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NEW GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF TYPE 2 DIABETES – AN UPDATED REVIEW

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ABSTRACT

Background: D.M is a metabolic disorder characterized by the presence of hyperglycemia due to impaired insulin action/sensitivity and β cell defect. India occupies the second position, after China, in the global list of countries with a total of 66.8 million cases. It has been predicted that the countries with the largest number of people with diabetes mellitus will be from India, China, and US in the year 2025.[1] **Discussion:** The cut off **HbA_{1c} value ≥6.5%** (NSGP standards) is taken as new criteria to diagnose T2 Diabetes and it can be used for predicting the complications. Management guidelines(2013) of ADA, ADA + EASD, AACE takes into account HbA1C level. On comparison of these 3 major guidelines AACE takes into account the weight control regime and also management of prediabetic conditions and other related metabolic conditions like HTN, Dyslipidemia. AACE takes into account Incretins(GLP1 agonists) as the 2nd line of drug in treatment of diabetes. **Abstract**: Studies shows a direct & linear correlation of HbA1C with the diabetic retinopathy and micro-albuminuria. It is very safe to say that HbA1C is better parameter than FBS & 2 hour PP BS level in diagnosing & predicting the complications of diabetes. The main objective of this study is To show the fact that strict control of HbA1C level to normal level can herald the progress of diabetic complications.

1) To evaluate the efficacy and safety of various hypoglycemic drugs
2) To update the latest criteria for diagnosis and management of T2 Diabetes
3) To evaluate various treatment guidelines and merits of new oral hypoglycemic drugs.

KEYWORDS: Type 2 diabetes, Fasting blood glucose, HbA1C, Diabetic retinopathy, Microalbuminuria.

ADA (American Diabetes Association), ADA-EASD (European Association for the Study of Diabetes)
AACE (American association of clinical endocrinology), HTN- hypertension, T2D (type 2 Diabetes)

Diagnostic criteria of T2 Diabetes – Recent updates

In Greek diabetes means "siphon - to pass through," and Latin word mellitus means "honeyed" or "sweet.". It was first reported in Egyptian manuscript about 3000 years ago. It is estimated that, by 2030 there would be 552 million cases of DM of which 439 million people would be type 2 DM.[1] Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion or action, or both.

1) Glycated haemoglobin **(HbA_{1c}) value ≥6.5%** - (NSGP standards)
2) **FPG ≥126 mg/dl (7.0 mmol/L) (8 hours fasting) & 2hPG ≥200 mg/dl (11.1 mmol/L)** (WHO :- OGTT using 75g Glucose)
3) **Random PG > 200 mg/dl (11.1 mmol/L**).[1,2,3]

Any one of the above Criteria + Typical Symptoms = DM

If patient is Asymptomatic, then repeat the test.

Setting the diagnostic thresholds

a) ADA **(**Aleast 1 or more criteria)
b) WHO recommends the use of FPG + 2hPG (OGTT) especially in asymptomatic individuals
c) FPG and 2h OGTT showed a linear increase in diabetic retinopathy at glucose levels beyond these two values.
d) Normal Fasting PG level is < 110 mg/dl (6.1 mmol/L) & 2h PG Is < 125 mg/dl
e) IFG (impared fasting glucose) - 110 mg/dl (6.1 mmol/l) to < 125 mg/dl (6.9 mmol/l)
f) IGT - 2hr OGTT value > 140 mg/dl (7.8mmol/L) to 199 mg/dl (11.0mmol/L).

