Diabetes

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Diabetes Mellitus is the disease of the Century

" Respect me I will respect you "

* D.M is an epidemic chronic metabolic (cardiometabolic) disorder of multiple etiology in which the body can't metabolize carbohydrate, fats and proteins because of defects in insulin secretion and / or action.

* D.M is a leading cause of morbidity and mortality, costly yet controllable with a prevalence of 17.1% in Jordan.

* Bd sugar management is only part of story. It is imp. to ensure that BdP and cholesterol level are tightly controlled in order to reduce the complications of diabetes.

- **Epidemiology**

  The overall prevalence is 10-15% of the population, more than 85% of whom have type 2 variety.

  NIDDM (type 2 diabetes) is much more strongly inherited than type I.

  The incidence of the two types of D.M varies significantly among and within different ethnic groups according to their culture and lifestyles.

Important Diabetic Studies

* Diabetic Control and Complication Trial **(DCCT)** 1993

* United Kingdom Prospective Diabetes Study **(UKPDS)** 1998

* Diabetes Prevention Program 2001 **(DPP)**

Classification of different types of Diabetes:

1) **Type 1 diabetes** (absolute insulin deficiencey)
    a) Autoimmune b) Idiopathic
2) **Type 2 diabetes** (constitutes 85% of all diabetics) is characterised by insulin resistance and variable insulin secretory defects
3) **Type 3 diabetes**
    a) Genetic defects in insulin production or action
    b) Exocrine pancreatic disease
    c) Associated with endocrinopathies
    d) Drug induced
    e) Infection
4) Gestational diabetes **(type 4 diabetes)**.

* **50% of type 2 DM are not diagnosed**

Clinical history, physical exam, ambient glucose levels and degree of ketosis usually suffice appropriate diagnostic Classification.

In equivocal setting.

a) C-peptide or insulin level (low in type I DM)
b) Glutamic acid decarboxylase a.b
c) Pancreatic islet cell a.b (+ in 90% of new onset type 1 D.M)

All action Allow correct classification

Criteria for the diagnosis of diabetes

1. **FPG** ≥ 126 mg/dl (7.0 mmol/L)
2. Symptoms of hyperglycemia and a **casual** plasma glucose ≥ 200mg/l) (11.1 mmol/L)

OR

3. 2 hr plasma glucose ≥ 200 mg/dl (11.1) during an OGTT

* In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day
* The classical symptoms of hyperglycemia include polyuria, polydipsia or unexplained wt. loss.
* Fatigue, blurred vision, recurrent monilial vaginites may present
* **OGTT** is not recommended for routine clinical use
* **HBA1C** diagnosis of D.M
* Normal HBA1C does not rule out D.M
* HBAIC is the standard indicator of long term sugar control

Indications for OGTT

1. Patients with Impaired Fasting Glycemia (IFG)
2. Pregnant women and postpartum (in women with GDM)

* OGTT is performed using a 75 oral glucose load in the morning after a noncaloric 8hr fast. Water is allowed but not coffee or smoking.

Types of Curves when performing OGTT

1. Normal curve
2. IGT
3. Diabetic curve
4. Lag storage curve
5. Flat curve

Pre-diabetes

1. Impaired Fasting Glucose **(IFG)**

   FPG 100mg/dl (5.6 mmol/L) to 125 mg/dl (6.9 mmol/L)
2. Impaired Glucose Tolerance **(IGT)**

   2 hr plasma glucose 140mg/dl (7.8 mmol/L) to 199 mg/dl (11.0 mmol/L)

Both IFG and IGT are risk factors for future diabetes and for cardiovascular disease and associated with insulin resistance and metabolic syndrome.

Unless lifestyle modifications are made most people with pre-diabetes develop type 2 diabetes within 10 years.

Diagnosis of Pre-diabetes and Diabetes

Test	Fasting Plasma Glucose (FPG)	Oral Glucose Tolerance Test (OGTT	Random/Casual Plasma Glucose (with symptoms)
How performed	Bd glucose is measured after at least an 8 hr fast	75 gm glucose load (drink) is ingested after at least an 8hr fast Blood glucose is measured at 2 hrs	Blood glucose is measured at any time regardless of eating
Normal	< 100mg/dl (5.6 mmol/L)	< 140 mg/dl (7.8 mmol/L)	
Pre-diabetes IFG	100-125 mg/dl (5.6-6.9 mmol/L)		
Pre-diabetes IGT		140-199 mmol/dl (7.8-11 mmol/L)	
Diabetes Mellitus	≥ 126 mg/dl (7 mmol/L)	≥ 200mg/dl (11.1 mmol/L)	≥ 200mg/dl (11.1 mmol/L) (with symptoms)

Who should be screened for D.M *(high risk)*

A) Type I diabetes: no indications for screening

B) Type 2 diabetes: Testing should be considered in all adults who are overweight (BMI) $\geq 25\ kg/m^2$) and have additional risk factors

1) Sedentary lifestyle
2) Family history of D.M
3) Prior history of Pre-diabetes (annual screening)
4) Hypertension, Hyperlipidemia, I.H.D.
5) History of gestational D.M or delivery of infant weighing over 4.5 kg
6) Pregnant ladies
7) History of PCOS

* Community screening outside a health care setting is not recommended

* In the absence of the above criteria testing should begin at age 40 years

* If results are normal testing should be repeated at least 3 years intervals

Metabolic Syndrome (MS)

Central obesity (waist circumference ≥ 102 cm for men and ≥ 88cm for women) plus any two of the following:

* **Triglycerides** ≥ 150 mg/dl (1.7 mmol/L)
* **HDL-cholesterol**: men < 40mg/dl (1.03 mmol/L), women < 50mg/dl (1.29 mmol/L)
* **BdP** ≥ 130/80 mmHg
* **Fasting glucose** ≥ 100mg/dl (5.6 mmol/L)

Pts should undergo a full cv risk assessment and management should be aggressive to reduce the risk of CVD and type 2 D.M

Features of IDDM and NIDDM

Feature	IDDM	NIDDM
1) Age of onset	Usually < 30	Usually > 30
2) Rate of onset	Rapid	Slow
3) Body weight	Thin	Obese
4) Ketosis	Common	Rare
5) Prevalence	< 0.5%	> 2%
6) HLA association	Present	Absent
7) Concordance – identical twins	< 50%	> 95%
8) Islet cell mass	Greatly reduced	Slightly reduced
9) Association with endocrinopathies	Occasional	Rare

Laboratory evaluation for newly diagnosed Diabetes

- Fasting glucose , Lipid profile, HbA1C, Urinanalysis, Creatinine, Electrolytes, TSH.
- ECG for patient over 40 years.
- Microalbuminuria should be measured annually.
- Physical Exam. must include height, weight, blood pressure.
- Vision measurement and exam. of eye grounds.
- Baseline neurological and cardiovascular exam. should be obtained.
- The foot exam. should include peripheral pulses, sensation.
- Skin exam. for diabetic dermopathy.

Patient Self-Care and Provider Practices to improve Outcomes

Pt. counseling, education and motivation are vital for short term and long term goal achievements.

