Management of diabetes

Presented by :

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Symptom	Cause
Polyuria	Glucose in renal tubule causes osmotic retention of water, causing a diuresis
Polydipsia	A physiologic response to diuresis to maintain plasma volume
Fatigue	Mechanism unknown, but probably due to increased glucose in plasma
Weight loss	Due to loss of anabolic effects of insulin
Blurred vision	Swelling of lens due to osmosis (caused by increased glucose)
Fungal infections	Fungal infections of mouth and vagina common—*Candida albicans* thrives under increased glucose conditions
Numbness, tingling of hands and feet	Neuropathy Mononeuropathy: due to microscopic vasculitis leading to axonal ischemia Polyneuropathy: etiology is probably multifactorial

screening

- SCREENING. According to ADA (2018) guidelines, Screen the following :
- 1-Screen all adults aged 35 years or older
- 2-Screen overweight adults (BMI>=25 or >= 23 in asian) with at least one additional risk factor :
- 3-High risk race /ethnicity
- 4-History of Gestational DM +History of cardiovascular disease
- 5- Physical inactivity
- 6-HTN.
- 7-HDL cholesterol < 35mg/dl (0.9 mmol/L) and/or TG >= 250mg/dl (2.8 mmol/L)
- 8-PCOS

diagnosis

- a. Fasting plasma glucose—criteria for DM: glucose >126 mg/dL.
- Preferred test for screening.

- If between 100 and 126 mg/dL, perform a 75 g oral glucose tolerance test (although this is rarely done) or recheck fasting glucose

- b. Random plasma glucose—criteria for DM: glucose >200 mg/dL in a person with diabetic symptoms.

- c. Two-hour postprandial plasma glucose level—criteria for DM: glucose >200 mg/dL after administration of the equivalent of a 75 g glucose load (more sensitive than fasting glucose level, but less convenient).

d. Hemoglobin A1c—criteria for DM: A1c >6.5%

TABLE 4-4 **Diagnostic Criteria for Diabetes Mellitus**

Glucose Test	Impaired Glucose Tolerance (mg/dL)	Diabetes Mellitus (mg/dL)
Random plasma	—	>200 with diabetic symptoms
Fasting	110–126	>126 on two occasions
2-hr postprandial	140–200	>200
Hemoglobin A1c (%)	5.7–6.4	>6.5

Of new cases of diabetes :

- 50% can be controlled adequately by diet alone
- 20–30% will need oral antidiabetic medication,
- 20–30% will require insulin.

Regardless of etiology, the choice of treatment is determined by **the adequacy of residual B cell function**

Ideal management allows the patient to lead a completely normal life, to remain symptom free and to escape the long term complications of diabetes.

The correct treatment may change with time as βcell function is lost

Diet and lifestyle

Lifestyle changes, such as taking *regular exercise*, observing a *healthy diet, reducing alcohol consumption* and *stopping smoking*, are important but difficult for many to sustain.

Healthy eating

Dietary measures are required in the treatment of all people with diabetes.

Nutritional advice should be tailored to individuals and take account of their age and lifestyle. The aims are to improve glycaemic control, manage weight, and avoid both acute and long term complications

Weight management

A high percentage of people with type 2 diabetes are overweight or obese, and many antidiabetic medications and insulin encourage weight gain.

Abdominal obesity also predicts insulin resistance and cardiovascular risk.

Weight loss is achieved through a reduction in energy intake and an increase in energy expenditure through physical activity.

In extreme cases, bariatric surgery can induce marked weight loss and improvement in HbA1cin patients with type 2 diabetes, sometimes enabling treatment withdrawal

exercise

All patients with diabetes should be advised to achieve a significant level of physical activity (e.g. walking, gardening, swimming or cycling) and to maintain this long

Recently, it has also been suggested that a combination of both aerobic and resistance exercise may lead to greater improvements in glycaemic control

Drugs to reduce hyperglycaemia

Most drugs used to treat type 2 diabetes depend upon a supply of endogenous insulin and therefore have no effect in patients with type 1 diabetes.

The sulphonylureas and biguanides have been the mainstay of treatment in the past, but a variety of newer agents are now available and the optimal place for these in treatment is yet to be determined

Biguanides (metformin)

It improves **1-**insulin sensitivity and **2**- peripheral glucose uptake, and **3**-impairs both glucose absorption by the gut and hepatic gluconeogenesis.

it does not increase insulin secretion and seldom causes hypoglycaemia.