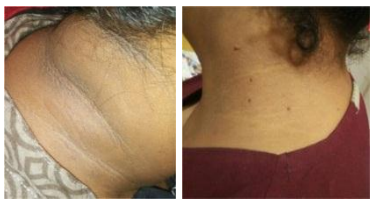
HbA1C[2,3]

Merits	Demerits
➢ More convenient to perform, as patients are not required to fast, and can be performed at any time of day ➢ HbA_{1c} has greater preanalytical stability ➢ No variation to acute illness or stress Linked with microvascular (Diabetic retinopathy) and (to a lesser extent) macrovascular complications	➢ The test is more costly & should be NGSP certified, and standardised to Diabetes Control and Complication Trial (DCCT) assay ➢ HbA_{1c} may vary with age and ethnicity of the patient ➢ Falsely Low HbA_{1c} - associated with increased RBC turnover (Hemolysis, hemorrhage recent BT, G6PD def. Rx of IDA, dapsone & anti-retroviral drugs. ➢ Haemoglobinopathies like Beta-thalassaemia. ➢ Falsely high HbA1C - associated with decreased RBC turnover like IDA

Recently, genes discovered to be significantly associated with developing type 2 DM, include TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX. KCNJ.

Type 2 DM (Risk factors)
Obesity, 2) Family history, 3) IGT/ Prediabetic, 4) HTN, 5) HyperLipidemia.

Clinical features
Type 2DM – 95% of all types of diabetics, starts around 40 years of age. Typical symptoms – polyphagia **(excessive eating)**, polyuria (frequent urination), Polydipsia **(more thirst)** & weight loss.



Acanthosis Nigricans. Skin tags
(Pigmentation of skin) Signifies – Insulin Resistance

Laboratory test

1) **HbA1C** - HbA1c >7% is directly related to - CVC, Diabetic nephropathy & retinopathy

False elevated in IDA, False reduced in – Hemolysis (so HbA1c not advised)

HbA1c % = $\frac{\text{Mean plasma Glucose (mg/dl)} + 77.3}{35.6}$ [1]

HbA1c (%)	eAG (mg/dL)	eAG (mmol/l)
5	97	5.4
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

2) **C peptide, (Bcell function) & insulin level**.
- C peptide level correlate with B cell function
- C-peptide level> 1 ng/dl suggests Type 2 Diabetes

3) Total Cholesterol, LDL, HDL & tryglycerides, Thyroid Function tests.

4) Renal function test - special emphasis **Microalbuminuria (30 -300 mg/day)**
Albumin/ creatinine ratio in mg/g = Albumin excreated in mg/day.

5) Asses Blood pressure, Eye examination, foot care, Nerve examination

Variable	Consensus Guidelines for Asian Indians	International Criteria [WHO]
Normal range	BMI 18.5-22.9	BMI 18.5-24.9
Overweight	BMI 23-24.9	BMI 25-29.9
Obesity	BMI ≥ 25	BMI ≥ 30
Abdominal obesity by waist circumference cut-offs (cm)	Females : WC ≥ 80 Males : WC ≥ 90	Females : WC ≥88 Males : WC ≥ 102

BMI, body mass index (kg/m^2); WC, waist circumference (cm).

Medical Management of Obesity and Diabetes

1) **Work out - plan /strategy (Physical Activity + Aerobics / Gym) & Healthy eating**.

a) Eating Habits
- Take low-calorie diet for weight reduction.
- Diet rich in fibers(25 to 40 g/day).- grains, cereals, pulses, vegetables & fruits
- Fats < 30% of total energy/day, low refined carbohydrat, trans & saturated fats;
- Increased omega-3 PUFA (reduce liver fat) - Fish, Cooking oil (Canola + Oliveoil) **Free sugars should be less than 5% of total calories/day.**

✓ **The (FDA) has approved 5 artificial sweeteners**;
✓ **saccharin (**Sweet 'N' Low, Sweet Twin, Necta Sweet**),**
✓ **aspartame (Equal, Sweetex, Sugar free, Sugar free gold)**
✓ **acesulfame-K, neotame and sucralose (Splenda, Zero, natura)**

b) Weight Reduction
➢ Increase physical activity (moderate to severe)
➢ Daily 40 minutes of brisk walking or moderate running.
➢ Both Aerobics + resistance exercise are essential to reduce HbA1C

(If you are obese then start weight management strategies & Healthy eating habits. Iphone & Android (play store) have weight reduction applications (for monitoring the weight serially, calorie intake & physical activity). **{FitSlip or Slimmer}**

WHO Global database or Average body wt = 50 kg + add 1.9 kg per inch over 5 feet)
Treatment of obesity as per BMI category.