(I) Patient Self-Care Practices

1. Regular medical appointments to assess control and for complication surveillance / prevention.
2. Healthful meal planning
3. Regular exercise
4. Regular medication use as prescribed
5. Glucose self-monitoring (take results to appointment)
6. Adjustment of medication based on glucose results
7. Daily foot check
8. Annual eye check
9. Annual dental check

(II) Provider Office Practices

1. **Patient education** (team approach)
   - Nutrition education for patient
   - Exercise prescription
   - Glucose self-monitoring
   - Medication adjustment
   - Foot Care

2. **Ask** about
   - Hyper / Hypoglycemic symptoms
   - Impotence and autonomic dysfunction symptoms
   - Cardiac and vascular disease symptoms

3. **Each visit**
   - Check weight, Blood Pressure, glucose, condition of feet
   - Check glucose self-monitoring results / make recommendations

Provider Office Practices **(Cont.)**

4. **Referrals**

   * Annual dilated eye exam
   * Family planning for women of reproductive age
   * Registered dietition
   * Diabetes self-management education
   * Dental exam
   * Mental health professional if needed

5. Laboratory: HbA1C measurement every 3-6 months

   Creatinine, lipids, urinanalysis yearly or as needed

6. Baseline **ECG**

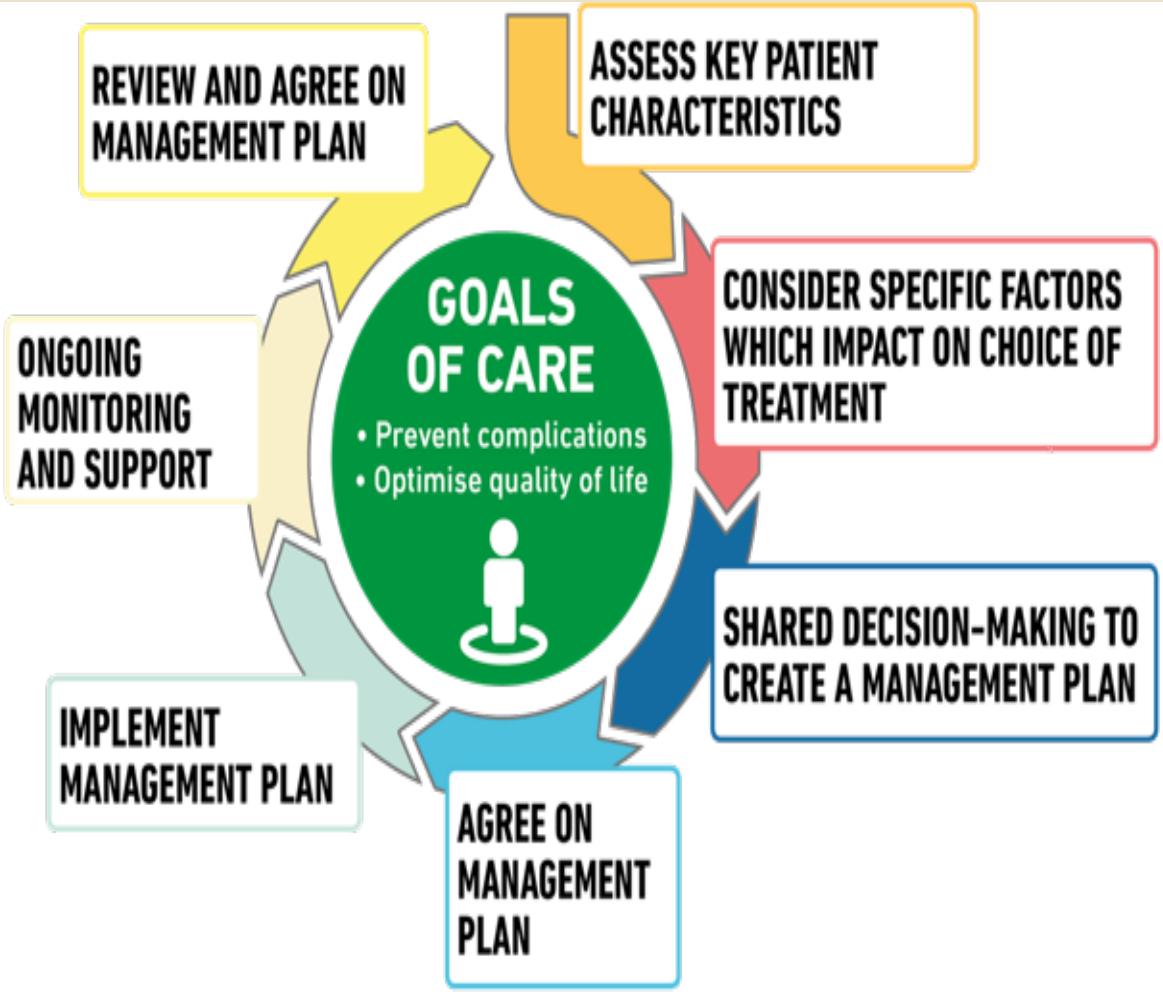
7. Influenza and pneumococcal **vaccines**

Management

A recent report indicated that only

* 37% of adult with diagnosed DM achieved an HbA1C of < 7%
* 36% had BdP < 130 /80 mmHg
* 48% total cholesterol < 200 mg/dl
* 7.3% of diabetic pts achieved all three Rx goals

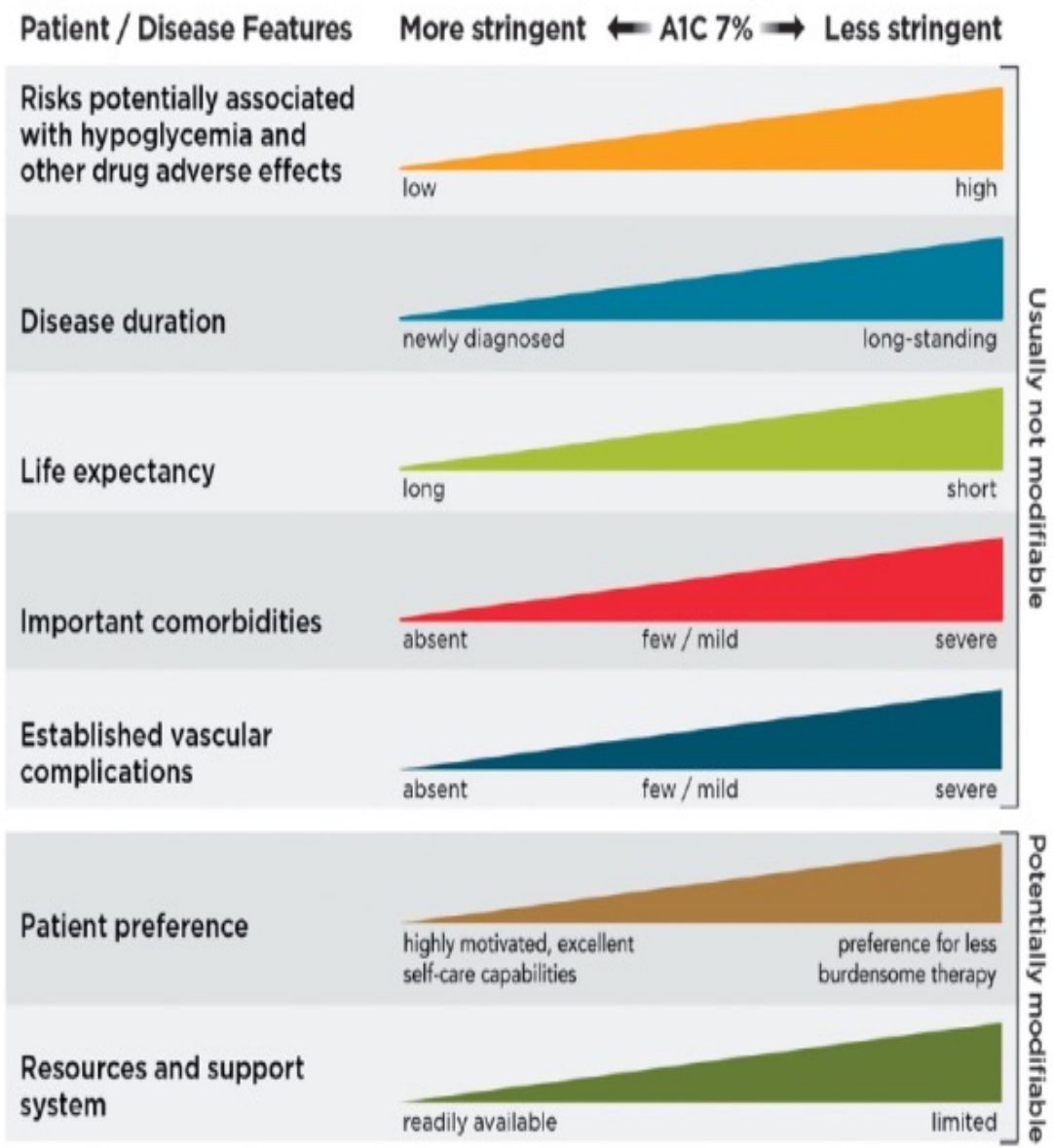
Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



