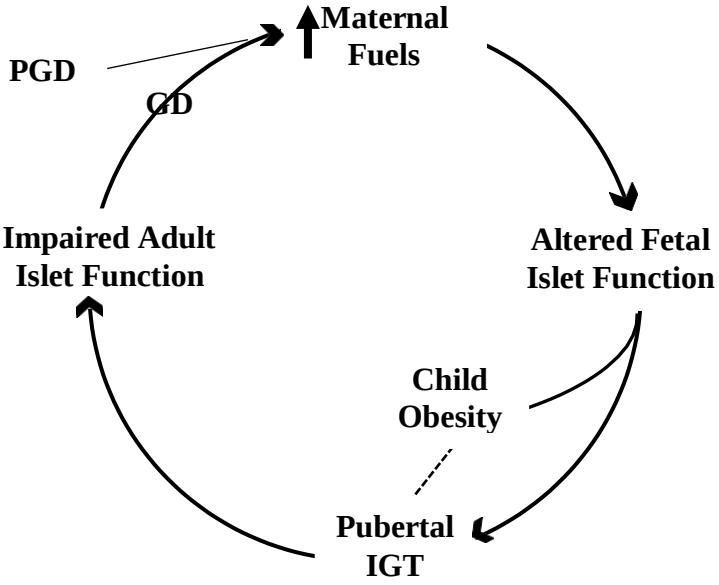


Figure 1: Altered fetal islet function occurred due to alteration of maternal fuel metabolism. This event further leads to Child obesityand later develops DM.

Current scenario of treating GDM: Indian prospective:

Due to uncertain quality control in laboratories special in rural area variability in biochemical analysis of blood glucose values the chance of misclassifying gestational diabetes is very high [13]. Modifiable and independent risk factors for GDM include pre pregnancy overweight, obesity and maternal excessive gestational weight gain and pre pregnancy overweight. In South-East Asia prevalece hyperglycaemia is very high and one in four pregnancies is affected by it. As the civilization progressed with urbanization prevalece of GDM is becoming an epidemic [14].
Prevalence of GDM was reached unto 13.9% as per the community based prospective study conducted in India and GDM prevalence were varies from 3.8 to 21% in different parts of the country [4]. As compared to Caucasian women, 11-fold increased risk of developing glucose intolerance during pregnancy found in Indian women who were experiencing pregnancy [15].

In India, to prevent the potential risk of shoulder dystocia and birth trauma in diabetic pregnancies the rate of cesarean delivery are increasing in numbers, among which elective cesarean are in higher proportion.
Despite WHO's report on Women and Health, which clearly mention that high blood glucose and high blood pressure are two leading risk factor for early date of young women specifically who are less than 20 years of age, still diagnosis of gestational diabetes often missed or neglected and women are not routinely screened for hyperglycaemia during their pregnancy. GDM is often mismanaged with inadequate postpartum follow-up and care. Many women get diagnosed with GDM with past history of spontaneous abortions in subsequent pregnancies. As per WHO reports, despite several risk factors have been described to clinically identify women with GDM, still many clinicians especially in rural areas fail to correctly identify more than half the women with GDM [16]. It has been already reported by Seshiah et al., that with pre pregnancy BMI of even less than

19, GDM prevalence rates of 8–10% among women of low socioeconomic status, whereas in urban environments it was significantly high with higher BMI [4].

Rationale for enhanced focus on GDM

In county like India, women are more vulnerable than compared to men and things get further worsen when they develop GDM as they have less access to care, fewer opportunities of being treated and receive less support to deal with the consequences of diabetes. Thus screening, diagnosis and treating GDM has emerged as an important opportunity for the implementation of various strategies for diabetes prevention.

Reports state that within five years about 50% of mothers with GDM develop type 2 diabetes and if they remains untreated children later in life are up to 8 times more likely to develop type 2 diabetes [17]. Before the age of 17 years about one third of children born of diabetes pregnancies develop glucose intolerance [18].

GDM also offers a window of opportunity for the long-term health of mother and child. Onset of type 2 diabetes for the mother can delay or even eliminate by treatment during and after pregnancy [19]. GDM is, as a first step, managed through mild to moderate exercise and improvements in nutrition which makes it a unique opportunity for clinician. Lifestyle interventions that target activity, awareness, diet modification, and behavioural strategies can effectively modify body weight and therefore having effects on reducing GDM incidence [20].

Scope for early intervention is the most important aspect of managing GDM and it has been seen that as high as 80% of GDM cases could be detected in the first trimester itself.

The Challenge:

A new window of opportunity for prevention of GDM has emerged, but when developing a T2DM or GDM prevention or intervention plane few factors that require consideration includes counselling of psychological impact of GDM, information regarding ways to handle future risk and offering a comparable intervention plan that fits with Indian women multiple roles in family. In India very few clinicians including gynecologist or obstetricians, physicians and even diabetologists do not follow any of the recommended guidelines for the diagnosis of GDM which mainly because of awareness about screening and diagnosis of GDM.

Therefor at present in India especially in rural the challenges of manning GDM includes mainly low awareness and prioritization of GDM, outdated standards of care, insufficient diagnosis and treatment, disempowered patients and proper concealing to manage the condition.

To overcome this challenge we need to build awareness, establish standards and quality of care by offering proper screening, diagnosis, counselling and treatment address these gaps and offer better management of GDM and pregnancy outcomes.

It should be always remember that in Indian scenario where women always pointed as responsible for families misfortune one needs to be careful not to create a platform for women to be blamed while advocating the cause for increasing attention to GDM, for adverse effects on their children. In worst cases especially for some culture in India it can create another agenda for stigmatization. Like other health problems which affecting our society public awareness and enhanced patient knowledge plays an important role in prevention of diabetes and its complications and as well as increasing treatment compliance.

Conclusion:

It is now an establish fact that GDM can lead to a lifelong diabetes and most of the patients leads to develop T2DM. It is Untreated GDM has serious consequences for maternal and newborn

health, and increases the risk of developing diabetes and other non-communicable diseases (NCDs) later in life. Timely diagnosis and treatment of diabetes in pregnancy offers an important window of opportunity, a chance to reduce short and long term health risks for women and children. It's a window of opportunity for Indian clinicians to initiate screening, early detection, concealing and intervention for diabetes in pregnancy and implement life style changes, avoid maternal and fetal adverse outcomes along with delay development of diabetes in high-risk individuals.

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AN INEVITABLE TRANSITION FOR GOOD GLYCAEMIA : ORALS TO INSULIN

An Inevitable Transition for Good Glycaemia: Orals to Insulin

Dr Madhukar Rai; Professor Department of Medicine Institute of Medical Sciences; BHU

Introduction

Clinic – Observation

A 58 years old male Diabetic for 8 years Presented to diabetes clinic for routine follow-up No H/O hypertension or heart disease, normal on general examination, The Reports are;
HbA1c – 8.3%, FPG - 196 mg/dl, PPG – 236 mg/dl
He is on -Metformin 1 gm BD, Glimepiride 2mg BD Sitagliptin 100 mg BD. Exploring further management

Type 2 diabetes mellitus (T2DM) is a progressive disorder that involves decline in β-cell function and rise in insulin resistance, thus requiring timely intensification of treatment to maintain adequate glycemic control[1].
Recent guidelines both National & International recommend:
Lifestyle modification (LSM) , to be followed by monotherapy with metformin and subsequent addition of more drugs, including oral antidiabetics (OADs) and injectables[2].Patients with uncontrolled glycaemia, according to recommended glycemic targets, may be at a higher risk of micro- and macrovascular complications[3].As T2DM progresses, combination of multiple OADs fail to control hyperglycemia and there is need for intensification of the therapy with addition of insulin to reduce glycemic parameters as well as prevent long-term complications[3].

When to Initiate Insulin Therapy: Guideline Recommendations for initiating insulin in T2DM

All major global guidelines including, American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA), have laid down the recommendations to initiate insulin early in T2DM patients with uncontrolled hyperglycemia on OADs.
ADA recommends insulin initiation in patients with type 2 diabetes not achieving glycemic goals on OADs/other therapies[4]. AACE recommends that even patients with newly diagnosed type 2 diabetes who are symptomatic and/or have HbA1c ≥9-10% and/or blood glucose levels ≥300 mg/dL should be prescribed insulin[5].

Indications to Initiate Insulin in T2DM?

Anytime when a patient with T2DM[4]:

- Is significantly hyperglycemic
- Has inadequate glycemic control on OADs/other therapies
- Is intolerant of OADs/other agents
- Is pregnant (subject to debate with GDM)
- Is in a perioperative/intensive care setting
- Is on steroid therapy
- Is with diabetic emergencies – DKA & HHS
- Is with diabetic foot

Need for early initiation of insulin

At diagnosis of a T2DM patient, β-cell function is already reduced to 50% of normal as seen through HOMA modeling and to a larger extent by dynamic testing. Although diet and oral therapy initially tend to reduce glucose levels, however, progression of the disease is associated with persistent decline in β-cell function[6].
United Kingdom Prospective Diabetes Study (UKPDS) Group has shown that in the 50% of subjects on sulfonylurea, β-cell function increased in the 1st year from 46 to 78 %p ($P < 0.0001$), but that was followed by decrease in the β-cell function to 52 %p ($P < 0.0001$) at 6 years. (Fig 1) [7].

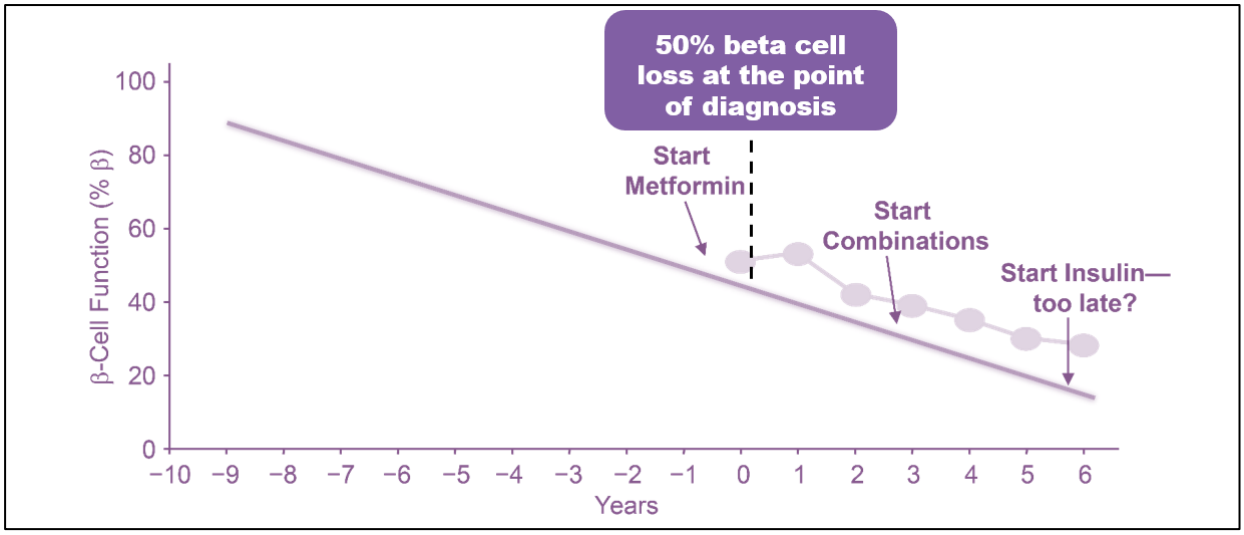

Fig 1. Decline of β-cell Function – Inevitable with Disease Progression

Hanfield M et. al in their study has shown that early insulin initiation can help to preserve β-cell mass and function, while also improving insulin sensitivity[8].

Owens D in his review article has mentioned that earlier initiation of insulin therapy, may be more effective in providing long-term efficacy against the complications of T2DM[9].

Del Patro S et. al have demonstrated that early initiation of insulin significantly improves patients' chances of reaching their goal (Fig 2) [10].