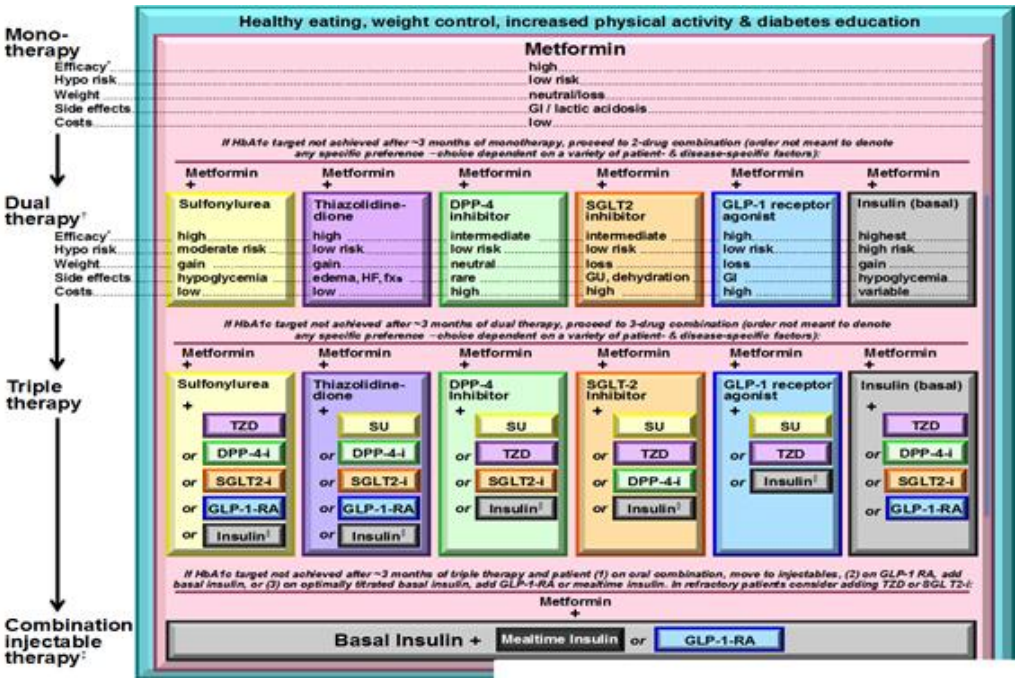
	BMI [kg/m^2]				
Treatment	≥23	≥25	≥27	≥32.5	≥37.5
Lifestyle changes	+	+	+	+	+
Medical weight loss		With comorbidities	+	+	+
Surgical weight loss				With comorbidities	+

Drugs for weight reduction
PCOD + IGT + Risk factors – Metformin alone(preferred here) or in combination with Orlistat (60 mg to 120 mg OD). GI symptoms

GLP -1 agonists – Liraglutide** (3 mg/d) in Non Diabetics
Bariatric surgery if BMI > 40 with comorbidities
(If more than 5% of body weight is not reduced in 3 months then change the drug)