Prevention of Cardiovascular Disease.

3.7 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. B

Approach to Individualization of Glycemic Targets



Pharmacologic Therapy for Type 1 Diabetes.

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. A

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A

9.3 Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. E

9.4 Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. E

Pharmacologic Therapy for Type 2 Diabetes.

9.8 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol)] or blood glucose levels (≥300 mg/dL [16.7 mmol/L)] are very high. E

9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic target. E

9.10 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient

Pharmacologic Therapy for Type 2 Diabetes.

9.11 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit (**Table 9.1**) are recommended as part of the antihyperglycemic regimen. A

9.12 Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium-glucose cotransporter 2 inhibitors are preferred. C

9.13 For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown

Pharmacologic Therapy for Type 2 Diabetes.

9.14 In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B

9.15 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

9.16 The medication regimen should be reevaluated at regular intervals (every 3-6 months) and adjusted as needed to incorporate new patient factors (**Table 9.1**). E

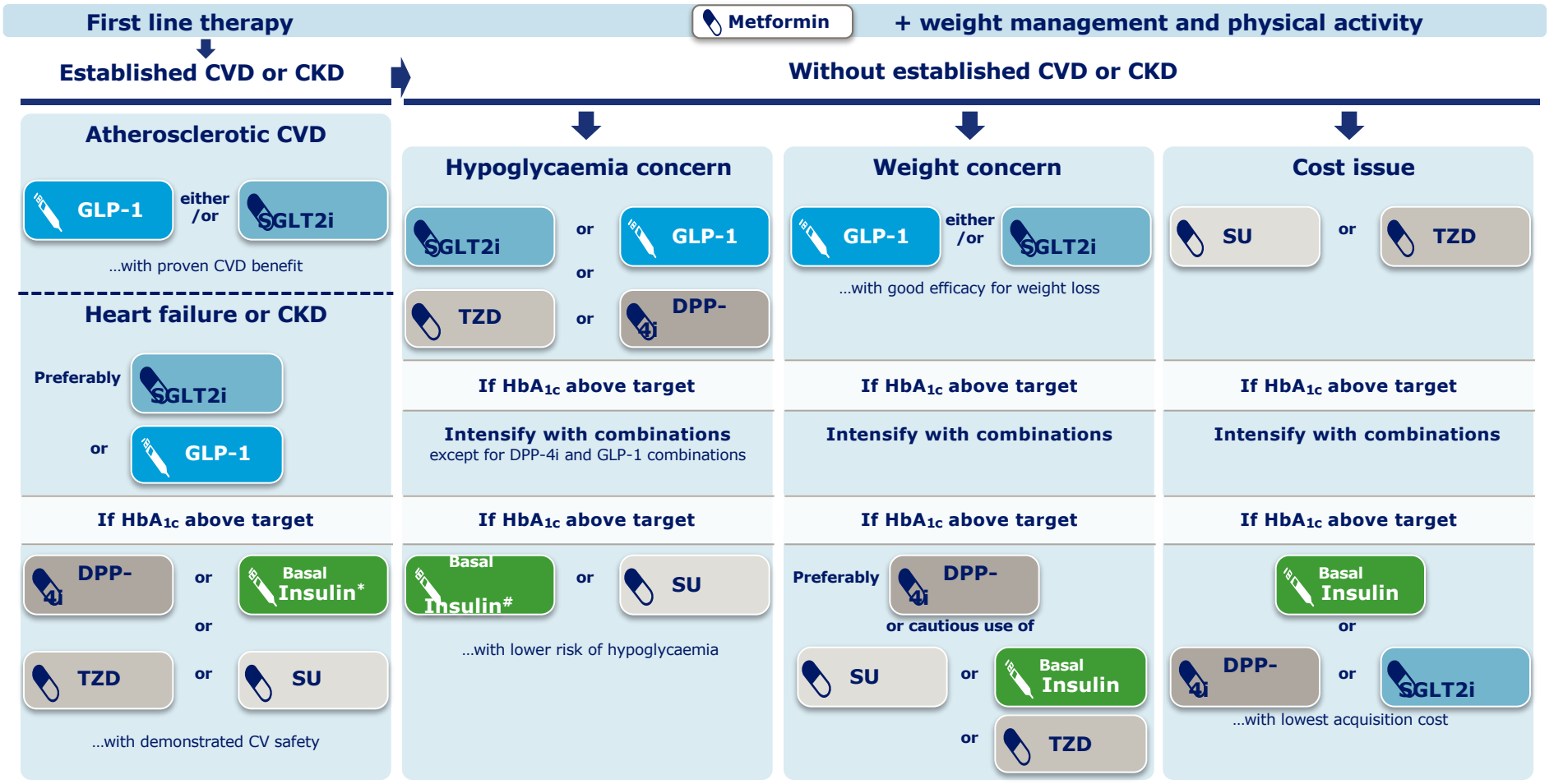
Table 9.2—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $93)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($82, $6,671)	$4 ($4, $1,267)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	$4	1,500 mg
		1,000 mg (ER)	$1,028 ($1,028, $7,214)	$311 ($311, $1,321)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$71 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$15	20 mg (XL)
	• Glyburide	6 mg (micronized)	$50 ($48, $71)	$10	12 mg (micronized)
		5 mg	$93 ($63, $103)	$13	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$4	45 mg
	• Rosiglitazone	4 mg	$407	$329	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$23	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$46	360 mg
	• Repaglinide	2 mg	$878 ($162, $898)	$48	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$170	25 mg
	• Saxagliptin	5 mg	$490 ($462, $490)	$392	5 mg
	• Linagliptin	5 mg	$494	$395	5 mg
	• Sitagliptin	100 mg	$516	$413	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$322	$257	15 mg
	• Dapagliflozin	10 mg	$557	$446	10 mg
	• Canagliflozin	300 mg	$558	$446	300 mg
	• Empagliflozin	25 mg	$558	$448	25 mg
GLP-1 receptor agonists	• Exenatide (extended release)	2 mg powder for suspension or pen	$792	$634	2 mg**
	• Exenatide	10 μg pen	$850	$680	20 μg
	• Dulaglutide	1.5/0.5 mL pen	$876	$702	1.5 mg**
	• Semaglutide	1 mg pen	$875	$704	1 mg**
	• Liraglutide	18 mg/3 mL pen	$1,044	$835	1.8 mg
Bile acid sequestrants	• Colesevelam	625 mg tabs	$712 ($674, $712)	$354	3.75 g
		3.75 g suspension	$674	$598	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$855	$685	4.8 mg
Amylin mimetics	• Pramlintide	120 μg pen	$2,547	$2,036	120 μg/injection†††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1, glucagon-like peptide 1; IR, immediate release; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [44] or NADAC [45] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.

