TYPE 2 DIABETES IN YOUTH

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- INTRODUCTION — Since the early 1990s, the incidence of type 2 diabetes mellitus (T2DM) has increased in children and adolescents and is linked to the rise in childhood obesity. T2DM and its co-morbidities are risk factors for vascular disease later in life. As a result, it is imperative for health care providers to identify and treat children and adolescents with this disorder. Type 2 diabetes, formerly thought to occur only in adults, is now developing in children and adolescents (between age of 12-18 years)as childhood obesity rates have

Characteristic of Childhood T2DM:

Disease in the child who typically

- Is overweight or obese (BMI ≥ 85th –94th and>95th percentile for age and gender, respectively).
- Has a strong family history of T2DM.
- Has substantial residual insulin secretory capacity at diagnosis (reflected by normal or elevated insulin and C-peptide concent).
- Has insidious onset of disease.
- Demonstrates insulin resistance (including clinical evidence of polycystic ovarian syndrome or acanthosis nigricans).

- lacks evidence for diabetic autoimmunity (negative for autoantibodies typically associated with T1DM). The appearance of diabetes-related autoantibodies has been shown to be able to predict the appearance of diabetes type 1 before any hyperglycemia arises, the main ones being islet cell autoantibodies, insulin autoantibodies, autoantibodies targeting the 65-kDa isoform of glutamic acid decarboxylase (GAD) autoantibodies targeting the phosphatase related IA-2 molecule, and zinc transporter autoantibodies (ZnT8)

- These patients are more likely to have hypertension and dyslipidemia than are those with T1DM.

EPIDEMIOLOGY – A rise in prevalence of type 2 diabetes mellitus (T2DM) is occurring worldwide in parallel with an increasing prevalence of obesity in children . In the early 1990s, T2DM represented about 3 percent of pediatric diabetes in the United States. By 2003, T2DM represented about 20percent of pediatric diabetes.

RISK FACTORS — The following factors are associated with an increased risk for childhood onset T2DM:

- Obesity
- Positive family history
- Specific racial and ethnic groups
- Female gender
- Conditions associated with insulin resistance as:

1- Obesity — Excess adipose tissue and obesity are the most important risk factors for T2DM. Body mass index (BMI) is commonly used as an index of weight in relation to height, and is equal to the body weight in kilograms divided by the height in meters squared The following terminology is used to describe states of excess weight in childhood and adolescence

- Overweight – BMI ≥85th and <95th percentile.
- Obesity – BMI ≥95th percentile.

2-Genetic susceptibility — Studies in adults suggest that T2DM is caused by a complex interaction of environmental and genetic factors in a susceptible individual. In the majority of patients with T2DM, genetic susceptibility appears to be due to the expression of multiple genes (polygenic). Evidence for a strong genetic component for T2DM is based upon observations that the risk of diabetes is significantly increased in close relatives of an affected patient.

3-Age and gender — About 40 percent of pediatric cases present between 10 and 14 years of age, and the remaining 60 percent between 15 and 19 years.

Girls are 1.3 to 1.7 times more likely than boys to develop T2DM during adolescence .Although the reason for this increased risk in girls is not clear, it may be related to an increased risk of insulin resistance, as seen in adolescent girls with polycystic ovary syndrome (PCOS). Many patients with pediatric T2DM present at the onset of puberty (mean age of 13.5 years) ,a stage of development when there is increased insulin resistance.

During puberty, insulin sensitivity decreases by approximately 30 percent ,related to the increased activity of growth hormone and insulin-like growth factor-1.

4-Prenatal exposures — One hypothesis suggests that prenatal exposure to maternal under nutrition or gestational diabetes causes metabolic and hormonal changes that promote obesity and insulin resistance and increase T2DM risk in adult offspring. This phenomenon has been termed “metabolic programming”.

5-Low birth weight for gestational age resulting from intrauterine undernutrition is associated with insulin resistance. The combination of low birth weight and weight gain in adult middle age increases insulin resistance and the risk for T2DM.

6- Polycystic ovary syndrome — Insulin resistance is a component of PCOS and may play a role in its pathogenesis. Patients with PCOS are at increased risk for developing T2DM.

- Gestational diabetes – The abnormal intrauterine metabolic environment of a diabetic pregnancy appears to increase the risk of T2DM. Intrauterine exposure to hyperglycemia and hyperinsulinemia may affect the development of adipose tissue and pancreatic beta cells, leading to future obesity and altered glucose metabolism.

CLINICAL PRESENTATION — Childhood type 2 diabetes mellitus (T2DM) can present in several ways

- Asymptomatic presentation – Approximately 40 percent.
- Symptomatic presentation (eg, polydipsia and polyuria) without ketonuria or acidosis – 57 to 70 percent.
- Diabetic ketoacidosis (DKA) – 5 to 13 percent
- Hyperglycemic hyperosmolar state (HHS) – Uncommon but serious.
- Asymptomatic — Approximately 40 percent of children and adolescents with T2DM are identified by screening and are asymptomatic at presentation. These patients may be screened for T2DM because of risk factors, or because glycosuria was detected on a urinalysis obtained as part of a routine physical examination.

- Symptomatic — The main symptoms of T2DM are due to hyperglycemia, and commonly include polyuria, polydipsia, and nocturia, as in patients with T1DM. Recent weight loss is infrequently reported in children who present with T2DM, whereas it is common among those presenting with T1DM

In adolescent girls, vaginal discharge or vulvovaginitis due to candidiasis can be the initial chief complaint.

