MANAGING HYPERGLYCEMIA IN TYPE 2 DIABETES MELLITUS

Dr. Badar Bashir

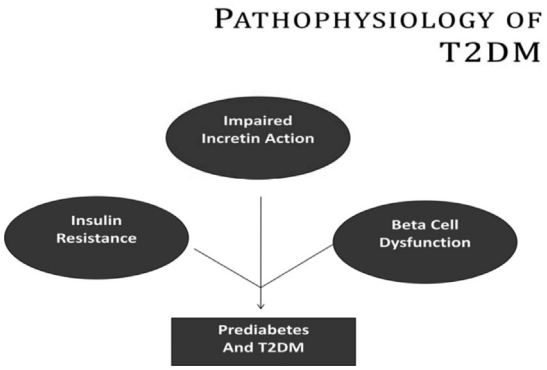
Abstract: Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to relative (Insulin resistance) or absolute deficiency of insulin. Hyperglycemia can lead to various microvascular or macrovascular complications. Good glycemic control with HbA1C level 6.5% - 7% is advisable to avoid the complications. This goal is achieved through diet modification, exercise and pharmacotherapy which include oral hypoglycemic drugs, incretin based therapy and insulin therapy. These therapies are tailored to age, weight and renal function of the patient.

Key words: Hyperglycemia, Insulin resistance, Hypoglycemia, Secretagogues.

Definition

A clinical Syndrome characterized by hyperglycemia due to relative or absolute deficiency of insulin. Epidemiology 415 million people worldwide. (IDF2015) One in Eleven of total population (9.09%). 318 million people have impaired glucose tolerance. Expected to reach 642 million in 2040. 85-90% cases are Type 2. Type 1 is relatively more common in countries near polar regions. Globally 5 million deaths in 2015 due to Diabetes associated problems. One death every 6 seconds. Diabetes accounts for 8% of all legal blindness and is the leading cause of end-stage renal disease in the U.S. Patients with diabetes are twice as likely as non-diabetic patients to develop cardiovascular disease Health care expenditure attributed to DM was estimated to be USD 670 billion in America.(More than military expenditure)

Pathophysiology of T2DM



Criteria for the diagnosis of diabetes mellitus Classic symptoms of diabetes -polyuria, polydipsia, unexplained weight loss + casual PG > 200 mg/dl, Casual = any time of day irrespective of time since last meal. FPG $\geq$ 126 mg/dl. (Fasting is defined as no caloric intake for at least 8 h) OR. 2-h PG $\geq$200 mg/dl during an OGTT. HbA1-c $\geq$ 6.5 % ADA,

Article Citation: Bashir B. Managing Hyperglycemia in Type 2 Diabetes Mellitus. Indep Rev Jul-Dec 2018;20(7-12): 124-129.

Date received: 07/09/2018
Date Accepted: 27/11/2018

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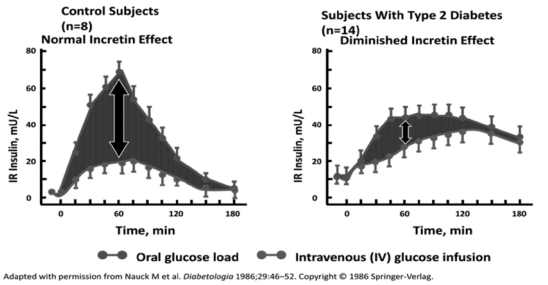
THE INCRETIN EFFECT IS DIMINISHED IN SUBJECTS WITH TYPE 2 DIABETES



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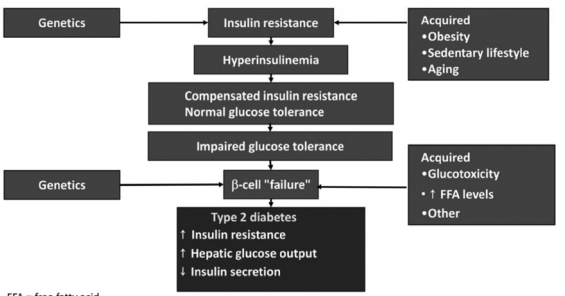
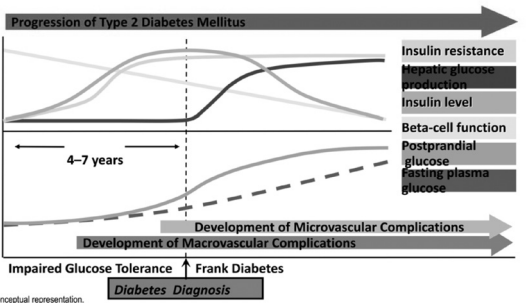
PROGRESSION TO TYPE 2 DIABETES



FFA = free fatty acid.