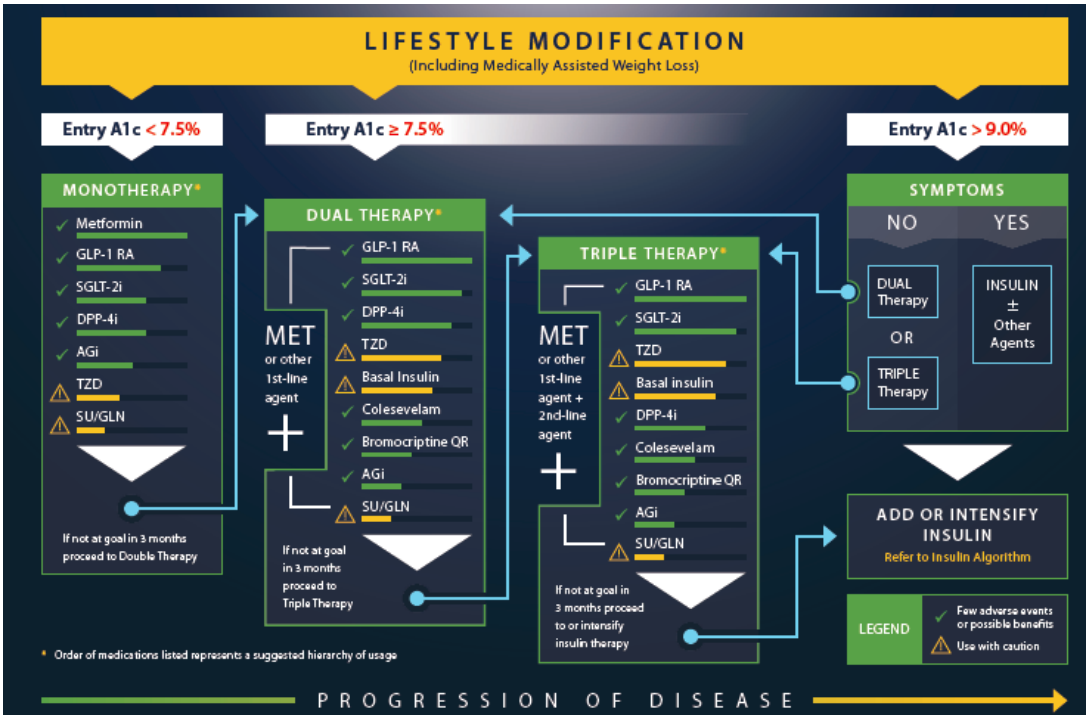
Drugs used in Treatment of DM
Metformin:- Safest drug, Most essential drug

1) **GLP-1 Agonists - exenatide and liraglutide (inject)**
2) DPP- **4 inhibitors** - sitagliptin, - (safest for CVS), vildagliptin, saxagliptin linagliptin
3) **SGLT-2 Inhibitors** (Newest) :- **dapagliflozin, canagliflozin, empagliflozin**
4) Sulfonylureas – Glipizide gliclazide glimepiride
5) Glitazones



ADA-EASD algorithm for management of diabetes. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)Diabetes Care. 2015;38:140–149. doi: 10.2337/dc14-2441.

AACE (2013)	**ADA-EASD (205)**
AACE guidelines preferred GLP-1 agonist as the second line agent (because it has superior PP glucose control & significant Weightt loss) along with metformin for patients who need dual therapy (A1C target of ≤ 6.5%,)	Second line of drugs are other hypoglycemics
Prediabetic treatment is outlined	Not outlined
Guidelines mentions weight reduction stratigies, obesity management	No such inclusions
Algorithm covers safedrugs in green and risky drugs in yellow	No clear mention of safety of drugs



AACE Comprehensive Diabetes Management Algorithm 2013

The most widely accepted strategy at diagnosis is the.[1,2,3,4,5]

- ✓ **Basically Start with Lifestyle modifications in the form of healthy eating and increased physical activity. (most important step)**
- ✓ **IF HbA1c < 7% Start single drug therapy, if > 7.5% then Dual / triple drug**
- ✓ **IF HbA1c > 8.5% directly start insulin**

1) **Step** :- Always start with single drug **" Metformin"**
2) **Step** :- If Blood glucose (fasting + PP) & HbA1c target is not achieved then

Next step is start with 2 drugs combination:- Metformin + Second hypoglycemic agent (which may be a sulfonylurea / thiazolidinedione / DPP-4 inhibitor / **GLP-1 agonist** / basal insulin**.**

The choice between these five agents is decided by
HbA1c- lowering efficacy
Weight-Changes
Hypoglycaemia
Cost of therapy
Besides being an insulin sensitizer, metformin has favourable effects on body weight, blood lipids and fibrinolytic system