Metformin does not increase body wt

Metformin is given with food, 2–3 times daily , the usual starting dose is 500mg twice daily (usual maintenance 1g twice daily).

Approximately 25% of patients develop mild **gastrointestinal side effects**

Its use is **contraindicated** in alcohol excess and in impaired renal or hepatic function due to the increased risk of **lactic acidosis**

sulphonylureas

Sulphonylureas stimulate the release of insulin from the pancreatic βcell (insulin secretagogue).

They are best used to treat non obese people with type 2 diabetes who fail to respond to dietary measures, as treatment is often associated with **weight gain**

They are known to **reduce micro vascular complications** with long term use.

Gliclazide and **glipizide** cause few side effects, but **glibenclamide** is long acting and prone to induce **hypoglycaemia** so should be avoided in the elderly.

Sulphonylureas are often used as an add on if metformin fails to produce adequate glycaemic control

1. First generation (chlorpropamide,tolbutamide)
2. Second generation (Glibenclamide,Gliclizide, glipizide)
3. Third generation as glimperide

Mode of action:

Act by stimulating a receptor on Beta cells,closing potassium channels and opening a Ca channel with subsequent insulin release

Alpha-glucosidase inhibitors

These delay carbohydrate absorption in the gut by selectively inhibiting disaccharidases. **Acarbose** or **miglitol** is taken with each meal and lowers post prandial blood glucose.

Side effects are **flatulence**, **abdominal bloating and diarrhoea**

Thiazolidinediones

These drugs (glitazones) bind and activate receptor found in **adipose tissue**, and work by enhancing the actions of endogenous insulin. Plasma insulin concentrations are not increased and hypoglycaemia is not a problem.

recently a number of adverse effects have become apparent and their use has declined. **Rosiglitazone** was reported to increase the risk of myocardial infarction and was withdrawn

The other TZD in common use, **pioglitazone,** does not appear to increase the risk of myocardial infarction but it does exacerbate cardiac failure by causing fluid retention, and recent data show that it increases the risk of bone fracture and possibly bladder cancer. These observations have reduced the use of pioglitazone dramatically.

Pioglitazone can be effective in patients with insulin resistance and also has a beneficial effect in reducing fatty liver and non alcoholic steatohepatitis (NASH)

incretin-based therapies: DPP-4 inhibitors and GLP-1 analogues

The incretin effect is the augmentation of insulin secretion seen when glucose is given orally rather than intravenously, due to the release of gut peptides (glucagon like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP)

These are broken down by dipeptidyl peptidase 4 (DPP4).

DPP-4 inhibitors: Prevent breakdown and therefore increase endogenous GLP1 and GIP levels. Examples include **sitagliptin**, **vildagliptin**, **saxagliptin** and **linagliptin**. They are well tolerated and are weight neutral

GLP-1 receptor agonists: Mimic GLP1 but are modified to resist DPP4

They have to be given by SC injection but have a key advantage over DPP4 inhibitors: they decrease appetite at the level of the hypothalamus. Thus lower blood glucose and result in **weight loss**

Examples include **exenatide** (twice daily), **exenatide MR** (once weekly) and **liraglutide** (once daily)

Incretin based therapies **do not cause hypoglycaemia**

SGLT2 inhibitors

- SGLT2 inhibitors(Empagliflozin, dapagliflozin, canagliflozin):increases glucose excretion in the proximal tubulesSide
- effects: UTI, candidal infections, euglycemic DKA
- Advantages: Weight loss, decreases CVD risk, slowsprogression of CKD

Insulin

Subcutaneous multiple dose insulin therapy

The rate of absorption of insulin may be influenced by the insulin formulation, the site, depth and volume of injection, skin temperature (warming), local massage and exercise

once absorbed into the blood, insulin has a half life of just a few minutes.

Excretion is hepatic and renal, so insulin levels are elevated in hepatic or renal failure.

11.10 Duration of action (hrs) of insulin preparations

Insulin	Onset	Peak	Duration
Rapid-acting (insulin analogues – lispro, aspart, glulisine)	<0.5	0.5–2.5	3–4.5
Short-acting (soluble (regular))	0.5–1	1–4	4–8
Intermediate-acting (isophane (NPH), lente)	1–3	3–8	7–14
Long-acting (bovine ultralente)	2–4	6–12	12–30
Long-acting (insulin analogues – glargine, detemir)	1–2	None	18–24

Insulin analogues have largely replaced soluble and isophane insulins, especially for type 1 diabetes, because they allow more flexibility and convenience. Unlike soluble insulin, which should be injected 30 mins before eating, rapid acting insulin analogues can be administered immediately before, during or even after meals.