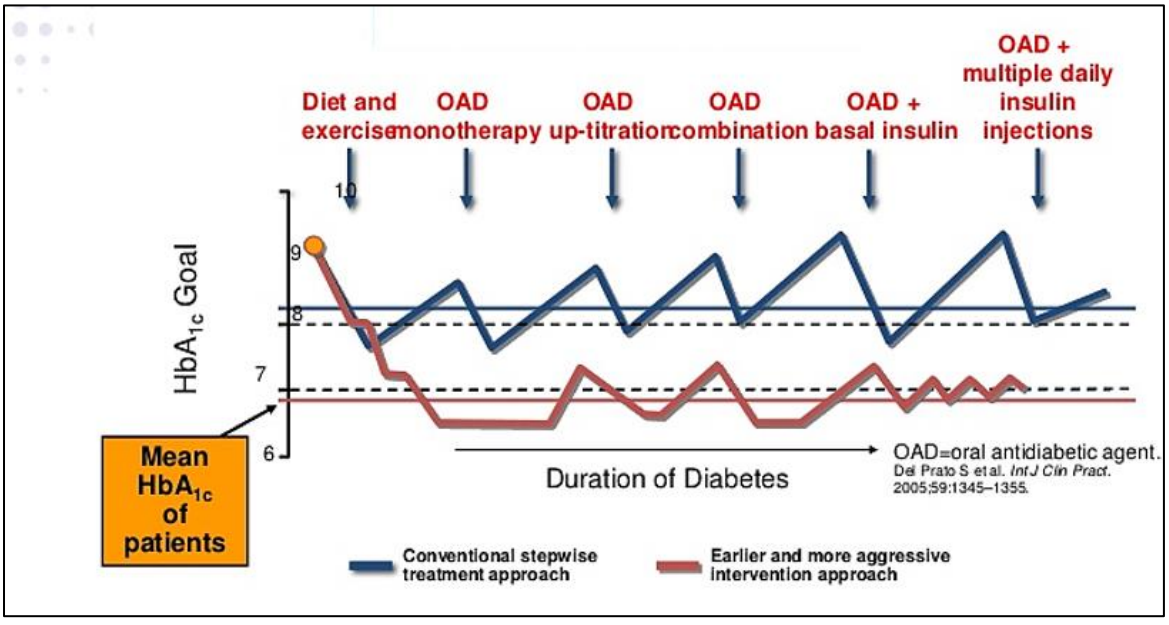

Fig 2. Higher chance of achieving glycemic goal with early insulin initiation

The conventional approach has been to initiate with one drug typically metformin, evaluate the response and add second drug to a failing regimen and proceed further. However, with this approach the patient spends considerable time in hyperglycemia and the benefit of early sugar control is lost (legacy effect). Now, it is advocated that early and effective control of blood glucose leads to better outcome. In patients on two or more than two OAD with HbA1c > 8.5, the chance of achieving target is < 30% on uptitration of OAD's Vs > 50% chance on addition of basal insulin.

Currently ongoing real world study LANDMARC trial on its 6 months interim data analysis as shown that addition of a fourth or more OAD over three OADs doesn't provide any additional reduction in HbA1c values as mean HbA1c reduction was found to be 0.3% in patients receiving up to three OADs as well as in patients achieving more than three OADs (Fig 3). However, patients on insulin have shown significantly greater reduction in HbA1c with mean reduction of 0.6% compared 0.3% with OADs (Fig 4) [11].

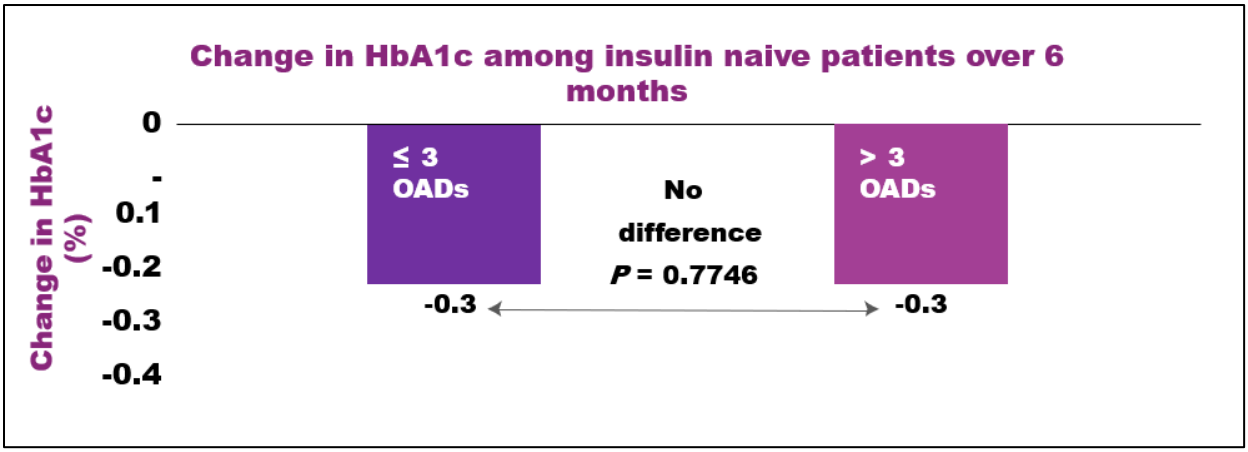

Fig 3. No improvement in HbA1c reduction despite increasing the number of OADs

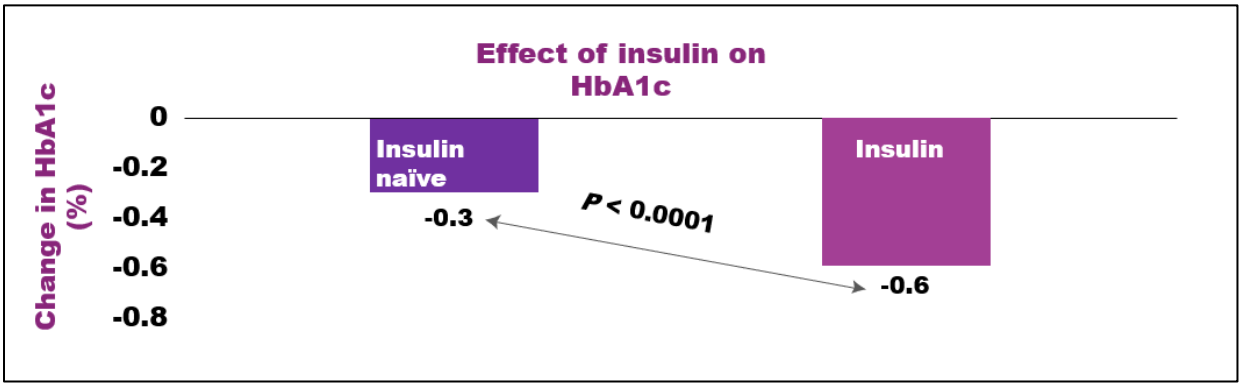

Fig 4. Significantly better reduction in HbA1c with insulin compared to OADs

Which insulin to start with?

Case management ;
Along with current , Patient was put on 10U Glar-100 , after 2 weeks , the insulin was up titrated by + 2U for 4 weeks , at the writing the case – patient has achieved good glycemic control HbA1c – 7.2% , FPG -130 mg/dL , PPG – 180 mg/dL

A significant shift in all the global and national recommendations on basal insulin being the preferred insulin at initiation can be noticed over the present decade. Most of the current global guidelines recommend basal insulin alone as the most convenient initial insulin regimen, to add over existing OADs[4, 5.Premixed] and bolus insulins are recommended mainly for intensification strategy. The recent Research Society for the Study of Diabetes in India (RSSDI) 2019 also recommends basal insulin alone as the most convenient initial insulin regimen[15].

How to initiate and continue therapy with basal insulin

Major current guidelines including ADA 2021 ,AACE 2020 and RSSDI 2019 recommend that initiation of basal insulin in insulin-naïve patients should depend on weight of the patient and HbA1c value. T2DM patients with A1c below 8% should receive 0.1-0.2 U/kg of basal insulin at initiation while those with HbA1c above 8% should be initiated with 0.2-0.3 U/kg.[5,15].

Once initiated, the dose of basal insulin should be titrated once or twice weekly based on FPG values to achieve glycemic goal for FPG of 90-120 mg/dL[21].

Conclusion

As T2DM progresses and combination of OADs fails to provide glycemic control, insulin initiation plays an important role to help the patients achieve their glycemic targets along with protecting the β-cell as well as

preventing long-term micro- and macro-vascular complications. All global and national guidelines recommend initiation with basal insulin as the most convenient, effective and safe insulin compared to other regimens like premixed and coformulation insulin.

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PRACTICAL APPROACH TO DEAL WITH HYPERGLYCEMIA WITHIN THE HOSPITAL

Practical Approach To Deal With Hyperglycemia Within The Hospital

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Diabetes and stress hyperglycemia are common in the hospital setting and are strongly linked with increases in hospital related complications, duration of hospital stay, and in hospital mortality.[1–3]and healthcare costs, and that better glycemic control improves clinical outcomes.

Longer hospital stay and poorer outcome is a very common observation amongst patients with diabetes mellitus (DM).[1-3] A large number of DM cases are diagnosed for the first time when they get admitted for various indications, which may or may not be related to DM. Although Indian data reveal that every sixth patient admitted to hospital has diabetes, in reality the number may be higher.[6]

In hospital Hyperglycemia, as defined by a blood glucose concentration over 140 mg/dl, may occur in hospitalized patients with known diabetes or in the acutely ill individual with previously normal glucose tolerance ('stress hyperglycemia') – the result of increased circulating counter-regulatory factors, such as cortisol and adrenaline. Irrespective of the cause, elevated blood glucose in the inpatient setting is an independent marker of adverse outcome, associated with increased morbidity and mortality [1-3]

For more than a decade now, insulin therapy has been considered the cornerstone of the management of patients with hyperglycemia in the hospital.[2.3]

Management ofHyperglycemia:

Hyperglycemia can have detrimental effects in both medical and surgical hospitalized patients.[9] TheIn-hospital Hyperglycemia can be broadly categorized into:
(1) non-critically ill, and (2) critically ill.

A. Management OF Non-Critically ill Patient

In comparison to critically ill patient, non-critical patient doesn't draw attention of the physician in the early stages. The primary concerns for the management is lack of proper monitoring facility and specified paramedicalstaff, unsupervised dietary intake and fear of inducing hypoglycemia are amongst the factors responsible. The targets proposed by American Diabetic Association (ADA) for Fasting blood glucose (FBG) is less than 140 mg/dLand RandomRBG less than 180 mg/dL are generally acceptable. These targets can be relaxed in the following situations: (1) stable patients with optimal glycemic control prior to admission, (2) postoperative ward and gestational DM patients in a background of available adequately trained staff for monitoring and treating hypoglycemia.[12,13] Patients who are able to eat adequately at regular intervals are right candidates for subcutaneous (SC) insulin, because intravenous (IV) insulin regimen is less flexible.

Sliding scale insulin (SSI) regimen has been found to be inferior to basal bolus (BB) regimen. In addition to achieving bettercontrol, the infection rate,the respiratoryfailure, and acute renal failure isreduced in patients that were put on analogs.

Recommendations for Non – Critically Ill Patient

Premeal BG target should be 110–130 mg/dL, and post meal target should be 140–180 mg/dL. The targets should be less stringent for the elderly and patients with significant comorbidities, non-critically ill patients on enteral nutrition should be preferably managed with insulin. Basal insulin can be used to cover the basal and correctional need, and bolus insulinshould be used to cover the nutritional need. SSI though popular are not recommended rather BB Insulin analogs should be preferred in hospitals as they are associated with less hypoglycemia and are more flexible to use.