2020 ADA/EASD treatment guideline

Recommendation for basal insulin use in T2D

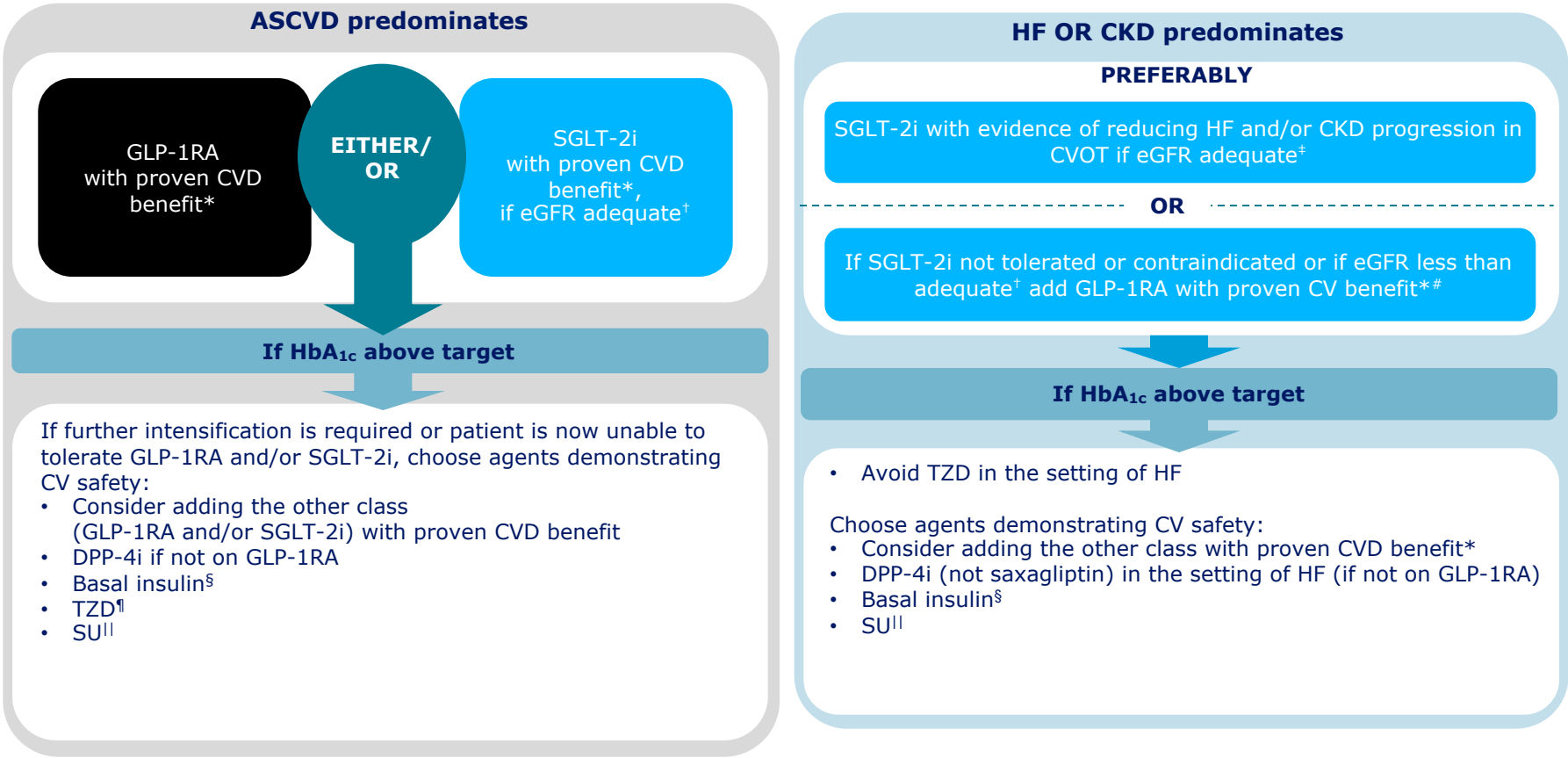


Also, consider basal insulin as the first injectable if HbA_{1c} is very high (11%), or if symptoms of catabolism are present, or if type 1 diabetes is a possibility

* Degludec/ glargine U100 have demonstrated CVD safety; # degludec/ glargine U300 < gargine U100/ detemir < NPH for risk of hypoglycaemia

ADA, American Diabetes Association; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; EASD, European Association for the Study of Diabetes; GLP-1, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SU, sulphonylurea. U, units/ml; Diabetes Care 2020 Jan; 43(Supplement 1): S98-S110.

ADA/EASD 2018 consensus for glucose-lowering medication in T2D



*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia'; #Caution with GLP-1RA in ESRD

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation **(canagliflozin)** ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors **(liraglutide, albiglutide, dulaglutide, exenatide extended release)** ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

Insulin Injection Technique.

- Ensure patients and/or caregivers receive adequate education and understand correct insulin injection technique to optimize glucose control and safety
  - Inject into appropriate body areas (abdomen, thigh, buttock, upper arm)
  - Injection site rotation to avoid lipohypertrophy
  - Appropriate care of injection sites to avoid infection
  - Avoidance of intramuscular (IM) insulin delivery
- Use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared to longer needles