Long acting insulin analogues are better able than isophane insulin to maintain 'basal' insulin levels for up to 24 hrs, so need only be injected once daily

The **complications** of insulin therapy include:

- Hypoglycaemia
- Weight gain.
- Peripheral oedema
- Insulin antibodies
- Local allergy (rare).
- Lipodystrophy at injection site

A common problem is **fasting hyperglycaemia** (the 'dawn phenomenon') caused by the release of counter regulatory hormones during the night, which increases insulin requirement before wakening

insulin dosing regimens

The choice of regimen depends on

the desired degree of glycaemic control, the severity of insulin deficiency, the patient's lifestyle, and their ability to adjust the insulin dose.

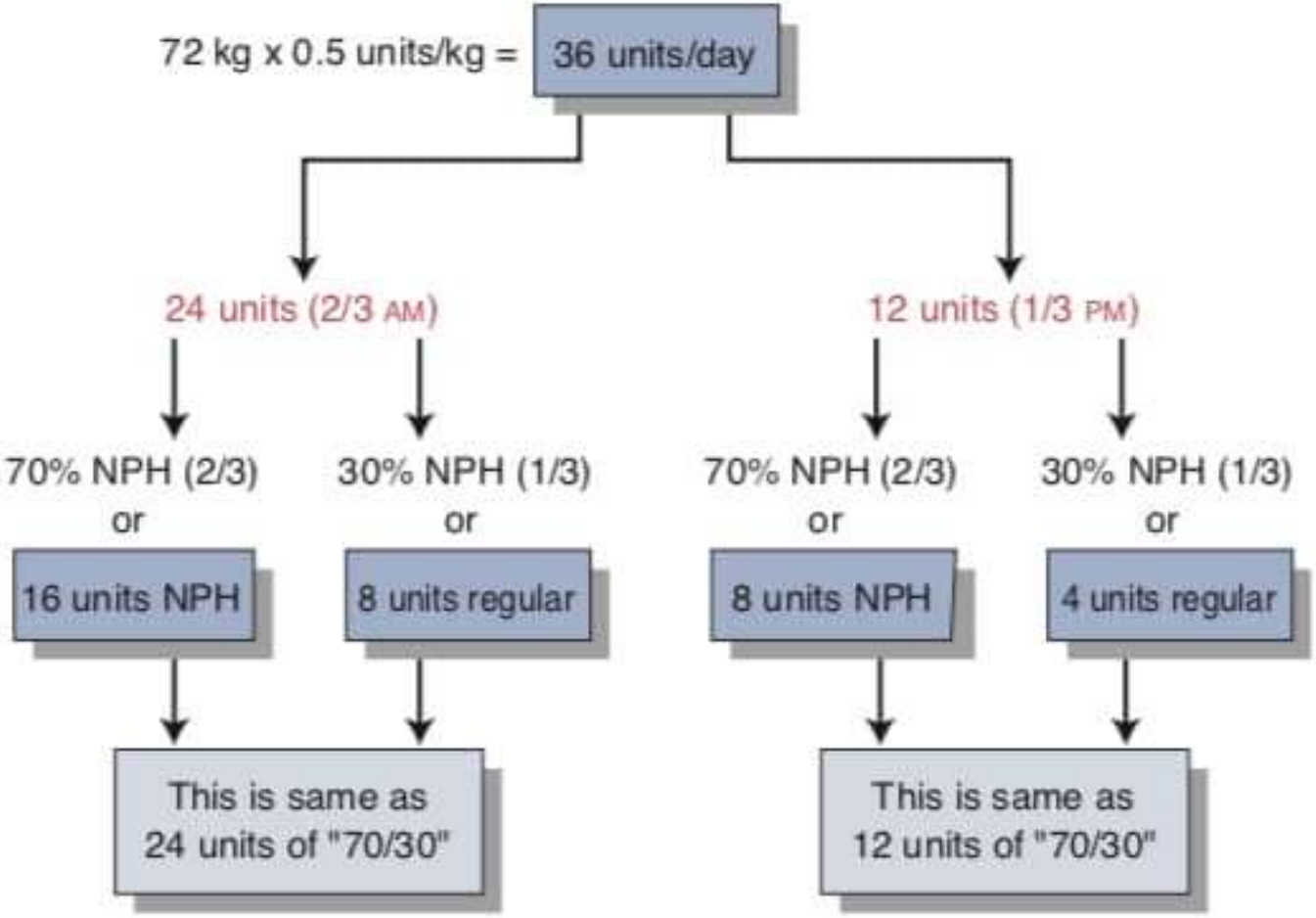
Most people with type 1 diabetes require two or more insulin injections daily. In type 2 diabetes, insulin is usually initiated as a once daily long acting insulin, with or without oral hypoglycaemic agents

Twice-daily administration:

A short acting and intermediate acting insulin (usually soluble and isophane), given before breakfast and the evening meal, is the simplest regimen. Initially, two thirds of the daily insulin is given in the morning in a ratio of short to intermediate acting of 1 to 2; the remainder is given in the evening.