Profile Based Management in Non-Critically

Patient profiles	Blood glucose levels	Action
Patient on OAD at admission/during follow-up	Pre-meal BG ≥ 140 mg/dL or post-meal BG ≥180 mg/dL	Start on basal-bolus insulin regimen
Newly detected with diabetes	Pre-meal BG ≥ 180 mg/dL or post-meal BG ≥ 250 mg/dL	Start on basal-bolus insulin regimen
On basal-bolus regimen at admission/during follow-up	Pre-meal < 140 mg/dL and post-meal < 180 mg/dL	.Continue existing regimen if here are no episodes of ypoglycemia 2.Monitor and review BG levels

Calculation of subcutaneous dose of insulin in a 60 kg adult male with body mass index (BMI) of 25 having moderate hyperglycemia:

• Total daily dose (TDD) = 0.5 units/kg body wt × 60 = 30 units
• Basal insulin dose = 50% of TDD = 50% of 30 units = 15 units basal insulin
• Bolus insulin dose per meal = (50% of TDD)/3 = (50% of 30 units)/3 = 15/3 = 5 units of rapid-acting insulin before each meal

B. **Management OF Critically ill Patient**

Regulating Normal Glycemia in critically ill patients is very challenging for the physicians, as mostly this set of patients have multiorgan dysfunction. And In spite of extensive evidence establishing aclear relation between uncontrolled hyperglycemia and poor outcome in critically ill, optimal glycemic targets are not precisely defined. The first & foremost important thing is Discontinuation of non-insulin medications & initiation of insulin therapy is recommended for in-hospital management of hyperglycemia in critically ill patients.

In comparison to non-critically ill patients the critically ill patients must be kept on tighter control in the range of 110–140 mg/ dL in surgical patients, slight relaxed target may suit medically ill patients.3,16. Now these stringent targets can lead to severe hypoglycemia (< 40 mg/dL), which turns out to be major cause of increased mortality in the critically ill.

The only acceptable &recommended modality of treatment is continuous IV insulin infusion, which should be initiated when BG levels are greater than 180 mg/dL . Though there are many IV insulin infusion regimens available, but those regimens are preferred, which contain orders that take into account both current BG values and rate of change of BG.

Insulin analogs are preferred as they have a predictable absorption mechanism and cause lower variability. The incidence of hypoglycemia is significantly minimized if pre- and postprandial regular insulin is replaced by rapid-acting insulin analogs. Predictable duration of action and comparatively lesser stacking effect enables the analogs to achieve euglycemia with minimal hypoglycemia.[19]

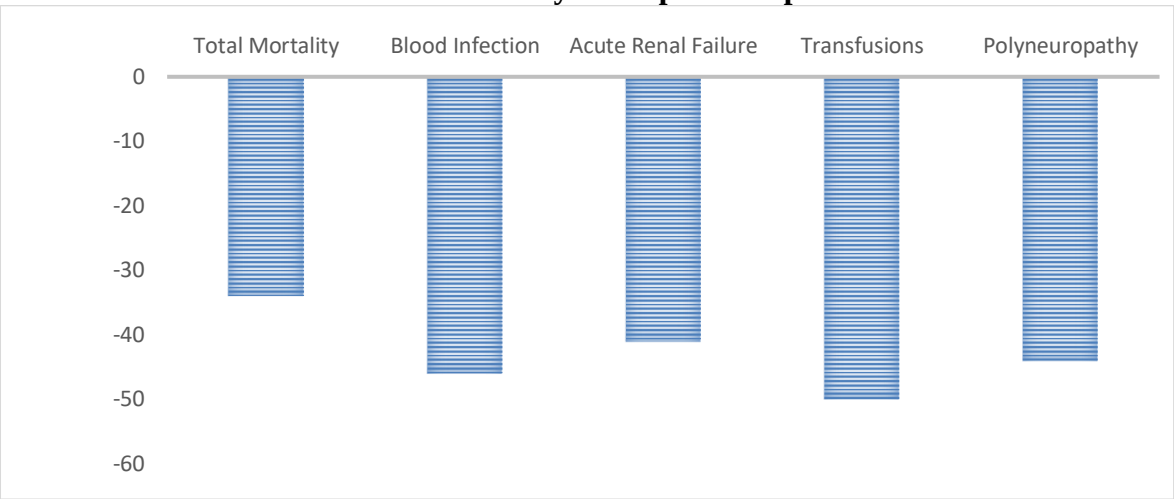
Suggested protocol for insulin infusion in ICU

A. Preparation	50U of regular insulin dissolved in 50 mL normal saline (NS) in a 50 mL disposable Syringe
B. Mode of administration:	IV infusion with an electronic syringe pump infusion pump
C. Primary target	To maintain blood sugar level within a predefined target 140 mg/dL
D. Control methodology	Blood sugar to be controlled gradually in case of severe hyperglycemia by titrating the dose of IV insulin
E. Pre-requisites	Initially 15–20 mL of solution should be flushed through plastic tubing to saturate the insulin binding sites in the tubing
F. Targets	Dose should be adjusted as per the levels of blood sugar
G. Monitoring	Either by capillary blood glucose or from the venous site/central line

Titration of insulin dose according to blood glucose (BG) levels

Blood glucose levels(mg/dL)	**Dosage of insulin infusion**
< 100	No insulin to be given
100–149	1–1.5 units/hour
150–199	2 units/hour
200–249	2.5 units/hour
250–299	3 units/hour
300–349	3.5 units/hour
350–399	4 units/hour
For any further increase in BG, consulting endocrinologist/physician/ intensivist needs to decide the rate subjectively. If BG does not fall more than 10%, insulin can be increased to 1.5 times the normal dose.	
If BG is < 50 mg/dL Administer 50 mL of dextrose (25 g), check blood sugar at 15 minutes and if blood glucose increases to more than 100 mg/dL, start insulin infusion after 1 hour	
BG between 50 mg/ dL and 75 mg/dL Infuse 50 mL dextrose (25 g) if hypoglycemia manifests clinically. If asymptomatic, give half dose of the above solution. Check blood sugar after 15 minutes and start insulin 1 hour after BG reaches > 100 mg/dL.	

Benefits of IV insulin infusion in critically ill hospitalized patients[1]



Blood Glucose Monitoring.

- **Check BG hourly until stable (3 consecutive values within target range)**
- **Then, check BG every 2 hrs. for 12-24 hours**
- **BG checks can then be spaced every 4 hours if:**
    - No significant change in clinical condition
    - No significant change in nutritional intake
- **Consider resumption of hourly BG monitoring, in any of the following situations:**
    - Any change in insulin infusion rate (i.e., BG out of target range)
    - Significant changes in clinical condition
    - Initiation or cessation of pressor or steroid therapy
    - Initiation or cessation of renal replacement therapy
    - Initiation, cessation, or rate change of nutritional support

Recommendations

Maintain BG level at a range of 140–180 mg/dL for majority of patients with medical morbidity, and 110–140 mg/dL for those with surgical morbidity, Use Of Only IV insulin is recommended. Subcutaneous regimens with premixed insulin, intermediate-acting or long-acting insulin and SSI are not recommended. Regular insulin or rapid-acting insulin analogs (aspart, lispro, glulisine) can be used as IV infusion.

Steps For Transition from IV to SC insulin in hospitalized patients

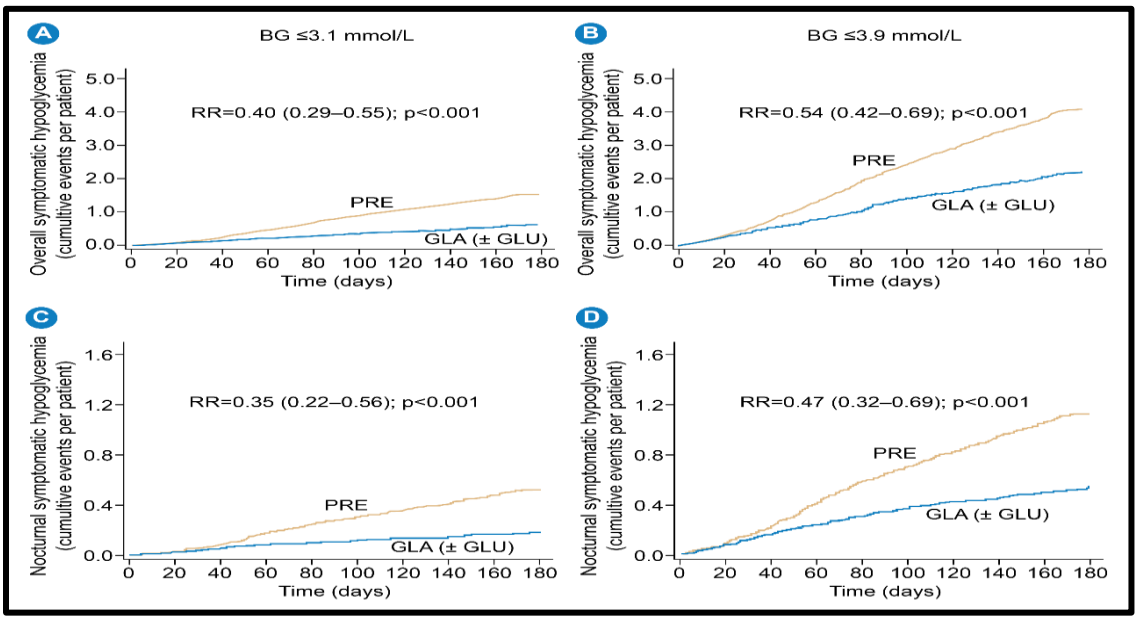
Transition to SC insulin required when patient begins eating regular meals, or when transferred to non-critical intensity care

- **Calculate IV insulin requirement in the previous 6 h stable control of BG**
- **Multiply by 4 to get the total insulin daily dose (TDD)**
- **Basal insulin dose is 50% of TDD given once daily SC**
- **Bolus insulin dose is 50% of TDD given SC as 3 divided doses of RAI administered with meals**

Insulin regimens at discharge

Discharge and outdoor management of patients with diabetes should be done only after prior stabilization of blood glucose levels. Physicians should be aware of the onset, peak and the effective duration of each type of insulin before writing out the treatment plan. It is prudent to follow a practical plan of switching over to SC insulin based on the most recent IV insulin requirement, rather than doing it arbitrarily with inconsistent results. The patient should be provided a simplified treatment plan including drug regime and its appropriate use, BG monitoring schedule, hypoglycemic symptoms and their management, and contact number of primary care physician whom they can contact during any major complaint or emergency. Though there are multiple plans such as premixed / Basal alone / Basal Bolus Or coformulations. Basal bolus however has shown significant advantage over any other regimen.

Reduced rates of overall (A, B) and nocturnal (C, D) hypoglycemia with glargine compared with premixed insulin



Conclusion

The management of hyperglycemia in hospitalized patients is easier in a way since the visibility of the patient profile & parameter is completely clear & also due to continuously available healthcare staff managing or facilitating a quick desired response. However, good coordination among various disciplines is much required. while there is need of a standard guideline on use of insulin and insulin analogs using IV or SC regimes as required to target euglycemia for ensuring better therapeutic outcomes. While this article shall surely guide the treatment of in hospital hyperglycemia. Proper knowledge of standard algorithm and the use of particularly basal analog based therapy is recommended for better outcome.

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UPDATE SOTAGLIFLOZIN

UPDATE SOTAGLIFLOZIN

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Diabetes, especially type 2 diabetes, is a chronic and complex disease with huge burden of complications particularly CVD and CKD.

Focus of this article is inhibitors to both SGLT:

The development of inhibitors targeting SGLT began with experiments with the compound phloridzin, first isolated in 1835 by French chemists from the root bark of the apple tree, and subsequently found to improve blood glucose levels in animals. SGLT is the acronym of the original name (sodium–glucose linked transporter; then modified to sodium-dependent glucose co-transporter) of a family counting at least six different isoforms in humans . Of these, SGLT-1 and SGLT-2 have been widely studied because of their fundamental role in glucose and sodium transport across the brush border of gut and kidney cells, through an active mechanism exploiting the Na + electrochemical gradient generated by active sodium extrusion by the basolateral sodium/potassium-ATPase.