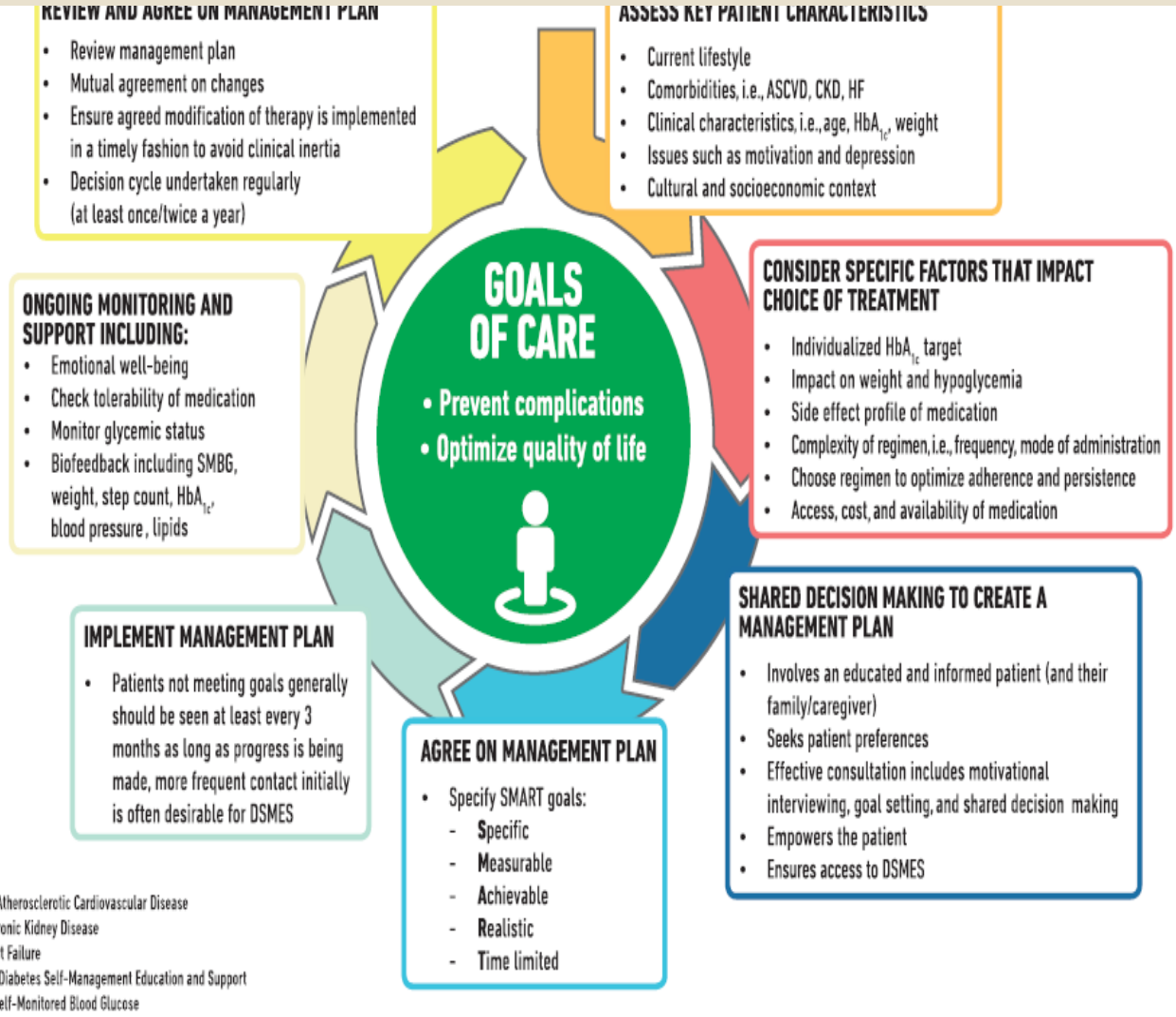
Pharmacologic Therapy for Type 2 Diabetes.

9.5 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

9.6 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A

9.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Treatment of Type 2 DM

* Weight reducing regime + Exercise + lifestyle measurements
* Majority are overweight, ↑ body weight is associated with ↑ risk of CVD
* Reduction of 5-10% in weight can have a major impact on the clinical course of type 2 DM
* Normal or near normal weight will:
  a) Optimize insulin sensitivity
  b) Minimize insulin requirement
  c) Minimize cardiovascular risks

Encourage a healthy lifestyle

1) Low fat, high fiber diet (CHD > 55%, fat < 30%, Protein 10-15%)
2) Encourage intake of monounsaturated fat.
3) Reduce salt intake.
4) Hypo caloric (500 k cal deficit) diet.
5) Limit alcohol intake < 21 units/week for women and < 12 units for women.
6) Encourage exercise.
7) Stop smoking.
8) Avoid stress.

Diet

- It is basically a diet for healthy living. Patient who are over weight should follow a hypocaloric diet of between 500-600kcal/day less than their normal intake aiming of 0.5kg/week weight loss.

- Recommendation is for high complex CHO, low fat diet.

- Caloric requirements vary with age, sex, ideal body weight, level of physical activity and concurrent illness

Physical Activity

Brisk walking for 30 minutes daily or every other day

Swimming or Gardening

Benefits of exercise:

* Improved glucose control
* ↓ C.V risk factors (Hypertension and hyperlipidemia)
* Weight reduction
* Reduced stress
* Decreased Osteoporosis

Glycemic Goals

* HbA1C < 7%
* Pre-prandial glucose 70-130 mg/dl (3.9-7.2 mmol/L)
* Peak postprandial < 180 mg/dl (<10 mmol/L)

HbA1C is the pry target for glycemic control.

Prevention of microvascular complic. Occurs through optimal glycemic control, normotension and avoidance of excess sodium and protein intake.

Prevention of macrovascular complic. is achieved via aggressive conventional risk factors reduction.

Oral hypoglycemic agents

- The majority of type 2 diabetic patients require oral hypoglycemic agents.
- At time of diagnosis pancreatic function is 50% of normal.
- Some type 2 diabetic patients may ultimately require insulin therapy because of :

  1) Failure of dietary and medication compliance

  2) Final exhaustion of beta cells.

-Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

-Once initiated, metformin should be continued as long as it is tolerated and not contraindicated;

other agents, including insulin, should be added to metformin. A

- Long-term use of metformin may be associated with biochemical

vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin treated patients, especially in those with anemia or peripheral neuropathy. B

- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (.10% [86 mmol/mol]) or blood glucose levels (>300 mg/dL [16.7 mmol/L]) are very high. E
- 9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C >1.5% (12.5 mmol/mol) above their glycemic target. E

- A patient-centered approach should be used to guide the

choice of pharmacologic agents Considerations include

1-comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease),

2-Hypoglycemia risk.

3-impact on weight.

4-cost.

5- risk for side effects,

6-patient preferences. E

- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor

agonists with demonstrated cardiovascular disease benefit

are recommended A

- Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose co transporter 2 inhibitors are preferred. C
- For patients with type 2 diabetes and chronic kidney disease consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C

- In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin.B
- Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B
- The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors

Biguanides: (↓ HbA1C 1-2%)

Metformin (insulin sensitizers) is the drug of choice for treatment of type 2 diabetic patient. It does not cause hypoglycemia and causes less weight gain and improve lipid profile. Metformin decrease blood glucose by:

a) Decrease hepatic gluconeogenesis

b) Increase glucose uptake in the muscles

c) Decrease glucose absorption ?

- Daily dose 1.5 – 2.5 gm
- Side effects = diarrhoea, nausea, lactic acidosis (avoid in patient with renal, hepatic and unstable heart failure).

Sulphonylureas: (↓ HbA1C 1-2%)

Act by stimulation of insulin release from B-cells of pancreas.

- e.g. Glibenclamide, glipizide, gliclazide.
- Glimepiride once daily with low risk of hypoglycemia.
- Side effects: weight gain, hypoglycemia, skin reaction and hematological complications.

Thiazolidinediones (Insulin Sensitizers)

- e.g. Pioglitazone and Troglitazone can be used as monotherapy or in combination with metformin, sulfonylurea or insulin.