(AACE guidelines preferred GLP-1 agonist as the second line agent (bcoz it has superior PP glucose control & significant Wt loss) along with metformin for patients who need dual therapy (A1C target of ≤ 6.5%)
Step 2 = Metformin + GLP-1 Agonists
Step 3:- In the third step, an agent that has not been used in step 2 is added
At any time only 3 Drugs can be used in combo if goal not achieved
Step 4:- Start with basal insulin & 3 drug combo if it fails to achieve the desired HbA1c target, one must proceed to a complex insulin strategy of multiple daily injections. One or two non-insulin agents may be continued along with insulin. According to ADA-EASD Committee & other guidelines.
Note :- (Newer combine a DPP-4 inhibitor with a GLP-1 agonist)

HbA1c- lowering efficacy	**Highest efficacy INSULIN**	**High efficacy Sulphonylurea GLP 1**	**Modest efficacy DPP -4 Inhibitors & glitazone**
Weight loss	**Marked GLP-1 Analoges**	Modest Metphormin	**Weight neutral DPP -4 Inhibitors**
Hypoglycaemia	**Insulin +++**	**sulphonylureas ++**	**No hypoglycemia GLP -1, Met.**
Weight gain[1,6]	**Insulin & sulphonyl ureas**		

Chronic Renal Failure	**Safely given** **GLP I** **Linagliptin** **Liraglutide**	**Given with dose Adjustment** DPP-4 inhibitors (preferred in elderly with CRF) **S**GLT -1 (hypotension)	**Contraindicated** **Metformin**
Effect on Cardiovascular system	**Cardioprotective** **Metphormin** **Acarbose** SGLT-1 (Empagliflozn canagliflozin CANVAS, EMPA-REGA	**Can Safely given** Sitagliptin (TECOS)	**Contraindicated** Liraglutide [1, 7,8,9]

To choose between GLP-1 agonist & DPP-4 inhibitors.[1,10]

DPP-4 Inhibitors	GLP-1 agonist
Oral	Injectable
Limited by endogenous incretin secretion	Not limited by endogenous incretin secretion
Moderate efficacy	Enhanced efficacy
Weight neutral	Weight loss
Well tolerated	GI side effects

In elderly T2DM patients with multiple comorbidities such as CKD and CAD, DPP4 inhibitors are preferable as compared to other agents who has potential to cause hypoglycaemia. In patients with slowing of gastric emptying (gastroparesis) worsened by GLP-1 agonists may make DPP-4 inhibitors preferable.

Cardiovascular outcome trials for incretin based therapies.[1,11]

- TECOS (sitagliptin) shows CV safety (published in 2015). SAVOR TIMI (saxagliptin) and EXAMINE (alogliptin) showed an increased risk of heart failure.
- Liraglutide showed a significant reduction in cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke in patients with diabetes and increased cardiovascular risk in the LEADER trial

When to start Insulin?

- T1DM (Type 1 Diabetes Mellitus)
- LADA (latent autoimmune diabetes of adults)
- T2DM (long duration, failed oral medications)
- Pancreatectomy, pancreatitis, Cystic fibrosis

Primary Insulin Therapy in patients with diabetes:[1,2,12,13]

- Severe infections, Pregnancy, Major surgery/trauma, Renal failure,
- Cirrhosis of liver, Unstable congestive heart failure, Steroid therapy
- Marked hyperglycaemia with osmotic symptoms (Polyuria, polydipsia
- For patients on oral agents with HbA1c greater than 8.5%, we suggest adding insulin.
- Insulin can be considered initial therapy with HbA1c greater than 10%, or ketonuria
- Initial dose of basal Insulin is 0.2 Units per kg daily, subsequent titration made to achieve fasting glucose in range 70-130 mg/dl.
- Patients who have achieved fasting glucose targets but still have elevated HbA1c, are likely to require addition of prandial insulin to their basal regimen.
- For any of the above insulin strategies, factors, such as the patient's age, lifestyle, competence, personal preferences and comorbidities should be considered when individualizing therapy.