In the kidneys, hSGLT-2 and hSGLT-1 were found on the brush border membrane (BBM) of proximal tubule S1/S2 and S3 segments. In the small intestine, hSGLT-1 was expressed on the BBM of enterocytes and subapical vesicles. SGLT-1 was also found in GLP-1-secreting L cells and GIP secreting K cells in mice. hSGLT-1 was expressed in the biliary duct cells of the liver, (as in rats). In the lungs, hSGLT-1 was found in alveolar epithelial type 2 cells and in bronchiolar Clara cells.In physiologic conditions, SGLT-1 is responsible for glucose absorption in the small intestine, and for the reabsorption of nearly10% of the filtered glucose load in the renal proximal tubule segment 3 (S3),while SGLT-2 is primarily expressed in the renal proximal tubule segment 1and 2 (S1–S2) and is responsible for the reabsorption of ≈ 90% of the filtered glucose load . Given its biological characteristics we would expect the inhibition of SGLT-2 to prevent the reabsorption of at least 80% of the glucose load . It is suggested that when SGLT2 is inhibited, SGLT1 is forced to work at maximal transport capacity. In the kidneys, hSGLT-2 and hSGLT-1were found on the brush border membrane (BBM) of proximal tubule S1/S2 and S3segments.

Sotagliflozin:

Sotagliflozin, also known as LX4211, is a small, orally available molecule,which inhibits both SGLT-1 and SGLT-2. In humans the selectivity for SGLT-2, however, is 20-fold greater compared to SGLT-1. Its chemical structure is(2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfanyloxane-3,4,5-triol.

Sotagliflozin's effectiveness in inhibiting SGLT-2 is similar to that of the selective SGLT-2 inhibitors dapagliflozin and canagliflozin, but it is > 10-foldmore potent than the latter molecules in inhibiting SGLT-1. Its effects on SGLT-1 in other tissues are, however, less known. As reported below, sotagliflozin does not seem to affect renal SGLT-1, suggesting that its low affinity has clinical effects only in tissues where SGLT-1 is highly expressed(i.e. the gut). Another possibility is that sotagliflozin acts as a potent intestinal SGLT1 inhibitor because there are higher levels of sotagliflozin in the intestinal lumen than in the general circulation.

In contrast to SGLT-2, SGLT-1 is reported to be highly expressed in both human autopsied hearts and murine perfused hearts in the sarcolemma of cardiomyocytesor more probably in the capillaries .

Moreover, Von Lewinski etal. Demonstrated that both GLUT-4 and SGLT-1 have an insulin-dependent inotropic effects on the heart, indeed the inhibition of PI3-kinase and either SGLT1 or GLUT4 results in a loss of these functions, probably due to the reduction of glucose substrates in the cardiomyocytes.

Sotagliflozin is a dual sodium–glucose co-transporter-2 and 1 (SGLT2/1)inhibitor for the treatment of both type 1 (T1D) and type 2 diabetes (T2D). Sotagliflozin inhibits renal sodium–glucose co-transporter 2 (determining significant excretion of glucose in the urine and intestinal SGLT-1, delaying glucose absorption and therefore reducing post prandial glucose.

Intestinal effects of SGLT-1 inhibition by sotagliflozin. By inhibiting SGLT-1sotagliflozin reduces PPG and improves glycemic control. Possible mechanisms are: (1) delayed glucose absorption in the distal small intestine;
(2) consequent increased GLP-1 secretion by L cells, mostly located in the cecum ,and (3) delayed glucose in the colon where it could promote changes in microbiota and increase production of SCFAs; the latter seems to independently increase GLP-1secretion.

Since the blood glucose lowering effect of SGLT inhibition is minimal in the presence of euglycemia ,and since the euglycemic action of these drugs is completely insulin independent, SGLT inhibitors might theoretically represent a valid adjunctive therapy in patients with type1 diabetes.

Trials:

In the main trial, in Tandem 3 the primary end point was a glycated hemoglobin level lower than 7.0% at week 24, without episodes of severe hypoglycemia or diabetic ketoacidosis, while secondary end points were the change from baseline to week 24 in glycated hemoglobin level and the possible reduction in daily bolus insulin dose, body weight and systolic blood pressure. Up to 28.6% of the sotagliflozin group achieved the challenging primary endpoint (HbA1c < 7% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis), with a greater reduction in the glycated hemoglobin level from baseline in the sotagliflozin group than in the placebo group(difference, − 0.46 percentage points; P < 0.001) . In the sotagliflozin group,the placebo-corrected reductions from baseline in the mean daily total, bolus, and basal doses of insulin were − 5.3 units per day (− 9.7%), − 2.8 units perday (− 12.3%), and − 2.6 units per day (− 9.9%), respectively (P < 0.001 for all comparisons). The decrease in body weight and in systolic blood pressure from baseline to week 24 was significantly higher in the sotagliflozin group than in the placebo group (difference, − 2.98 kg;P < 0.001; difference, − 3.5mmHg; P = 0.002 respectively).

Sands et al. conducted another randomized, multicenter, placebo-controlled, double-blind study to evaluate sotagliflozin, as adjunct therapy in adult subjects with type1diabetes.The primary outcome of the study was the effect of sotagliflozin therapy on change from baseline of total daily bolus insulin dose during the treatment period. The results demonstrated a percent variation from baseline in total daily bolus insulin administration that was − 32.0% in the sotagliflozin group and − 6.4% in the placebo group (P = 0.007) respectively. HbA1c decreased by 0.55% from baseline after treatment with sotagliflozin, compared with 0.06% in the placebo group (P = 0.002).
Moreover, sotagliflozin treatmental soreduced mean body weight compared with an increase in the placebo group (− 1.7kgvs0.5kg) (P = 0.005).

In summary, these studies concluded that treatment with sotagliflozin in combination with insulin in subjects with type 1 diabetes, significantly decreased glycated hemoglobin level, insulin dosage body weight and systolic

blood pressure, and, more importantly, without increasing the occurrence of hypoglycemia. Its key effect could be related to the reduction in postprandial glucose, which consequently leads patients on

sotagliflozin to decrease insulin bolus.

Sotagliflozin and DKA: A formal warning for the increased risk of DKA with SGLTs has been issued by the FDA . Different mechanisms have been proposed to explain this important side effect. First, the reduced glucose concentration partially switches ATP generation from glucose to FFA (Freefatty acids); while this mechanism is responsible for loss of fat mass, it might also determine a mild increase in the genesis of ketones(similar to that usually reached during fasting). Further, the reduced insulin dose, when SGLT-2 inhibitors are associated with insulin therapy, may not be sufficient to block gluconeogenesis in the liver, with a net consumption of oxaloacetate (for gluconeogenesis) impeding the entrance of FFA-derived AcCoA, which in turn are converted to ketones.A vicious circle may also be induced by the inhibition of SGLT-2 in alpha cells which leads to an increase in glucagon with consequent stimulation of ketogenesis in the liver . Moreover, a reduction inrenal clearance of ketones with SGLT-2 inhibition has been described in animal models and may represent another mechanism responsible for DKA with SGLT-2 inhibitor drugs.

In conclusion, sotagliflozin seems to represent a promising treatment for both type 1 and type 2 diabetes, either alone or in combination with metformin or DPP-4 inhibitors in type 2 diabetes or, with an adequate insulin protocol, intype 1 diabetes. The dual inhibition of both SGLT-1 and SGLT-2 improves the efficacy of this SGLT inhibitor also in mild and severe CKD, suggesting an extended use also in frail patients where therapeutic options are currently limited.

Sotagliflozin and cardiovascular outcome trials:

Though prematurely stopped after losing funding from the study sponsor amid the ongoing COVID-19 pandemic, both SCORED and SOLOIST-WHF trials were able to give lots of insight into the CV outcomes. The SCORED and SOLOIST-WHF trials, both presented at the virtual American Heart Association 2020 Scientific Sessions and published simultaneously in the *New England Journal of Medicine*, showed that sotagliflozin reduced the risk of hospitalizations for heart failure(HF) in diabetic patients with chronic kidney disease (CKD) and decompensated HF,respectively,and this benefit was largely evident after just a few months.

In the SOLOIST-WHF study, in which the use of SGLT2 inhibitors was pushed further upstream by starting treatment in patients hospitalized with acute HF or within 3 days of discharge. Reporting outcomes on 1,222 patients—they had initially planned to enroll roughly 4,000 patients—investigators showed that use of sotagliflozin significantly lowered the risk of death from cardiovascular causes and hospitalizations or urgent visits for HF.

With SCORED,investigators focused on patients with diabetes and chronic kidney disease, with and without albuminuria, and at least one major cardiovascular risk factor. The two original coprimary endpoints were a classic MACE endpoint (death from cardiovascular causes, non fatal MI, or non fatal stroke), designed to assess the safety of the diabetes drug, as well the composite of cardiovascular death and hospitalizations for HF. Due to the early trial stoppage and fewer than planned events, the primary endpoint was changed to deaths from cardiovascular causes, hospitalizations for HF, and urgent visits forHF. Sotagliflozin significantly reduced HbA1c levels in SCORED patients with estimated glomerular filtrations rates (eGFR) < 30 mL/min/1.73 m2 and those with less impairment. There seems to be a greater HbA1c reduction at low levels of eGFR in [SCORED and SOLOIST] compared with what we've seen with conventional SGLT2 inhibitors, per se. SCORED is the first trial to demonstrate a reduction in stroke with an SGLT2 inhibitor.The results indicate that Sotagliflozin has salutary effects on CV outcomes among patients with T2DM and CVD though reduction in renal events was not observed due to early cessation of the trial.

Concludsion: All key opinion leaders has opined that results are encouraging and major takeaways are - use at hospitalization or within 3 days of discharge, it may work in patients with normal albuminuria in CKD,it might work in HFpeF patients or across all HF patients and lastly might have ischemic benefits as stroke benefits are clearly seen. Still more studies are needed to outline its huge potentiality.

OBESITY, FAMILY HISTORY OF DIABETES, AND CONSANGUINEOUS MARRRIAGES ARE RISK FACTORS AMONG URBAN POPULATION IN SOUTH INDIAN CITY OF BENGALURU

Obesity, Family History of Diabetes, and Consanguineous Marriages are Risk Factors among Urban Population in South Indian City of Bengaluru

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In 2017, approximately 424.9 million adults (age 20- 79 yrs) were affected by diabetes, with 4 million deaths. Global diabetes burden is estimated to increase up to 628.9 million people. Moreover, diabetes care costed approximately $727 billion in 2017. In addition to mortality and economic cost, diabetes exerts huge effect on a patient's life. It affects the adults at their most productive years which may lead to less productivity, mobility, and considerable expenditure. Diabetes has become one of the leading causes of mortality and morbidity in India as well. According to international reports, over 73 million adults were affected with diabetes in India in 2017. The total economic burden was estimated at around $32 billion. Of note, India will be home to the world's largest population with diabetes by 2045 with approximately 134.3 million patients suffering from type 2 diabetes mellitus (T2DM). Approximately, 1 million are attributable to diabetes. India also houses the second largest population of T2DM patients with undiagnosed disease at around 42.2 million. Furthermore, India also reports more 16,000 cases of type 1 diabetes every year in children and adolescents with 128,500 children and adolescents suffering from type 1 disease in 2017. India also have the third largest population of elderly with T2DM of about 11 million patients. Diabetes is also responsible for loss of billions of dollars in GDP in India as well as worldwide [1].

With the increasing number of diabetes patients in India, it is necessary to diagnose the disease at an early stage for early intervention and reduced risk of subsequent complications. Diabetes is a multifactorial and heterogenous disease owing to several genetic and environmental factors.

Over the decades, several risk factors have been identified for development of T2DM in adults. Obesity and family history of diabetes are two of the major risk factors for onset of the disease in adults. In addition, several systematic studies have revealed that parental consanguinity may also a risk factor for developing T2DM. Thus, individual with obesity, family history of diabetes, and parental consanguinity should be screened to diagnose T2DM. As detection of disease at early stage may lead to better prognosis.