DEVELOPMENT AND PROGRESSION OF TYPE 2 DIABETES AND RELATED COMPLICATIONS



[a]Conceptual representation.
Reprinted from *Primary Care*, 26(4), Ramlo-Halsted BA, Edelman SV, The natural history of type 2 diabetes. Implications for clinical practice, 771–789, © 1999, with permission from Elsevier.

AACE, and IDF Guidelines:

Treatment Goals for HbA1c, FPG, and PPG
ADA: The general goal of <7% appears reasonable for many adults with diabetes. Less stringent HbA1c goals may be appropriate for other patients especially those with a history of hypoglycemia.

Parameter		ADA[1] Goal	AACE/ACE[2,3] Goal	IDF[4] Goal
FPG, (mmol/L)	mg/dL	70–130 (3.9–7.2)	<110 (<6.1)	<100 (<5.5)
PPG, (mmol/L)	mg/dL	<180 (<10)	<140 (<7.8)	<140 (<7.8)
HbA_{1c}, %		<7[a]	⩽6.5	<6.5

AACE: Achieving an HbA1c of 6.5% is recommended as the primary goal, but this goal must be customized for the individual patient, with consideration of numerous factors, especially hypoglycemia.

1. ADA. Diabetes Care. 2010;33(suppl 1):S11–S61.
2. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. Endocr Pract. 2007;13(suppl 1):3–68.
3. Rodbard HW et al. Endocr Pract. 2009;15(6):540–559.
4. International Diabetes Federation. www.idf.org/webdata/docs/Guideline_PMG.pdf. Accessed September 2, 2010.

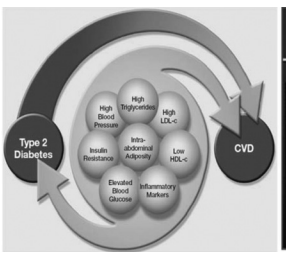
Goals of Treatment

Type 2 Diabetes is a Global Cardio-metabolic Risk (CMR)

The ticking clock

ADA Targets for Glycemic Control and Recommended Action Levels

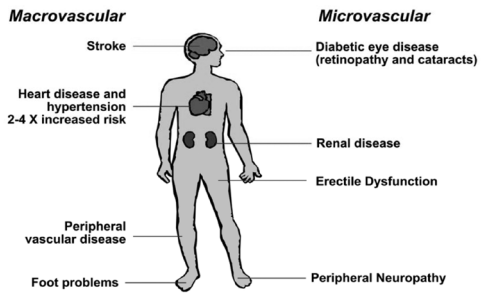
Biochemical Index	Goal	Action Suggested
FPG (preprandial), mg/dL	80 – 120	>140
Bedtime glucose, mg/dL	100 – 140	>160
HbA_{1c}, %	<7	>8



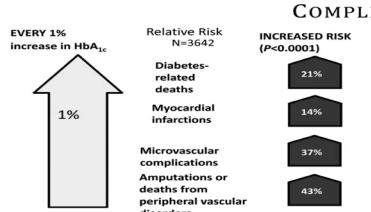
"Ticking Clock" Hypothesis

For	The "clock starts ticking"
Microvascular complications	At onset of hyperglycemia
Macrovascular complications	Before the diagnosis of hyperglycemia

Diabetes: Complications



UKPDS: Worse HbA1c Control and Increased Diabetes-Related Complications



UKPDS=United Kingdom Prospective Diabetes Study.
Epidemiologic data adjusted for age, sex, and ethnic group, expressed for white men aged 50–54 years at diagnosis and with mean duration of diabetes of 10 years. These data should not be used to infer specific microvascular and macrovascular benefits of interventions to lower HbA_{1c}.
Stratton IM et al. UKPDS 35. *BMJ* 2000;321(7258):405–412.

A	• Diet and Exercise
B	•Oral hypoglycaemic therapy
C	• Incretin Based Therapy
D	• Insulin Therapy

A. Diet Dietary treatment should aim at: ensuring weight control providing nutritional requirements allowing good glycaemic control with blood glucose levels as close to normal as possible correcting any associated blood lipid abnormalities

Dietary fat should provide 25-35% of total intake of calories but saturated fat intake should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.

Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.

Carbohydrates provide 50-60% of total caloric content of the diet. Carbohydrates should be complex and high in fibre.