  Dosing independent of food intake and can be used in end stage renal failure.

Contraindications: Hepatic Impairement. H.F

- **Newer insulin secretagogues**
- e.g. Repaglinide (result in insulin secretion)

  Exenatide (enhance insulin secretion)

α – Glucosidase inhibitors

- e.g. A carbose (lead to reduction in the rise of postprandial glucose)

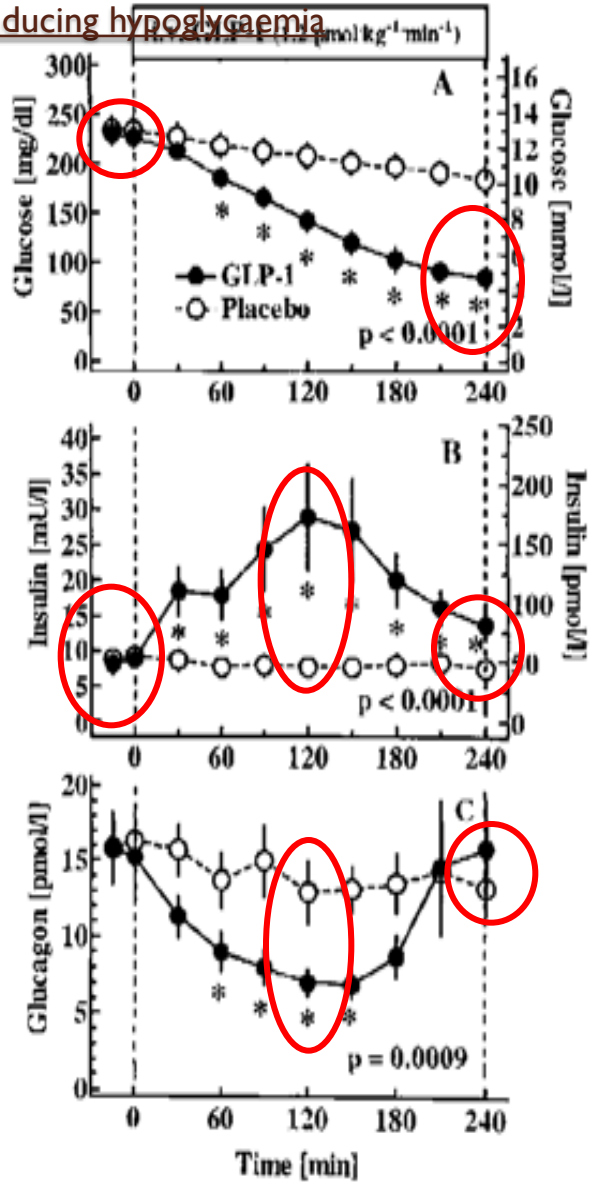
GLP-1 normalises fasting glucose levels

In patients with poorly controlled T2D without inducing hypoglycaemia

Glucose

Insulin

Glucagon

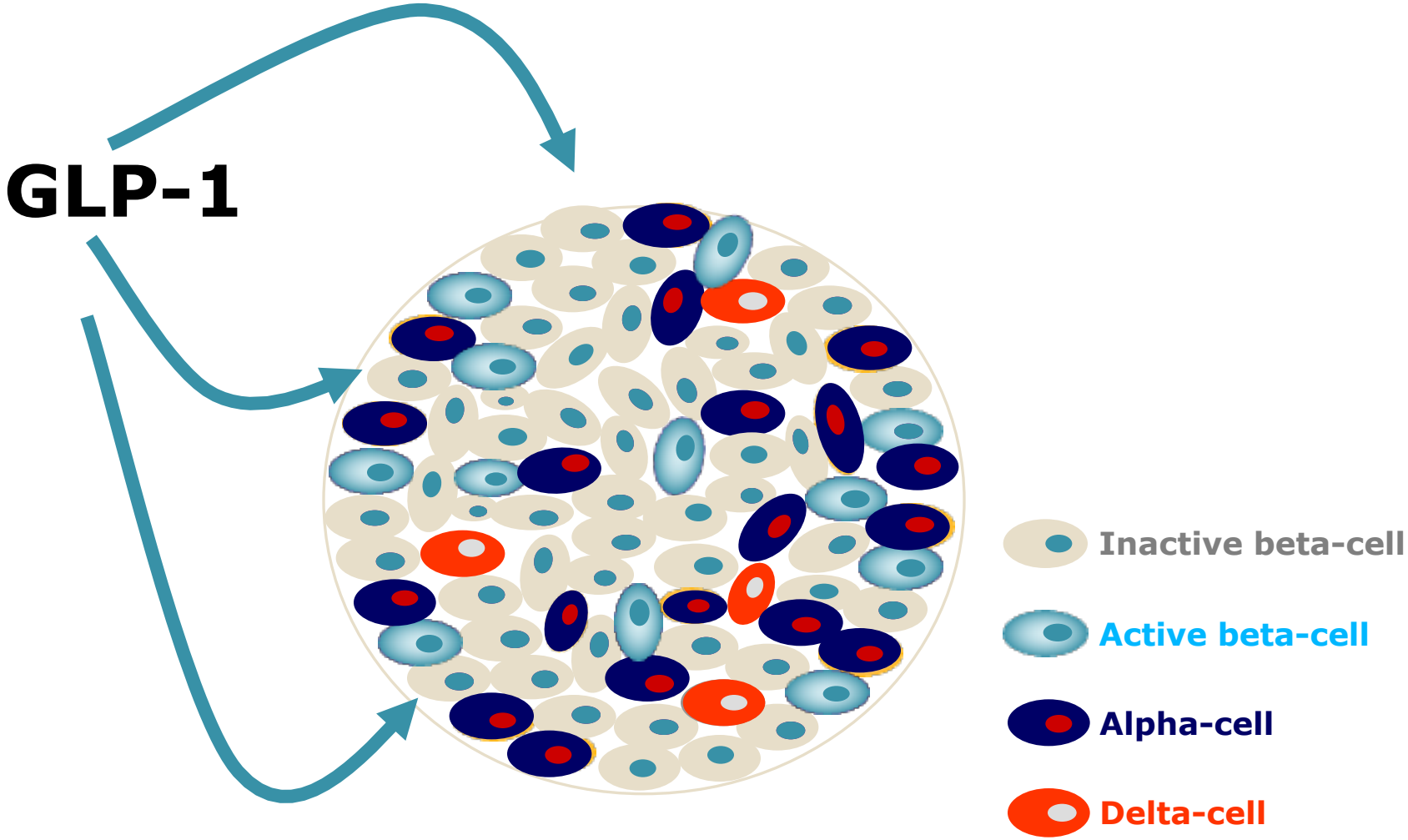


GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

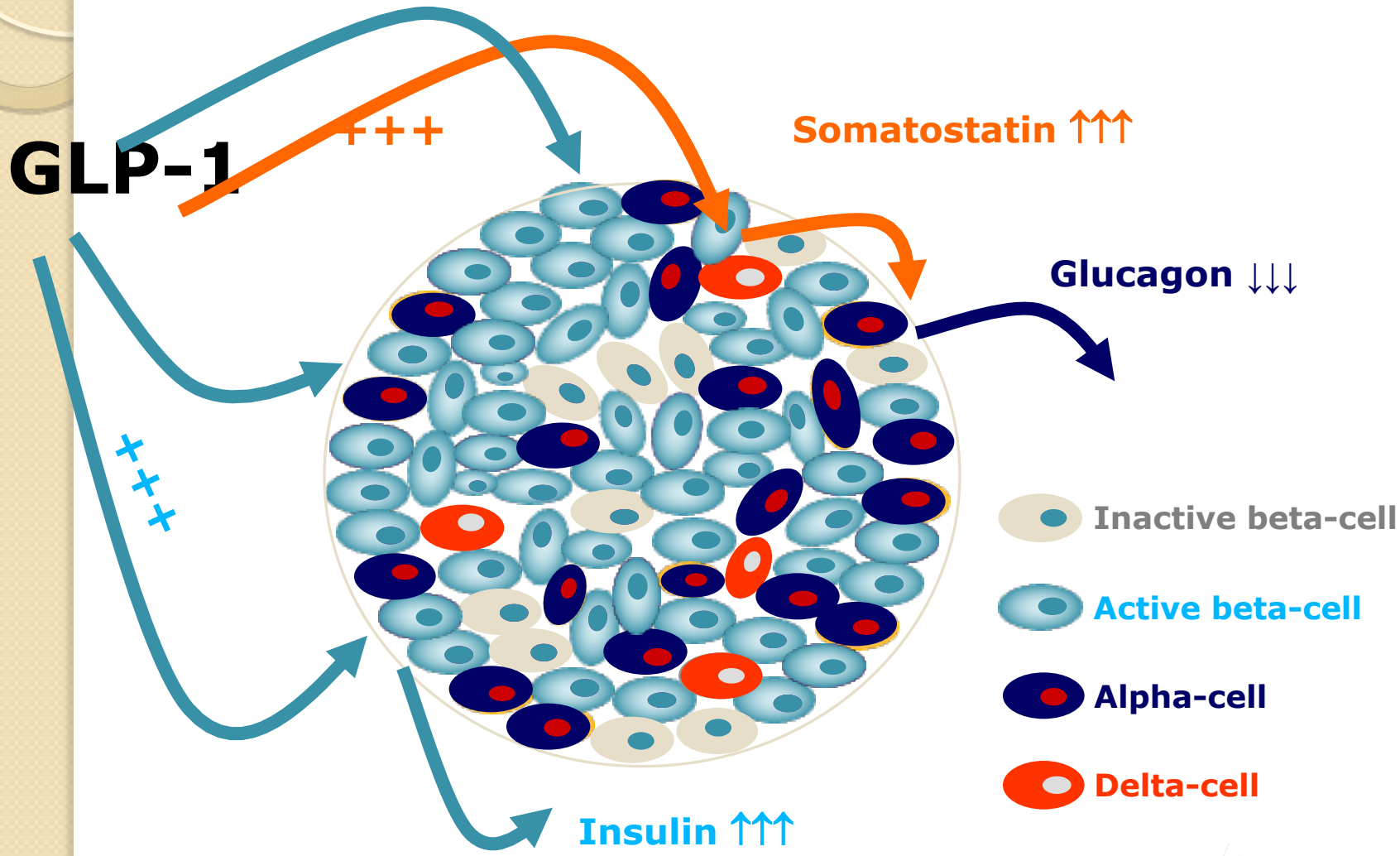
GLP-1: 1.2 pmol/kg-1/min-1

Nauck et al. *Diabetologia* 1993;36:741–4

Islet effects of GLP-1



Islet effects of GLP-1



Insulin

Basal Insulin accounts for approximately 50% of total insulin secreted each day where as the remaining 50% of the insulin is secreted in response to meals.

Types of Insulin:

1) Rapid-acting analogue e.g Aspart, Lispro
2) Short-acting e.g Regular
3) Intermediate-acting e.g NPH
4) Long-acting e.g Glargin, Detemir
5) Premixed Insulin

Insulin

- Combination of depot and regular insulin are designed indivually for patient .The most popular plan entails 2/3 of the day's requirement given s.c before breakfast as a mixture of

  2/3 N-type insulin and 1/3 R-type insulin. The remainder third is given before the evening meal as 2/3 type N and 1/3 type R.
- When patient is stable and when close nursing follow up and patient education and training are available insulin therapy is initiated on an outpatient basis for better prediction of outpatient energy, dietary and insulin needs.
- An average starting estimation of insulin requirement is about 25

  units depending on the mass of patient.

Gestational D.M (GDM)

Non diabetic women who develop D.M during pregnancy. (screening is performed at 24-28 wks by one step or two-step approach)

The diagnosis of GDM requires at least 2 of the following glucose vaules