To this end, we have studied these risk factors in urban population in South Indian city of Bengaluru [2]. In a retrospective data analysis, we analysed data of 519 patients who attended the diabetic out-patient clinic. Patients provided the aetiological data through a questionnaire during their routine clinic visit. Obesity, family history (maternal history of T2DM) and parental consanguinity were found to be important risk factors for early onset of T2DM. Obesity is increasing at an alarming rate worldwide. In the United States, more than two-thirds of the adult population is overweight or obese. In India, 180 million adults and 14 million children are obese. It has been doubled in children and tripled in adults from 1980 to 2015. Obesity affect medical, psychological, and social condition of the individuals and may lead to type 2 diabetes in adults. T2DM and obesity are linked with insulin resistance. Non-esterified fatty acids, glycerol, hormones, cytokines, proinflammatory substances, and other substances are in obese individuals which leads to insulin resistance. In addition, insulin sensitivity and the modulation of β-cell function decreases in the condition of obesity. In diabetes, β-cell dysfunction reduces insulin secretion resulting in increase in fasting blood glucose and postprandial blood glucose. Thus, insulin resistance along with impairment of β-cell function leads to the development of diabetes in obese individuals. We also found that obesity was a major risk factor for T2DM which is in line with previous studies. Our results showed that the proportion of patients with T2DM being obese or overweight patients was eight times higher than patients who were non-obese/non-overweight. High-fat diet and physical inactivity may be responsible for obesity apart from genetic traits. However, in this study, we observed that obesity was comparable between patients with active or strenuous lifestyle and sedentary group of patients. Thus, nutritional transition, to highly saturated fats, sugar, and refined foods and the transport facilities and increased stress, particularly in the urban populations may play an important role in increasing obesity. Of note, several systematic studies have shown that obesity management leads to delay in progression to T2DM from pre-diabetes [3].

Weight loss in obese patients with T2DM also improve glycemic control and reduce the need for glucose-lowering medications. American Diabetes Association (ADA) recommended following for weight management in diabetic patients: 1. Diet, physical activity, and behavioural therapy to achieve 5% weight loss for overweight and obese patients with type 2 diabetes. 2. Such interventions should be high intensity and focus on diet, physical activity, and behavioral strategies to achieve a 500-750 kcal/day energy deficit.

3. Diets that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss. 4. For patients who achieve short-term weight loss goals, long-term comprehensive weight maintenance programs should be prescribed. Such programs should provide at least monthly contact and encourage ongoing monitoring of body weight (weekly or more frequently), continued consumption of a reduced calorie diet, and participation in high levels of physical activity (200-300 min/week). 5. To achieve weight loss of >5%, short-term (3-month) high-intensity lifestyle interventions that use very lowcalorie diets (≤ 800 kcal/day) and total meal replacements may be prescribed for carefully selected patients by trained practitioners in medical care settings with close medical monitoring. To maintain weight loss, such programs must incorporate long-term comprehensive weight maintenance 6. Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents who are overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes.

World Health Organization (WHO) and American Diabetes Association (ADA) considered family history of diabetes as the most important risk factor for diabetes. They are 2-6 times more likely to develop T2DM compared to patients without family history of diabetes. It has been long observed that non-diabetic male with family history of diabetes has elevated levels of fasting plasma glucose compared to males without family history of diabetes. Moreover, in Asian adolescents with both diabetic parents, higher FPG was observed compared to adolescents with only one diabetic parent. Hence, first degree relatives of diabetics are at high risk of having prediabetes and eventually develop diabetes. However, it is important to distinct “Diabetes family history” and “genetic risk” as both are not the same. Both genetic and environmental factors which mostly remain same in terms of cultural and behavioural aspects such as shared environment, shared behaviours, and epigenetic effects are represented by family history. Of note, energy metabolism and cardiovascular risk associated with family history and sedentary behaviours contribute to the development of prediabetes and diabetes in patients with family history of diabetes. It is important to note that individuals with family history of diabetes have more knowledge about symptoms of diabetes and more aware of organs affected by diabetes compared to individuals without family history of diabetes [4]. However, other studies have reported otherwise. Family history of diabetes is also associated with other metabolic abnormalities. In this study, more than half of the patients diagnosed with T2DM had positive family history of diabetes. Interestingly, the risk was greater with maternal than paternal family history of T2DM. Same has been reported elsewhere as well [5]. Subgroup analysis revealed that the proportion of patients diagnosed with T2DM in the younger age group (≤ 40 years -50 yrs) was two times than the older patient group (>50 yrs) (p50 years. Patients with family history of T2DM were twice at higher risk of YOD than patients who did not have family history of T2DM. Thus, individuals with family history of T2DM should be screened for early diagnosis of T2DM. If patients with prediabetes are diagnosed early, lifestyle modification may delay onset of the disease. Moreover, early detection of diabetes will improve patients’ outcome and possibility of complications, if managed well. Consanguineous marriages have been attributed for development of numerous disorders which has genetic risk factor. Marriage between first cousins are the most common among consanguineous marriages. Along with other cultural and environmental factors, consanguineous marriages have also been found to be a risk factor for developing diabetes. Parental consanguinity has been found to be a modifier of effect of family history of diabetes on impaired fasting glucose [6]. It has also been found to be a risk factor for developing impaired fasting glucose in populations with higher number of consanguineous marriages [7]. In this study, we observed that the parental consanguinity was a significant risk factor for developing early onset diabetes (age ≤ 40 years) after adjusting for obesity as a risk factor. However, consanguinity was not a significant independent risk factor in non-obese patients. Thus, such individuals also should be screened for prediabetes and diabetes as recommended.

In summary, our results are in line with previous studies suggesting that obesity, family history of diabetes, and consanguineous marriages are risk factors for developing diabetes in South Indian city of Bengaluru. Regular screening as recommended by standard professional guidelines should be performed of such individuals with high risk.

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MANAGEMENT OF DIABETIC FOOT IN PHYSICIAN'S OFFICE

Management of Diabetic Foot in physician's office

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Diabetes is chronic metabolic disorder affecting nerves, eyes, kidney, blood vessels and heart. Diabetic foot is the result of either neuropathy or vasculopathy or from its combination and **Diabetic foot disease** is a result of complex interplay between neuropathy, peripheral arterial disease, foot deformities and infection.
In India 75-90% of major foot problem in diabetes is due to neuropathy. Diabetic foot has become a matter of concern because it is a major cause of morbidity and mortality with great economic burden.

Magnitude of the problem
Inadequate management of diabetic foot disease (DFD) can end in amputation of limb.It is the commonest cause of non-traumatic amputation of limb (70%).In every 30 second one limb is amputated somewhere in world. ADA has estimated that 50% of limb with foot ulcer can be saved if both health care provider and patient fulfill their respective responsibilities.Spectrum of complications includes superficial cellulitis to chronic osteomyelitis and gangrene necessitating lower limb amputation.

Prevalence and Risk factors
Globally prevalence of DFD ranges from 1.5%- 16.6%. In India, the prevalence is 11.6% .Risk factors are Smoking, DPN with LOPS, PAD,Foot deformity,CKD, Callus or Corn, history of DFU or amputation, poor glycaemic control and visual impairment

Human foot is a great mechanical marvel.It has 26 bones,29 joints and 42 ligaments; a very sensitive & protective skin blanket with exquisite nerve supply.It has great vascularity with rich collaterals.

Why diabetic foot disease? Why not diabetic hand? It is due to attainment of erect posture from tetra pod to bipedal posture. Which resulted in weight bearing of whole body on two limbs instead of four and secondly less care taken by the body because the distance of feet from the eye is increased. Lastly neuropathy and vasculopathy affects peripheral parts classically in diabetes.Why to give more attention to diabetic foot? Because of poor healing of wound due to abnormal cellular/inflammatory pathway-fibroblast,neutrophil,AGEs(advanced glycation end products) associated peripheral neuropathy with loss of protective sensation. Other factors are poor neuro inflammatory response (autonomic neuropathy) and wound hypoxia (micro & macro vascular disease)

Diabetic foot ulcer(DFU)- There is 25% risk of developing a ulcer in life time.It results from mech. trauma unnoticed due to LOPS.Commonest site is fore foot.Ulcer develops at sites of high pressure zone on either side planter or dorsal surface caused by bony prominence/ill- fitting foot wear/toe deformity.Continuous abnormal pressure causing tissue ischemia.LJM(limited joint mobility) is another contributory factor for development of foot ulcer.Bony deformity and callus is the marker of elevated planter pressure.

Examination- Inspection for dry skin cracks, fissure,callosity,corn,fungal infection of toes,cellulitis and ulceration.
Neuropathy detection by 10g nylon monofilament and 256 Hz tuning fork.**Vasculopathy detection**- by palpation of peripheral pulses and ankle brachial index (ABI) measurement by vascular Doppler.

Foot wear examination-Impression on insole & wearing out of out sole points high pressure area of foot.A rigid out sole, soft in sole(MCR) roomy toe box, wide mouth, extra depth of shoe with a counter are the features of good diabetic foot wear.

MANAGEMENT-

It is a team work and a Multi-disciplinary approach is required .Physician or Diabetologist has a key role to play.Other members of team – Surgeon, Nutritionist, Diabetic nurse, Foot care worker, Diabetic educator & Diabetic cobbler; all are important for salvaging of a diabetic foot.Proper workup of diabetic patient is essential to establish neuropathy/ vasculopathy or both.Tight metabolic control is an essential factor.

First step is to classify DFD –It may be one of the three types.(a) Non limb threatening (uninfected/infected) (b)limb threatening and(c) life threatening(metabolic instability)

Non limb threatening conditions like:-callosity and corn; Dermatophytosis of web space, deformities like hallux vulgas, hammer toes, fissures and cracks, hypertrophic bursitiscan be managed in outpatient basis by giving proper advice regarding foot care and foot wear,minor OPD procedures for callus and corn removal, anti-fungal drug for Dermatophytosis, moisturizing lotions for cracks and fissures, advice regarding customized preventive footwear for foot with structural deformity and foot at risk (foot with LOPS) .

If mild infection is present then empirical antibiotics like: -Moxifloxacine (400 mg OD for 7 days) ;Cefdinir (300mg BD for 5-7 days); Linezolid (600mg BD for 5-7 days); Cephalexin (500mg TDS for 5-7 days); Azithromycin (500mg OD for 5-7 days) can be used.Limb threatening and life threatening diabetic foot conditions needs indoor admission and help of surgeon for proper management. So identification of such condition is important for early referral but before sending to a surgeon a physician must talk to the surgeon and discuss the modality of management regarding correction of dehydration by appropriate intra-venous fluid, insulin infusion for correction of hyperglycemia, selection of empirical antibiotics in consideration to renal status before the results of culture sensitivity comes.

In limb- threatening conditions preferred intra-venous antibiotics are--Cefeperozone/ Sulbactam (2g 12 hrly) + Metronidazole (500mg 8hrly) or Moxifloxacin (400mg OD) + Metronidazole (500mg 8 hrly)For life threatening-Pipperacillin / Tazobactam(4.5g 8hrly) + Amikacin (15mg per kg OD) or Meropenem (1g 8hrly) or Clindamycin (600mg 8hrly) + Amikacin((15mg per kg OD) .A physician must discuss with the surgeon that the best dressing material for diabetic foot is normal saline and use of savlon, betadine, H_2O_2 , Eusol is not suitable for diabetic wound because they have direct cyto-toxic effect to fibroblast and Keratinocytes. Use of Topical antibiotics is good for keeping the wound moist because moist environment is ideal for healing of diabetic wound. Oint. of Metrozyl, Silver Sulphadiaze,Mupirocine (gram positive cocci MRSA), Nadifloxacin (gram positive cocci, anaerobes, gram negative bacteria), Ensamycine (pseudomonas). Always remember the final choice of antibiotics depends on the results of culture sensitivity.Clindamycin, Azithromycin and Moxifloxacin can be safely used for patients with impaired renal function, but for rest mentioned antibiotics dose adjustment is necessary .

Wound off-loading is very important for proper management. So to conclude tight metabolic control, extensive debridement, appropriate antibiotics and off-loading of wound are the principle of management of diabetic foot.

Preventive care is most important daily inspection of foot, use of appropriate foot wear, use of moisturizing lotion all are important. And not only this every patient should follow the rule of DOS &DON'TS as advised by doctor.