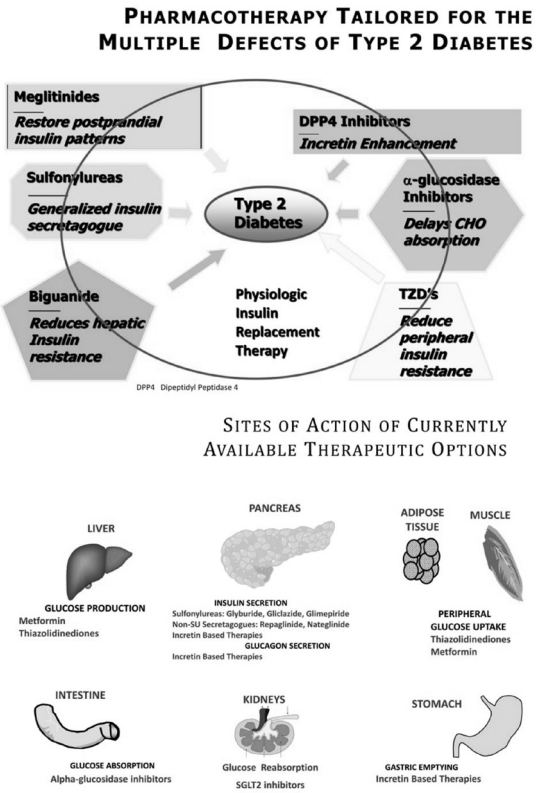
Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.

Exercise

Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person. Such a programme must be tailored to the individual's health status and

fitness. People should, however, be educated about the potential risk of hypoglycaemia and how to avoid it. B. Oral Anti-Diabetic Agents

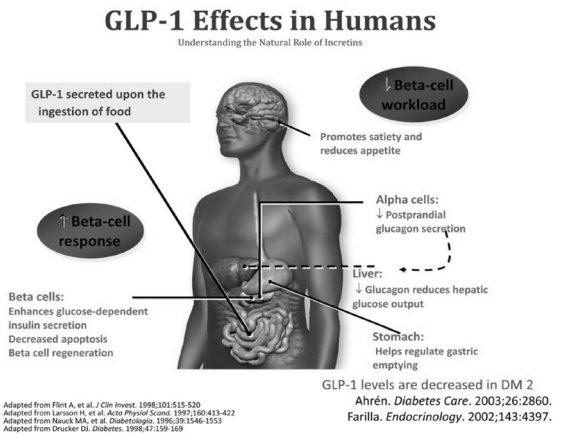
i. Biguanides
ii. Insulin Secretagogues – Sulphonylureas
iii. Insulin Secretagogues – Non-sulphonylureas
iv. α-glucosidase inhibitors
v. Thiazolidinediones (TZDs)
vi. DPP4 Inhibitors

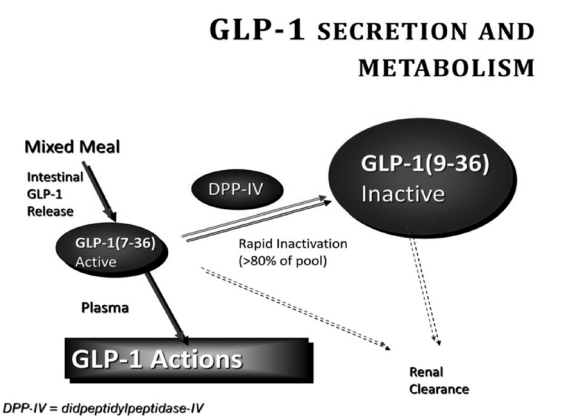


SGLT2 inhibitors

C- Incretin Based Therapy. Peptide hormones secreted by enteroendocrine cells in the GI tract modulate pancreatic islet secretions as part of the "enteroinsular axis". Other effects on nutrient homeostasis. Two major incretins that affect glucose metabolism.

GLP-1: glucagon-like peptide 1
GIP: glucose-dependent insulinotropic peptide (gastric inhibitory polypeptide)





General Guidelines for Use of Oral Anti-Diabetic Agent in Diabetes

In elderly non-obese patients, short acting insulin secretagogues can be started but long acting Sulphonylureas are to be avoided. Renal function should be monitored. Oral anti-diabetic agents are usually not the first line therapy in diabetes diagnosed during stress, such as infections. Targets for control are applicable for all age groups. However, in patients with co-morbidities, targets are individualized. When indicated, start with a minimal dose of oral anti-diabetic

agent, while reemphasizing diet and physical activity. An appropriate duration of time between increments should be given to allow achievement of steady state blood glucose control. D. Insulin Therapy

Short-term use:

- Acute illness, surgery, stress and emergencies
- Insulin may be used as initial therapy in type 2 diabetes
- In marked hyperglycaemia
- Severe metabolic decompensation (diabetic ketoacidosis, hyperosmolar nonketotic coma, lactic acidosis, severe hypertriglyceridaemia)

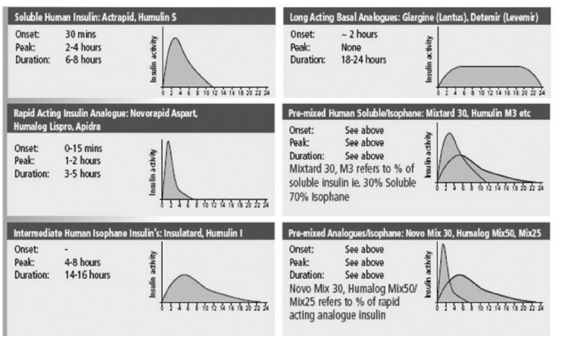
Long-term use:

- If targets have not been reached after optimal dose of combination therapy or basal insulin regimen, consider change to multi-dose insulin therapy. When initiating this,insulin secretagogues should be stopped and insulin sensitisers e.g. Metformin or TZDs, can be continued.

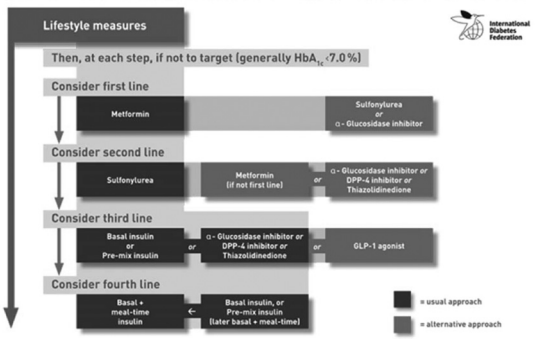
Insulin regimens

- Once-daily injection of a long acting preparation (basal insulin) may be effectively used in some patients.
- Twice-daily mixtures of regular- and intermediate-acting insulin is a commonly used regimen.
- In some cases, a mixture of short- and intermediate-acting insulin may be given in the morning. Further doses of short-acting insulin are given before lunch and the evening meal and an evening dose of intermediate-acting insulin is given at bedtime.
- Other regimens based on the same principles may be used.
- A regimen of multiple injections of short-acting insulin before the main meals, with an appropriate dose of a long-acting insulin given at bedtime, may be used, particularly when strict glycaemic control is mandatory.

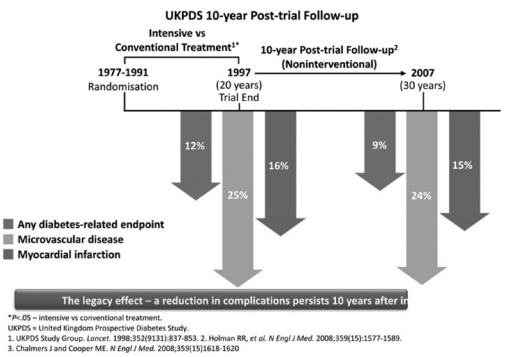
OVERVIEW OF INSULIN AND ACTION



IDF Treatment Algorithm for People with Type 2 Diabetes



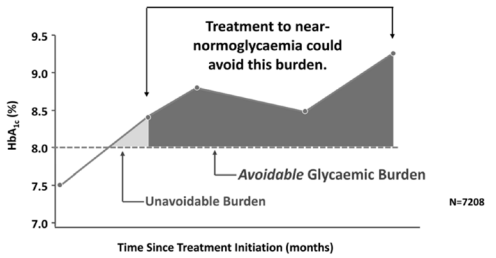
THE LEGACY EFFECT AND BENEFITS OF EARLY INTENSIVE CONTROL



*P<.05 – intensive vs conventional treatment.
UKPDS = United Kingdom Prospective Diabetes Study.
1. UKPDS Study Group. *Lancet*. 1998;352(9131):837-853. 2. Holman RR, *et al. N Engl J Med*. 2008;359(15):1577-1589.
3. Chalmers J and Cooper ME. *N Engl J Med*. 2008;359(15)1618-1620

The Negative Impact of Treatment Failure in Type 2 Diabetes Is Avoidable

26.5 to 35.1 months elapsed before a new or additional treatment was started.



Brown JB, *et al. Diabetes Care.* 2004;27(7):1535-1540.

EARLIER AND APPROPRIATE INTERVENTION MAY IMPROVE PATIENTS' CHANCES OF REACHING GOAL