Fasting ≥ 94mg/dl (≥ 5.3 mmol/L)

1 hr ≥ 180 mg/dl (≥ 10.0 mmol/L)

2 hr ≥ 155 mg/dl (≥ 8.6 mmol/L)

3 hr ≥ 140 mg/dl (≥ 7.8 mmol/L)

Oral hypoglycemic drugs should not be used in pregnancy.

The glycemic control target for GDM is preprandial

≤ 105 mg/dl (5.8 mmol/L) and either

1 hr post meal ≤ 155 md/dl (8.6 mmol/L) or

2 hr post meal ≤ 130 mg/dl (7.2 mmol/L)

Uncontrolled D.M is associated with spontaneous abortion and major fetal abnormalities. In majority gestational D.M resolve after pregnancy but is likely to recur.

Acute Complications of Diabetes Mellitus

1) Diabetic ketoacidosis
2) Hyperosmolar Nonketotic Hyperglycemia
3) Hypoglycemia
4) Lactic acidosis

Hypoglycemia in Diabetic Patient

Prevention of hypoglycemia is a critical component of diabetes.

- Hypoglycemia may be asymptomatic, mildly symptomatic or severely symptomatic and require assistance. Different patients are affected to different degrees as happens with hypoxia.
- Teaching people with diabetes to balance insulin use, carbohydrate intake & exercise is imp.
- Clinical manifestations: perspiration, tremor, hunger, nausea, tachycardia, pallor, irritability, headache, lethargy, confusion, bizarre behavior. If severe coma, seizure, permanent neurological impairment and even death.

- Rx: Feeding rapidly with absorbed food.
- I.V solution of 25gm glucose.
- Hypoglycemia corrected by glucose last only 1-2 hrs therefore a meal with complex CHO and protein must follow within that period.
- Glucagon 1mg i.m also helpful.

Causes of Coma in Diabetic Patient

1) Related to diabetes

Hypoglycemia. Diabetic ketoacidosis, nonketotic hyperglycemic coma, lactic acidosis.

2) Unrelated to diabetes

Alcohol or other toxic drugs, C.V.A or head trauma, uremia.

Macrovascular Complications of Diabetes

Atherosclerotic vascular disease (a) Coronary artery disease (b) MI with sudden death (c) C.V.A (d) Peripheral vascular dis. (e) Intestinal ischemia (f) Renal artery stenosis

Up to 80% of pts. with type 2 diabetes will develop or die of macrovascular disease.