DIABETES AND CANCER

DIABETES AND CANCER

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INTRODUCTION

- Diabetes and cancer are two common, complex, diverse, chronic, and fatal diseases with tremendous impact on public health all over the world. Both Diabetes and cancer share complex underlying pathophysiologies that are not well understood to date.
- Over more than half a century these two diseases were considered as two independent entities. This very perspective changed when several cases of concurrent occurrences of both diabetes and cancer among patients have been reported in the early 1960s.
- Extensive research over the last few decades has shown that patients with diabetes are at significantly higher risk (1.2 to 2-fold or higher) for certain forms of cancers compared to non-diabetic individuals.
- Similarly, some types of chemotherapy drugs are also known to cause diabetes among cancer patients and some medications used to treat hyperglycemia are associated with either increased or reduced risk of cancer which further affirms the theory of them sharing common risk factors, potential biologic links, etc. However, the exact pathophysiological pathways that lead to the development of one another among these patients remain uncertain.
- Several aspects still need to be explored and understood in this regard which mainly include- common risk factors between cancer and diabetes; a significant association between their incidence or prognosis; possible biological links etc.
- In this chapter, we will explore the reasons for some of the above aspects, as well as how the relationship between diabetes and cancer opens up new avenues for the treatment of cancer.

EPIDEMIOLOGY note:

- A significant rise in the global prevalence of diabetes was estimated from 422 million in 2014 to 592 million in 2035 and that for cancer was estimated from 14 million in 2012 to 22 million in 2032 as per World Health Organization (WHO) consensus report, 2014. Among the population above 65 years of age, overall, 8–18% of diabetic patients have concurrent cancer.
- Both cancer and diabetes are known to be the high-risk factors for and leading causes of higher mortality and morbidity worldwide. Cancer is the second leading cause of death, while diabetes is the seventh leading cause of death. Data available from several epidemiological meta-analyses and observational studies have indicated that diabetes may serve as an independent risk factor for increased rates of heterogeneous types of cancer occurrence and death.
- The incidence rate of cancer is higher among patients with T2DM compared to non-diabetic individuals. There is a growing body of evidence published in recent years that patients with diabetes are at significantly higher risk (2-fold or higher) for many forms of cancers such as liver, urinary tract, biliary tract, pancreas, endometrium, etc. which develop more commonly in patients with diabetes with about 2-fold or higher rate predominantly among Type 2 Diabetes Mellitus (T2DM). While the cancers of the colon, rectum, breast, and bladder have about 1.2–1.5-fold risk.
- Male diabetic patients are less prone to prostate cancer compared to normal individuals which show that diabetes may be a protective factor for prostate cancer. Other types of cancers such as lung cancer are most likely not associated with an increased risk in patients with diabetes.
- The incidence rate of cancer among women with diabetes is 27% and among men with diabetes is 19% compared to non-diabetic women and men. While women with diabetes are 6% more likely to develop cancer compared to men with diabetes.
- Women with diabetes have a higher incidence rate of 11% for developing kidney cancer, 13% for oral cancer, 14% for stomach cancer, and 15% for leukemia compared to men with diabetes. On the contrary,

men with diabetes have a higher incidence rate of 12% for developing liver cancer compared to women with diabetes.

- Diagnosis of diabetes has also been known to exhibit deleterious effects on cancer prognosis. Higher mortality rates and reduced survival rates are often reported across all types of cancers among patients with diabetes especially those undergoing surgical procedures such as resection of colorectal cancer; hepatectomy due to colon cancer metastases, as well as esophagogastrectomy, etc. Epidemiologic studies documented that survival rates in cancer patients with diabetes are linearly proportional to the decreasing glycaemic controls.

UNDERLYING PATHOPHYSIOLOGY AND BIOLOGIC LINK

Different mechanisms influence the neoplastic process (initiation, promotion, and progression of malignant cells) and enable a higher rate of incidence of cancer among diabetic patients. These include:

- The insulin/insulin growth factor axis,
- Insulin Resistance (IR) or hyperglycemia,
- Endogenous or exogenous hyperinsulinemia and,
- Inflammatory cytokines and/or chronic inflammation.

The Insulin/Insulin Growth Factor axis

- Most cancer cells have insulin as well as IGF-1 receptors with the 'A' isoform of the receptor predominantly expressed. The 'A' receptor isoform can induce insulin-mediated mitogenesis, even in cells that are deficient in IGF-1 receptors. Apart from its metabolic functions, the insulin receptor can also stimulate cancer cell proliferation as well as metastasis. The glucose uptake in neoplastic cells is independent of insulin binding to receptors. Therefore, the effect of insulin on cell activation has more to do with cell survival and mitogenesis rather than enhanced glucose uptake. The following processes take place after insulin receptors and IGF-1 receptors bind with their ligands:
  - Insulin receptors and IGF-1 receptors bind with their ligands, leading to phosphorylation of adaptor proteins, most notably the insulin receptor substrate family (IRS). This initial kinase activity is linked to downstream signaling pathways.
  - Once activated, these signaling pathways stimulate multiple cancer phenotypes such as proliferation, protection from apoptotic stimuli, invasion, and metastasis. These enhance the progression and promotion of cancer cells.
  - Insulin/IGF also stimulates normal cells that may be involved in the growth of a tumor. For example, in hyperglycaemic conditions, IGF-1 stimulates vascular smooth muscle cell proliferation and migration. This leads to abnormal vasculature, a hallmark of cancer cells.
  - Increased Insulin levels act on insulin receptor IGF-1 receptor which activated PI3K, AKT pathway which is a well-known tumor-related pathway promoting oncogenesis (See Figure 1 below).

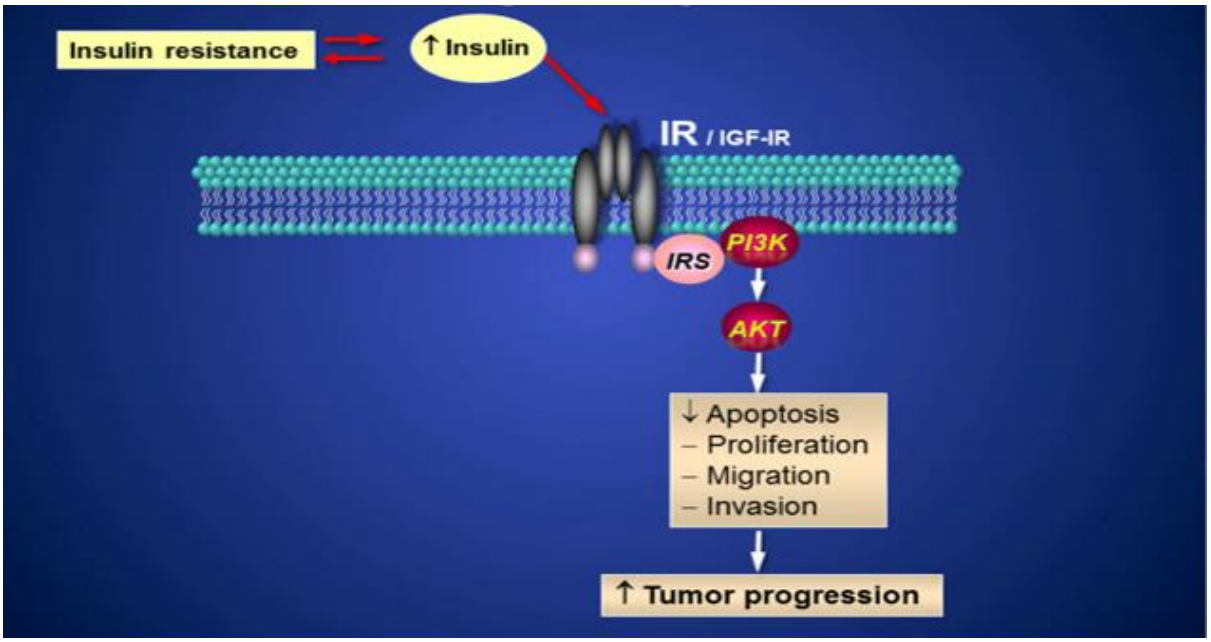

Figure 1: Molecular Mechanisms Underlying Tumour-Promoting Activity in T2DM

- Apart from the direct effects of insulin on cancer cells, it has also been theorized that hyperinsulinemia may also be a contributing causative factor of carcinogenesis. It has an indirect effect on IGF-1. Insulin reduces the hepatic production of IGF binding protein (IGFBP)-1 and possibly IGFBP-2 with the resultant increase in the levels of circulating free, bioactive IGF-1.
- The IGF-1 has more potent mitogenic and anti-apoptotic properties than insulin and can act as a growth stimulus in preneoplastic and neoplastic cells that express insulin and IGF-1. Human tumors have been found to over-express these receptors and thus cancer cells show mitogenic action in response to physiological concentrations of insulin.
- Patients with diabetes associated with higher levels of IGF-1 are more susceptible to increased risk of developing many types of cancer such as colorectal, breast, and prostate cancers. IGF-1 is more frequently expressed in breast cancer cells compared to other cancer types. Both IR and IGF-1 receptors in the combined state have higher phosphorylation levels, causing hyperinsulinemia leading to the elevated growth of mammary tumors through the insulin/IGF axis.

Insulin Resistance and Hyperglycaemia

- It is still unclear if the association between cancer and diabetes is directly due to IR and hyperglycemia or indirect due to common risk factors such as obesity, age, physical inactivity, etc. Whether cancer risk is influenced by the duration of diabetes is a critical and complex issue and may be further complicated by the multidrug therapy often necessary for diabetes treatment.
- Hyperglycemia accelerates mitochondrial dysfunction and the generation of free radicals and other reactive molecules, such as reactive oxygen species (ROS), triggering the formation of advanced glycation end products (AGEs) and activating protein kinase C isomers. ROS can not only directly damage DNA, inducing genetic mutation, but regulate mitogen-activated protein kinases and p21 activated kinase, promoting tumor metastasis.
- AGEs receptor exists in many types of cancer cells, such as immune cells, neurons, osteoblasts, activated endothelial cells, and vascular smooth muscle cells. Furthermore, it can be triggered by AGEs, leading to chronic inflammation which links to many cancer-related signaling pathways, eventually increasing cell genetic mutation and evolution and resulting in advanced stages of cancer.
- Warburg's hypothesis and cancer energetics emphasize the dependence of many cancers on glycolysis for energy, creating a high requirement for glucose since ATP generation by glycolysis requires far more glucose than oxidative phosphorylation. This forms the basis of FDG-PET imaging of cancers, which detects tissues with a high rate of glucose uptake. However, a fact relevant to the matter is that most cancers have highly effective upregulated, insulin-independent glucose uptake mechanisms and therefore may not derive a further growth advantage from hyperglycemia. It is hence considered most likely that hyperglycemia may not indicate that glucose mediates the growth of neoplastic cells, rather, hyperglycemia may serve as a surrogate for a causative factor such as hyperinsulinemia.

Exogenous or Endogenous Hyperinsulinemia

- The elevated cancer risk for patients with diabetes arises from hormonal dysregulation. In patients with T2DM, the insulin regulation is disrupted leading to the ineffective supply of glucose to the cells which again leads to the excessive endogenous release of insulin hormone by the pancreas or administration of exogenous insulin causing hyperinsulinemia. In addition to controlling blood glucose levels, the hormone insulin can stimulate cell growth, possibly leading to cancer.
- Increased levels of circulating insulin cause a reduction in the hepatic synthesis and levels of sex hormone-binding globulin, leading to increased levels of bioavailable estrogen in both men and women and testosterone only in women. Hyperinsulinemia in premenopausal women is caused due to the increased synthesis of androgens in the ovaries and the adrenals while elevated endogenous sex steroid levels are associated with a higher risk of hyperinsulinemia among postmenopausal women causing breast and endometrial cancers.

Inflammatory Cytokines and/or Chronic Inflammation

- Obesity and hyperinsulinemia are common risk factors among T2DM patients which often simulate the release of cytokines and inflammatory mediators leading pathways involved in the progression of malignant cells.
- Adipose tissue acts like an active endocrine organ producing free fatty acids, interleukin-6 (IL-6), monocyte chemoattractant protein, plasminogen activator inhibitor-1(PAI-1), adiponectin, leptin, and tumor necrosis factor-α. Some of these have been linked to cancer. For example, the plasminogen system has been associated with cancer with the expression of PAI-1 linked with poor prognosis in breast cancer. Activation of signal transducer and activator of transcription protein (STAT) signaling, via cytokines such as IL-6, is known to enhance cancer cell proliferation, survival, and invasion while also suppressing host anti-tumor immunity.