Insulin preparations	Onset of action	Peak (hr)	Duration of action (hr)
Lispro/aspart/ Glulisine	10-25 min	1-2	2-4
Regular Human	30- 60 min	2-4	5- 8
Human NPH	1-3 hr	4-12	10-20
Glargine	2-4 hr	Flat	24
Detemir	1-2 hr	Flat	16- 24
Degludec	1-2 hr	Flat	>40
Premixed (NPH/Regular) Lispro 75/25 Aspart 70/30	25- 50 min	2.4	12- 24
Lispro 50/50	C/w above		
U- 500 Regular	1- 1.5 hr	3.5- 8.5	6 to >10

Continuous Glucose monitoring (CGM)

CGM helps measure the glucose content of interstitial fluid (which correlates well with plasma glucose) using an electrochemical enzymatic sensor. CGM has the greatest potential value in patients with hypoglycaemic unawareness who are at risk for or have severe hypoglycaemia, including pregnant women. It also has relevance in patients with Type 1 diabetes who have significant hyper and hypoglycaemic excursions. CGM devices can be used with multiple injections or insulin pump therapy.

Continuous subcutaneous insulin infusion (CSII)-Insulin pump.[14]

Physiological insulin secretion could be closely simulated by appropriately programmed insulin pump. With pump therapy, basal insulin is supplied in the form of a continuous infusion (comprising between 40 and 60 percent of the total daily dose, TDD) with premeal bolus doses given to minimize post-prandial glucose excursions. Only short (regular) or rapid-acting insulins are used with CSII. Most pumps allow for pre-programmed changes in basal rate to accommodate these requirements. Insulin is delivered in a manner mimicking pancreatic beta cell, allowing setting of multiple basal rates with sophisticated bolus calculators which deliver boluses based on carbohydrates consumed.

Treatment goals in T2DM	
Fasting Glucose	80-130 mg/dl
Postprandial Glucose	<180 mg/dl
HbA1c	<7.0 %
Blood Pressure	<130 mg/dl
LDL	<100 mg/dl
HDL-C	>40 mg/dl
Triglycerides	<150 mg/dl

Lipid Targets in Diabetes Mellitus		
LDL	<100 mg/dL	(If CAD negative)
	<70 mg/dL	(If CAD positive)
Triglycerides	<150 mg/dL	(After LDL goal)
HDL	>40 mg/dL	(In males)
	>50 mg/dL	(In females)

Metformin
Formulations:-
Immediate release - 500 mg, 850 mg, 1000mg.
Extended release - - 500 mg, 750 mg, 1000 mg
Taken Orally, along with food, plenty of water, avoid dehydration
Immediate-release tablet or solution
Initial: 500 mg BD orally **or 850 mg OD** (prevention Type 2 DM), taken with meals; increase for every 2Weeks
Maintenance: 1500-2550 mg/day PO divided for 8-12hr with meal
Not to exceed 2550 mg/day
eGFR <30 mL/min/1.73 m²: - Contraindicated.
Adverse Effects :- GI – Nausea, vomiting, dyspepsia, Diarrhea, Flatulence, constipation Weakness, Myalgia, Low serum vitamin B-12, Hypoglycemia

Dyslipidemia.[1,2,15,16]
Protocols of Rx of Hypercholesterolemia
first target **is LDL** reduction & next **is TGs** & then **HDL & Non HDL-C**
First target LDL < 100 mg/dl or 40% less than basal value
LDL < 70 mg/dl in CAD
If TGs - > 500 mg/dl then first target TGs

2nd target – Triglycerides < 150 mg/dl HDL > 40 mg/dl (M) & > 50 mg/dl (F). Non- HDL C < 130 mg/dl).

1) Life style modification + Statins (if Goal not achieved) 2) Statin + fenofibrate (If elderly & RF then fenofibrate is CI). 3) Combo of (Statin + PUFA) or High dose statins as single drug or PUFA only (if statins & fenofibrate not tolerated)

Statins:- Rosuvastatin :-20 to 40 mg/day. more potent(lower TGs & Incr HDL). Atorvastatin: - 40–80 mg/day
Statins provides long term safety. Myopathy rare
Caution:- Statins can cause hyperglycemia (negated by intensification of therapeutic lifestyle change
If TGs > 200 & HDL < 35 better to start a dual therapy (statin and fenofibrate).

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