Premixed formulations containing fixed proportions of soluble and isophane insulins are useful if patients have difficulty mixing insulins, but the individual components cannot be adjusted independently. Fixed mixture insulins also have altered pharmacokinetics, i.e. the peak insulin and time to peak effect are significantly reduced compared with the same insulins injected separately

FIGURE 4-7 **A typical two-third to one-third insulin dosing regimen in a 72 kg patient.**



Multiple injection regimens:

These are popular, with short acting insulin before each meal, plus intermediate or long acting insulin injected once or twice daily (basal bolus regimen). This regimen allows greater freedom of meal timing and more variable day to day physical activity.

Portable pumps:

Pumps infusing continuous SC or IV insulin can achieve excellent glycaemic control but will not be widely adopted until they become cheaper and incorporate a miniaturised glucose sensor

Transplantation

Whole pancreas transplantation presents problems relating to exocrine pancreatic secretions and long term immunosuppression is necessary. At present, the procedure is usually undertaken only in patients with **ESRF** who require a combined pancreas/kidney transplantation and in whom diabetes control is particularly difficult, e.g. because of recurrent hypoglycaemia.

Transplantation of **isolated pancreatic islets** (usually into the liver via the portal vein) has been achieved safely in an increasing number of centres around the world. Progress is being made towards meeting the needs of supply, purification and storage of islets, but the problems of transplant rejection, and of destruction by the patient's autoantibodies against β cells, remain

SPECIFIC TREATMENT OF CHRONIC DIABTIC COMPLICATION

- Macrovascular disease ; reduction of risk factors , daily aspirin, strict glycemic control .
- Nephropathy ;

ACI inhibitors

- Neuropathy ;

(NSAIDS, tricyclic antidepressants and gabapentin)

- Diabetic foot ;

the best treatment is prevention(regular foot care, podiatrists visits) .Amputation is the last resort .

- Retinopathy ;

referral to ophthalmologist and possible photocoagulation

Metformin	• Good glucose-lowering effect • Oral route • Low cost • No hypoglycemia	• Risk of lactic acidosis in patients with impaired kidney function, heart failure, hypoxemia, alcoholism, cirrhosis, contrast exposure, sepsis, and shock • Gastrointestinal side effects
Insulin secretagogues: • Sulfonylureas: glyburide, glibenclamide, glipizide, gliclazide, and glimepiride • Glinides: repaglinide and nateglinide	• Good glucose-lowering effect • Low cost • Oral route	• Risk of hypoglycemia • Significant drug-to-drug interactions • Risk of cardiovascular events
Thiazolidinediones: pioglitazone	• Good glucose-lowering effect • Oral route • No hypoglycemia	• Slow onset of action • Contraindicated in patients with heart failure, hemodynamic instability, and hepatic dysfunction
Sodium glucose co-transporter 2 inhibitors: canaglifozin and dapaglifozin	• Modest glucose-lowering effect • Oral route • No hypoglycemia	• Increased risk of urinary and genital tract infections • Risk of dehydration
α-Glucosidase inhibitors: acarbose and miglitol	• Mild glucose-lowering effect • Oral route • No hypoglycemia	• Gastrointestinal side effects • Contraindicated in patients with inflammatory bowel disease, partial bowel obstruction, or severe renal or hepatic disease
Glucagon-like peptide-1 receptor agonists: exenatide and liraglutide	• Good glucose-lowering effect • No hypoglycemia • Reduction of insulin requirement	• Subcutaneous injections • Gastrointestinal side effects • Decreased appetite and weight loss • Concern regarding acute pancreatitis
Dipeptidyl peptidase-4 inhibitors: sitagliptin, saxaglitpin, linagliptin, and alogliptin	• Moderate glucose-lowering effect • Oral route • No hypoglycemia	• Concern regarding acute pancreatitis

- **Thank you**