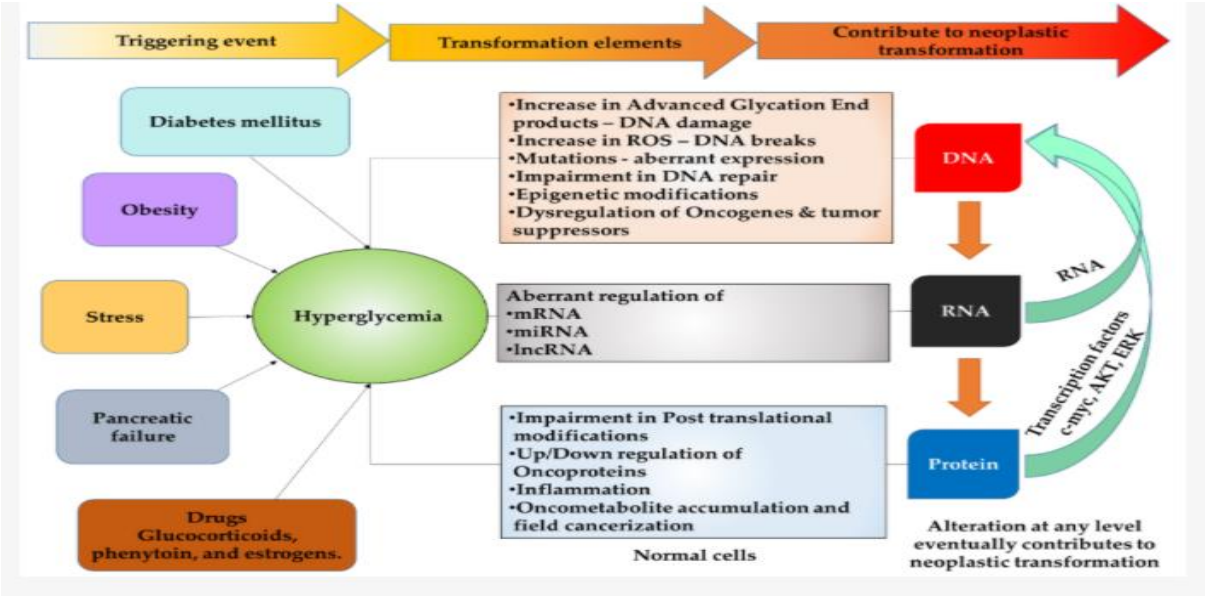

Figure 2:: Summary of Potential Association Between Hyperglycemia and Cancer
Adapted from: Pranay Ramteke et al; Cancers 2019; 11(9), 1402.

RISK FACTORS COMMON BETWEEN CANCER AND DIABETES

Potential risk factors common to both cancer and diabetes include:

Non-modifiable risk factors -Age, sex, race/ethnicity

- AGE: Incidence of cancer increases with age. Almost, 78% of all newly diagnosed cancer occur among individuals aged 55 years and older.
- SEX: Certain cancers are sex-specific e.g., cervix, uterine and breast cancers occur only in women while testicular and prostate occur only in men. Overall cancer occurs more frequently in men due to their slightly higher age-adjusted risk of diabetes than women.
- RACE/ETHNICITY: African Americans are more likely to develop and die from cancer compared to other race or ethnic groups such as non-Hispanic whites, Native Americans, and Asian Americans/Pacific Islanders which have lower cancer incidence and mortality.

Modifiable risk factors – Overweight, obesity and/or weight change; physical inactivity; improper diet; alcohol and smoking (See Figure 3 below):

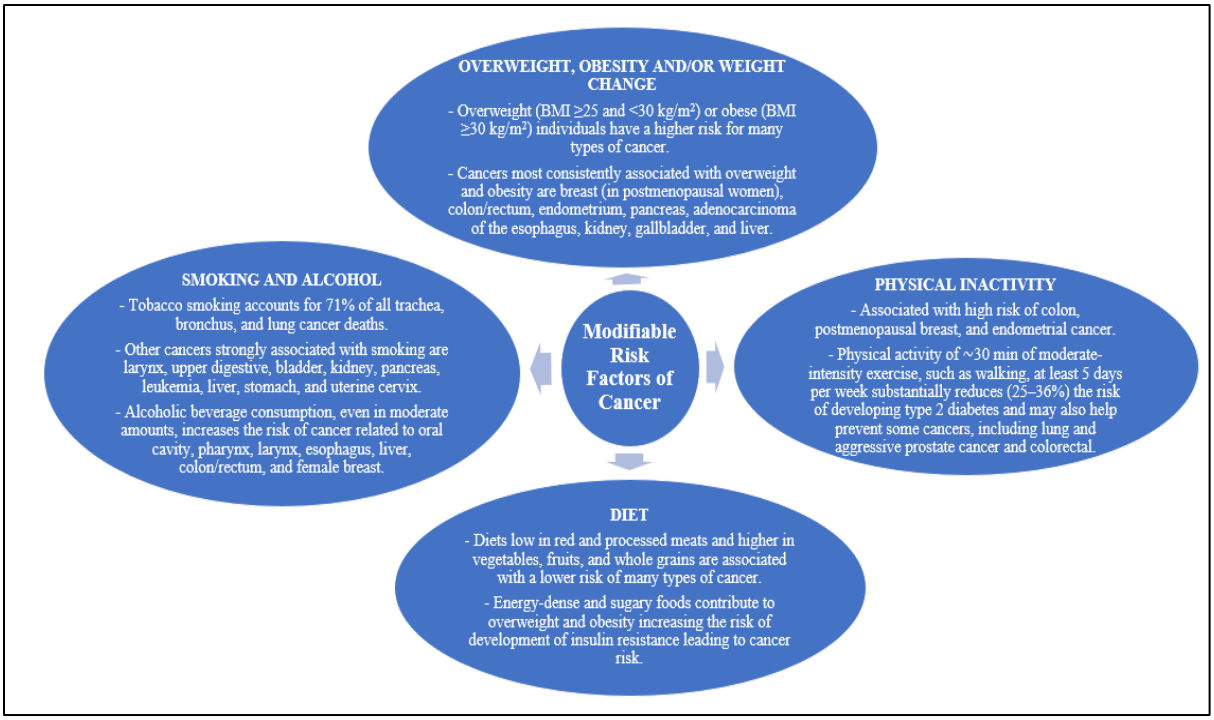

Figure 3: Modifiable Risk Factors Common Between Cancer and Diabetes

BIOMARKERS

There is a dearth of data on common biomarkers of diabetes and cancer. Among the various diabetes-related biomarkers, such as Fasting Blood Glucose (FBG), glycated hemoglobin (HbA1c), glycated albumin, adiponectin, serum insulin, and C-peptide; increased levels of serum insulin and C-peptide are often considered as potential biomarkers of various forms of cancer. However, the effectiveness of these biomarkers is yet to be studied.

EFFECT OF ANTI-DIABETIC DRUGS ON CANCER TREATMENT

There is no clear supporting evidence showing that anti-diabetic drugs have the potential to cause cancer. This issue has very recently come into the limelight and extensive research is on-going. Therefore, physicians should exercise caution while selecting appropriate pharmacologic agent(s) for each patient and follow a thorough decision-making process that includes an ongoing risk/benefit analysis. The effect of major anti-diabetic drugs on cancer treatment is summarized below.

Metformin

- Metformin, a biguanide is the most commonly prescribed anti-diabetic drug among patients with prediabetes or T2DM, either alone or as a combination therapy due to its lower side effects. Metformin generally reduces levels of both circulating glucose and insulin in patients with IR and hyperinsulinemia. In laboratory studies, metformin has been shown to inhibit cell proliferation, reduce colony formation and cause partial cell cycle arrest in cancer cell lines. The mechanism of action, in this case, seems to be the metformin-induced activation of AMP-activated protein kinase (AMPK) in tumor cells leading to growth inhibition, partially by inhibition of protein synthesis (see Figure 4 below). Available data suggest that treatment with metformin also reduces the risk of cancer or cancer mortality and improves cancer prognosis among patients. However, its effect on individual complex forms of cancer is still not well understood.

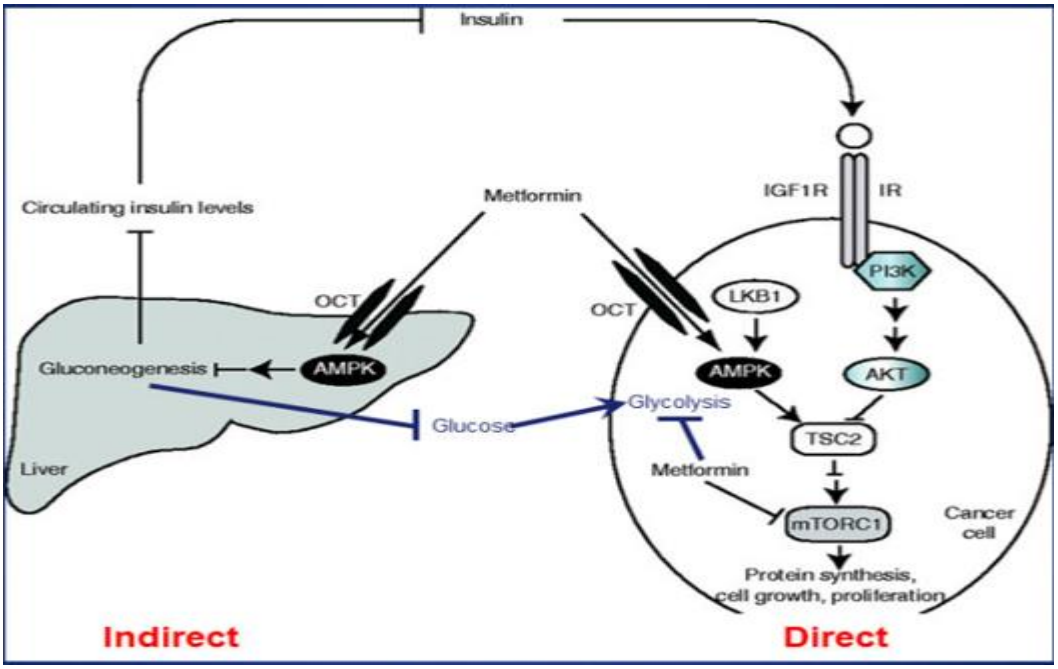

Figure 4: Mechanisms of Metformin Action in Cancer
Adapted from: Dowling RJ et al; Mol Endo 2012; 48: R31-43

Thiazolidinediones

- Thiazolidinediones (TZDs) are insulin-sensitizing peroxisome proliferator-activated receptor (PPAR)γ agonists that do not increase insulin secretion directly or cause hypoglycemia when used alone. Two drugs-pioglitazone and rosiglitazone(restricted use) are currently available.
- PPAR- γ is known to have several anti-cancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation. PPAR- γ is currently considered a target for both chemoprevention and cancer therapy based on data available from studies conducted earlier. However, several studies conducted in recent years seem to indicate that the effects of PPAR- γ agonists on cell growth are often independent of the presence of PPAR- γ. This puts the relevance of the earlier studies conducted on TZDs under a huge question mark.
- Preclinical or animal studies indicate that PPAR- γ agonists can potentiate tumorigenesis. On the contrary, there is no such promising evidence found from various epidemiological studies conducted among patients with diabetes. These studies showed that rosiglitazone showed no statistically significant increase or decrease in the risk of cancer. Therefore, TZDs may increase, decrease or have a neutral effect on the risk of cancer or cancer progression in humans, although the results of a few clinical trials of TZDs for cancer treatment have been largely negative.

Insulin Secretagogues

- Secretagogues, including sulphonylureas and the rapid-acting glinides, stimulate β-cells to release insulin by binding to specific cell receptors, resulting in β-cell depolarization and the release of insulin stores. Insulin secretagogues have been the oldest class of drugs used to treat diabetes. While this class of drugs is more effective in lowering HbA1C, they can cause hypoglycemia as well as weight gain.
- Several observational studies have found that there is a higher risk of incidence of cancer in individuals with diabetes being treated with sulphonylureas relative to those being treated with metformin. However, it is difficult to determine whether the findings reflect excess cancer among users of the secretagogues or reduced risk in those using comparator drugs, which often include metformin therapy.
- Furthermore, the mechanism of action is yet undetermined involves direct action on transformed cells, as compared with indirect effects mediated by increased insulin levels. Another point to be noted is that since glinide secretagogues are newer and less commonly used, there is no published data between the use of these drugs and cancer risk.