Microvascular Complications of Diabetes

1) Diabetic nephropathy
2) Peripheral neuropathy
3) Autonomic neuropathy
4) Diabetic retinopathy

Prevention & Management of Diabetic Complications

a) **Cardiovascular Complications:**

* D.M has 2-3 fold ↑ risk of developing CVD
* Up to 75% of type 2 DM & 35% of type 1 DM die from CVD
* CVD is the largest contribute to the direct and indirect costs of diabetes
* Numerous studies have shown the efficacy of controlling cardiovascular risk factors in preventing or slowing CVD in people with diabetes

1) **Hypertension**

* Hypertension affects majority of diabetes pts and is a major risk factor for both CVD & microvascular complications
* Lowering BdP will reduce the incidence of coronary heart disease, stroke and nephropathy
* Target BdP is < 140 /90
* Multiple drug therapy is generally required
* Medication either ACE inhibitor or ARBs (Calcium channel blockers are warranted in cases of intolerance or contraindication to ACE inhibitors

2) **Dyslipidemia**

* Low HDL which are often associated with elevated VLDL level are the most prevalent in type 2 DM
* All pts with significant elevation of VLDL should be screened for DM
* Statin therapy should be added to lifestyle therapy regardless of baseline lipid levels for diabetic pts with overt CVD
* The pry goal in an LDL choles. < 100 mg/dl (2.6 mmol/L)

3) **Antiplatelet agents**

* Aspirin therapy either as 2ry prevention

4) **Smoking Cessation**

Advice all pts not to smoke

b) **Diabetic Nephropathy**

* Diabetic nephropathy occurs in 20-40% of pts. with diabetes & is the single leading cause of end-stage renal disease (ESRD)
* Microalbuminuria (persistent albuminuria in the range of 30-299 mg/24 hr) is the earliest stage of diabetic nephropathy and a marker of CVD risk
* The most Useful screening test is the albumin: creatinine ratio on the 1st morning urine sample. More than one positive test is required over a few weeks or months

* Control of diabetes and BdP will reduce the risk or slow the progression of nephropathy
* ACE inhibitors usage is associated with significant reduction in progress to overt proteinuria & ↑ regression to normoalbuminuria

c) **Diabetic Retinopathy (DR)**

* D.R is the leading cause of blindness and diabetic pts have 10% chance of acquiring blindness from retinopathy
* Glaucoma, cataracts and other disorders of the eye occur earlier & more frequently in people with diabetes
* Screening by yearly fundoscope exam or fundal photography
* Laser photocoagulation is indicated in pts with PDR, macular edema and some cases of NPDR

d) **Diabetic Neuropathy**

* Distal symmetrical polyneuropathy, mononeuropathy, autonomic neuropathy are the main types
* Up to 30% of diabetic develop neuropathy
* 50% may be asymptomatic
* Numbness, parasthesia, pain, absence sensation, ulcer may occur
* Tricyclic antidepressants, capsaicin, anticonvulsants (carbomazepine, Gabapentin, pregabalin) may help to control pain

8) **Foot Care**

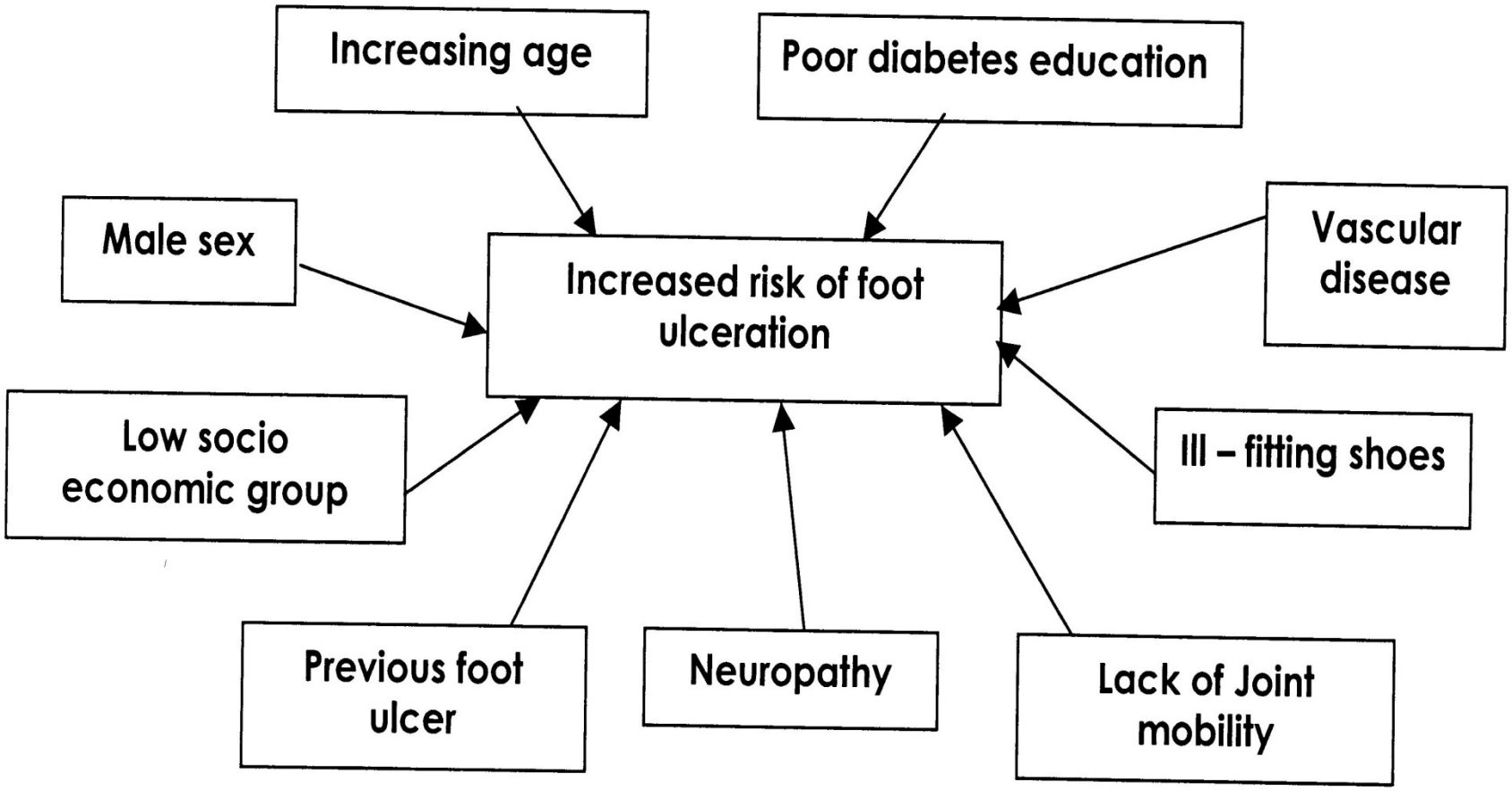
* Foot ulcer occurs in 5-10% of diabetic patient

* Three path. Physiologic process result in injury predisposition and potential amputation

a) Neuropathic b) Ischemia c) Sepsis

* Foot self-care education includes cleaning & drying, nails cutting, shoes, sockets, smoking, avoid hot objects, never go barefoot, taking advise of doctors for any foot problem

Factors increasing the risk of foot ulceration:



Skin changes

Most dermopathy occurs in type 1 DM.

Necrobiosis lipoidica, Diabetic dermopathy, Garrods knuckle pads, skin may become thick and waxy, A canthosis nigricans.