Incretin-based Therapies

- These consist of two recently developed classes of drugs- analogs of human GLP-1 and DPP-4 inhibitors. These mimic the effect of gut-derived incretin hormones that improve glucose-dependent insulin secretion, suppress postprandial glucagon levels, and delay gastric emptying.
- The first class of drugs i.e GLP-1 analogs consists of Exenatide, which has 50% homology with incretin hormone glucagon-like peptide-1, while the more recent drug-liraglutide is an analog of human GLP-1. They both bind to the GLP-1 receptor to exert agonist activity. Liraglutide was found to increase the risk of medullary cancer in rats and mice in preclinical tests. Exenatide and Liraglutide were also observed to have increased β-cell proliferation in animal studies.
- The second class of drugs-DPP-4 inhibitors inhibits the action of the ubiquitous enzyme that rapidly degrades many peptides including GLP-1.In animal studies, DPP-4 inhibitors were also associated with β-cell proliferation. In one study of a transgenic rodent model, the DPP-4 inhibitor Sitagliptin was demonstrated to increase pancreatic ductal hyperplasia.
- No impact of incretin-based therapies on the incidence of cancer in humans has ever been noted, but this is because these new drugs are not assessed in a sufficient number of individuals for long periods to fully assess any possible effect on cancer risk.

Insulin and Insulin Analogues

- Insulin is required for all patients with T1DM and is also necessary for many patients with T2DM to combat hyperglycemia, in part due to progressive loss of β-cell function over time. About 40-80% of T2DM end up using insulin to achieve targets.
- There are different types of insulin-short acting insulin (regular insulin), intermediate-acting insulin (NPH insulin), rapid-acting insulin (lispro, glulisine, aspart), and long-acting insulin (glargine, detemir).
- Subcutaneous injection of insulin is the most common method of administration of insulin. It results in higher levels of systemic circulating insulin than endogenous insulin secretion, thereby increasing links between hyperinsulinemia and cancer risk. One major drawback regarding the use of insulin among patients with T2DM is that it is prescribed in patients with a longer duration of T2DM and is used more often in those with one or more comorbid conditions, which increases the fatality rate among this population.
- Potential mechanisms by which administration of insulin or insulin analogs may affect cancer include both direct and indirect actions. Direct actions include the interaction of ligands with cancer cells, partially transformed cells, or cells at risk of transformation. Indirect mechanisms have been relatively lesser studied but would involve interactions of signaling molecules whose levels (eg-glucagon, adiponectin, IGFBPs) or activity are influenced by administered insulin on target cells.
- Substantial prior research has provided evidence that insulin glargine has a much higher affinity than other human insulins for the IGF-1 receptor than the insulin receptor, indicating higher mitogenic potency. This affinity for the IGF-1 receptor is important because the IGF-1 receptor plays a much bigger part in the proliferation of malignant cells than the insulin receptor.
- The type of insulin regimen also influences the role of insulin in the development of cancer. Classic subcutaneous therapy involves transient exposure to cells to high insulin levels, while subcutaneous therapy involving synthetic insulins results in prolonged exposure of cells to high insulin levels. Another important factor is that cancer cells in T2DM patients may be exposed to years of abnormally high insulin levels before the administration of exogenous insulin.

DIABETES CAUSED DUE TO CANCER

- Current studies suggest that approximately 20% of non-diabetic cancer patients receiving chemotherapy combined with the antiemetic dexamethasone for the prevention of vomiting develop steroid-induced diabetes; this was particularly significant for patients receiving repetitive chemotherapy with high cumulative doses of dexamethasone.
- The most likely mechanism for the development of permanent diabetes is the high degree of insulin resistance instilled in cells due to the prolonged use of long-acting steroids. Corticosteroids have also been found to increase the incidence of postprandial hyperglycemia in patients under treatment.

- To optimize patient care and outcomes, patients receiving chemotherapy with antiemetic dexamethasone should receive adequate support and monitoring to prevent the development of dexamethasone-induced diabetes.

Editor's Note:

- Diabetes is often known to be associated with an increased risk of certain types of cancers such as liver, pancreas, endometrium, colon and rectum, breast, bladder, and reduced risk of prostate cancer.
- Possible underlying pathophysiological mechanisms for a direct biological link between diabetes and cancer may include hyperinsulinemia, hyperglycemia, and inflammation.
- The association between diabetes and some cancers may partly be due to shared risk factors between the two diseases, such as aging, obesity, diet, and physical inactivity.
- Supporting evidence for specific anti-diabetic drugs affecting cancer risk is very limited, and observed associations may have been confounded by indications for specific drugs, effects on other cancer risk factors such as body weight and hyperinsulinemia, etc.
- Clinical outcomes of T2DM and some types of cancer can be improved by following a proper healthy diet, regular physical activity, weight management, and regular cancer screening, etc.
- Cancer risk should not be a major factor in choosing between available treatment options for diabetes for the average patient. While more careful consideration should be given in specific patients with very high risk for cancer occurrence (or for recurrence of specific cancer types) and benefit-risk analysis should be performed.

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DIABETES & KIDNEY

DIABETES & KIDNEY

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Diabetes mellitus, usually called diabetes, is a disease in which your body does not make enough insulin or cannot use normal amounts of insulin properly. Insulin is a hormone that regulates the amount of sugar in your blood. A high blood sugar level can cause problems in many parts of your body.

Are there different types of diabetes?
The most common ones are Type 1 and Type 2. Type 1 diabetes usually occurs in children. It is also called juvenile onset diabetes mellitus or insulin-dependent diabetes mellitus. In this type, your pancreas does not make enough insulin and you have to take insulin injections for the rest of your life.
Type 2 diabetes, which is more common, usually occurs in people over 40 and is called adult onset diabetes mellitus. It is also called non insulin-dependent diabetes mellitus. In Type 2, your pancreas makes insulin, but your body does not use it properly. The high blood sugar level often can be controlled by following a diet and/or taking medication, although some patients must take insulin. Type 2 diabetes is particularly prevalent among African Americans, American Indians, Latin Americans and Asian Americans.

What does diabetes do to the kidneys?
With diabetes, the small blood vessels in the body are injured. When the blood vessels in the kidneys are injured, your kidneys cannot clean your blood properly. Your body will retain more water and salt than it should, which can result in weight gain and ankle swelling. You may have protein in your urine. Also, waste materials will build up in your blood.
Diabetes also may cause damage to nerves in your body. This can cause difficulty in emptying your bladder. The pressure resulting from your full bladder can back up and injure the kidneys. Also, if urine remains in your bladder for a long time, you can develop an infection from the rapid growth of bacteria in urine that has a high sugar level.

How many diabetic patients will develop kidney disease?
About 30 percent of patients with Type 1 (juvenile onset) diabetes and 10 to 40 percent of those with Type 2 (adult onset) diabetes eventually will suffer from kidney failure.

What are the early signs of kidney disease in patients with diabetes?
The earliest sign of diabetic kidney disease is an increased excretion of albumin in the urine. This is present long before the usual tests done in your doctor's office show evidence of kidney disease, so it is important for you to have this test on a yearly basis. Weight gain and ankle swelling may occur. You will use the bathroom more at night. Your blood pressure may get too high. As a person with diabetes, you should have your blood, urine and blood pressure checked at least once a year. This will lead to better control of your disease and early treatment of high blood pressure and kidney disease. Maintaining control of your diabetes can lower your risk of developing severe kidney disease.

What are the late signs of kidney disease in patients with diabetes?
As your kidneys fail, your blood urea nitrogen (BUN) levels will rise as well as the level of creatinine in your blood. You may also experience nausea, vomiting, a loss of appetite, weakness, increasing fatigue,

itching, muscle cramps (especially in your legs) and anemia (a low blood count). You may find you need less insulin. This is because diseased kidneys cause less breakdown of insulin. If you develop any of these signs, call your doctor.

Signs of Kidney Disease in Patients with Diabetes

Albumin/protein in the urine
High blood pressure
Ankle and leg swelling, leg cramps
Going to the bathroom more often at night
High levels of BUN and creatinine in blood
Less need for insulin or antidiabetic medications
Morning sickness, nausea and vomiting
Weakness, paleness and anemia
Itching

What will happen if my kidneys have been damaged?

First, the doctor needs to find out if your diabetes has caused the injury. Other diseases can cause kidney damage. Your kidneys will work better and last longer if you:
Control your diabetes
Control high blood pressure
Get treatment for urinary tract infections
Correct any problems in your urinary system

Avoid any medicines that may damage the kidneys (especially over-the-counter pain medications)
If no other problems are found, your doctor will try to keep your kidneys working as long as possible. The use of high blood pressure medicines called angiotensin converting enzyme (ACE) inhibitors has been shown to help slow the loss of kidney function.

How are the kidneys kept working as long as possible?

The kidney doctor, will plan your treatment with you, your family and your dietitian. Two things to keep in mind for keeping your kidneys healthy are controlling high blood pressure in conjunction with an ACE inhibitor and following your renal diabetic diet. Restricting protein in your diet also might be helpful. You and your dietitian can plan your diet together.

What is end stage renal failure in patients with diabetes?

End stage renal failure, or kidney failure, occurs when your kidneys are no longer able to support you in a reasonably healthy state, and dialysis or transplantation is needed. This happens when your kidneys function at only 10 to 15 percent.

How is kidney failure treated in diabetic patients?

Three types of treatment can be used once your kidneys have failed: kidney transplantation, hemodialysis and peritoneal dialysis.
Consult your Nephrologist and Physician for any help and advice. Don't fall in the Tantrums of Ayurveda and Homeopathic treatment or you miss the game.

TOP 10 PAPERS AT EASD

Name:	Dr N.K.SINGH,MD,FICP,Chairman,RSSDI-Jharkhand,Editor: www.cmeindia.in
City:	Dhanbad,Jharkhand.
	
Topic:	Top 10 Papers at EASD
Take Home Messages:	
The best 10 papers are of practice changing impact in diabetology,presented at EASD 2020	
1. In future adding Semaglutide on the top of standard of care can be a very appropriate norm as 20% risk reduction in 10 year of getting cardiovascular events.	
2. A straight use of early combination therapy for cardio-renal risk reduction by prescribing metformin with SGLT-2 Inhibitors and GLP-1 RA has been suggested by PDCE symposium.	
3. EMPEROR-Reduced trial has emphasized on the efficacy of empagliflozin in reducing the risk of cardiovascular death and hospitalization for heart failure in patients with or without diabetes.	
4. Real world study has provided a moderate level of evidence to use SGLT2inhibitors or GLP-1RAs in new users of type 2 diabetes patients.	
5. Targeting combined risk factors appear to be most effective in preventing CVD risk than targeting single risk factors.	
6. DAPA CKD coins a new option for treatment for many patients of CKD, regardless whether they have diabetes or not. The ability of dapagliflozin to reduce the cardio-renal risk is spectacular indeed.	
7.New VERTIS CV shows that Ertugliflozin reduces risk for worsening renal function, dialysis or renal death in comparison with placebo in patients with type 2 diabetes patients.	
8. New data presented from ACCORD trial shows that intensive blood glucose and blood pressure interventions in type 2 diabetes reduced the risk of cardiac autonomic neuropathy.	
9. It is a transformational news that once-weekly insulin ICODEC has shown significant promise in phase 2 trial. This might change the way we treat insulin requiring type 2 diabetes.	
10. RESCUE trial data shows that more time in range (TIR) is associated with fewer microvascular complications, chronic complications in comparison with glycemic variability in type 1 diabetes.	
▪ EVOLVE STUDY was also presented-In pregnant women with pre-existing diabetes, insulin detemir was not associated with excess risk of major congenital malformations, or perinatal or neonatal deaths compared with other basal insulins.	