- Diabetic ketoacidosis — Occasionally, children with T2DM present with DKA (hyperglycemia, ketonuria, and acidosis). The reported frequency of diabetic ketoacidosis (DKA) as the initial presentation for childhood T2DM varies from 5 to 13 percent .Presentation with DKA appears to be most common in ethnic minority youth, in whom up to 25 percent present with DKA.

- Hyperosmolar hyperglycemic state — Adolescents with T2DM may present with hyperosmolar hyperglycemic state (HHS), a condition characterized by marked hyperglycemia (plasma glucose >600 mg/dL), hyperosmolality (serum osmolality >330 mOsm/kg) and severe dehydration, but little or no ketonuria .It is usually seen in adult patients with poorly controlled T2DM, but has been reported in a few case series of adolescents, most of whom were African-American. Recognition of HHS is important because it is characterized by more severe dehydration than typical DKA, and has high morbidity and mortality if not adequately treated.

Differential diagnosis :

- Type 1 DM.
- Atypical diabetes mellitus (ADM).
- Maturity-onset diabetes of the young (MODY).
- Diabetes secondary to mutations in mitochondrial deoxyribonucleic acid (DNA).
- Genetic defects of the beta cell.
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.
- Endocrinopathies.
- Drug- or chemical-induced diabetes.

1- Type 1 DM

differentiating between the two types is based upon a combination of the clinical presentation and history, often supported by laboratory studies

Clinical characteristics:

- Body habitus – Patients with T2DM are usually obese, (body mass index (BMI) ≥95th percentile for age and gender). In contrast, children with type 1 diabetes (T1DM) are often not overweight and usually have a recent history of weight loss, although up to 25 percent are overweight or obese (BMI ≧85th).

- Age – Youth with T2DM generally present after the onset of puberty, at a mean age of 13.5 years, and almost all present after 10 years of age .By contrast, about 50 percent of youth with T1DM present prior to 10 years of age.
- Insulin resistance – Patients with T2DM usually have clinical features associated with insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovary syndrome (PCOS), which are not commonly seen in children with T1DM.

- Family history – 75 to 90 percent of those with type 2 diabetes have an affected close relative, whereas up to 10 percent of patients with type 1 diabetes have an affected close relative.
- Ethnicity – In the United States, most pediatric patients with T2DM belong to minority racial and ethnic groups including non-Hispanic Black, Hispanic, Native American, Asian American, and Pacific Islanders.
- Insidious onset of diseases
- Ketoacidosis ,Patients with T1DM are somewhat more likely to present with ketoacidosis, due to severe insulin deficiency, but this presentation occurs in 5 to 10 percent of adolescents with T2DM.

Laboratory testing:

- Pancreatic autoantibodies – If present, these autoantibodies support the diagnosis of T1DM. Up to 10 percent of adolescents with phenotypically diagnosed T2DM will have evidence of beta cell autoimmunity, supporting the value of antibody testing to help distinguish between the two types of diabetes.

- Insulin and C-peptide levels – A C-peptide level (and/or a serum insulin level if insulin therapy has not yet been initiated) obtained after glycemic control has been established may also provide clinically useful information. Low C-peptide levels support a diagnosis of T1DM, but should be interpreted with caution, because they can also be low at the time of diagnosis of T2DM.

2- **Atypical diabetes** (Ketosis-prone diabetes)

Diagnosis:

1. Sudden in onset
2. No obesity
3. Positive FH
4. May present with DKA
5. Absence of markers of autoimmunity
6. No insulin resistance
7. There is decrease in first phase insulin secretion.

3- MODY

- is defined by the following criteria

1. Its prevalence is 5% of all patients with type 2 DM.
2. The onset of MODY is early in life (possibly immediately after birth.
3. Hyperglycemia is diagnosed before 25 years of age in at least one or two member of family.
4. Normal c-peptide level.
5. Over weight and obesity is uncommon.
6. MODY is non-insulin-requiring and non ketotic.
7. MODY is inherited as an autosomal dominant.

SCREENING:

Indications — The American Diabetes Association (ADA) recommends screening asymptomatic children for T2DM if they meet the following screening criteria:

- Overweight or obese (BMI ≥85th percentile) **and** have two or more of the following additional risk factors.
- T2DM mellitus in a first- or second-degree relative.
- Member of a high-risk racial/ethnic group: Native American, non-Hispanic Black, Hispanic, Asian American, or Pacific Islander.
- Signs of insulin resistance or conditions associated with insulin resistance (eg, hypertension, dyslipidemia, acanthosis nigricans, and polycystic ovary syndrome, or small for gestational age birth weight).
- Maternal history of diabetes or gestational diabetes during the child's gestation.

- The ADA recommends beginning screening for asymptomatic individuals at age 10 years or at onset of puberty (whatever comes first), and repeating the screening every three years.
- Clinicians should also screen for diabetes in patients with typical presenting symptoms, such as polydipsia, polyuria, blurred vision, or weight loss, regardless of risk factors.
- Screening tests — Screening for diabetes can be done by measuring hemoglobin A1C (A1C), fasting plasma glucose (FPG), or performing an oral glucose tolerance test (OGTT). Abnormal results should be confirmed either by repeating the initial test on another day, or performing a different test.

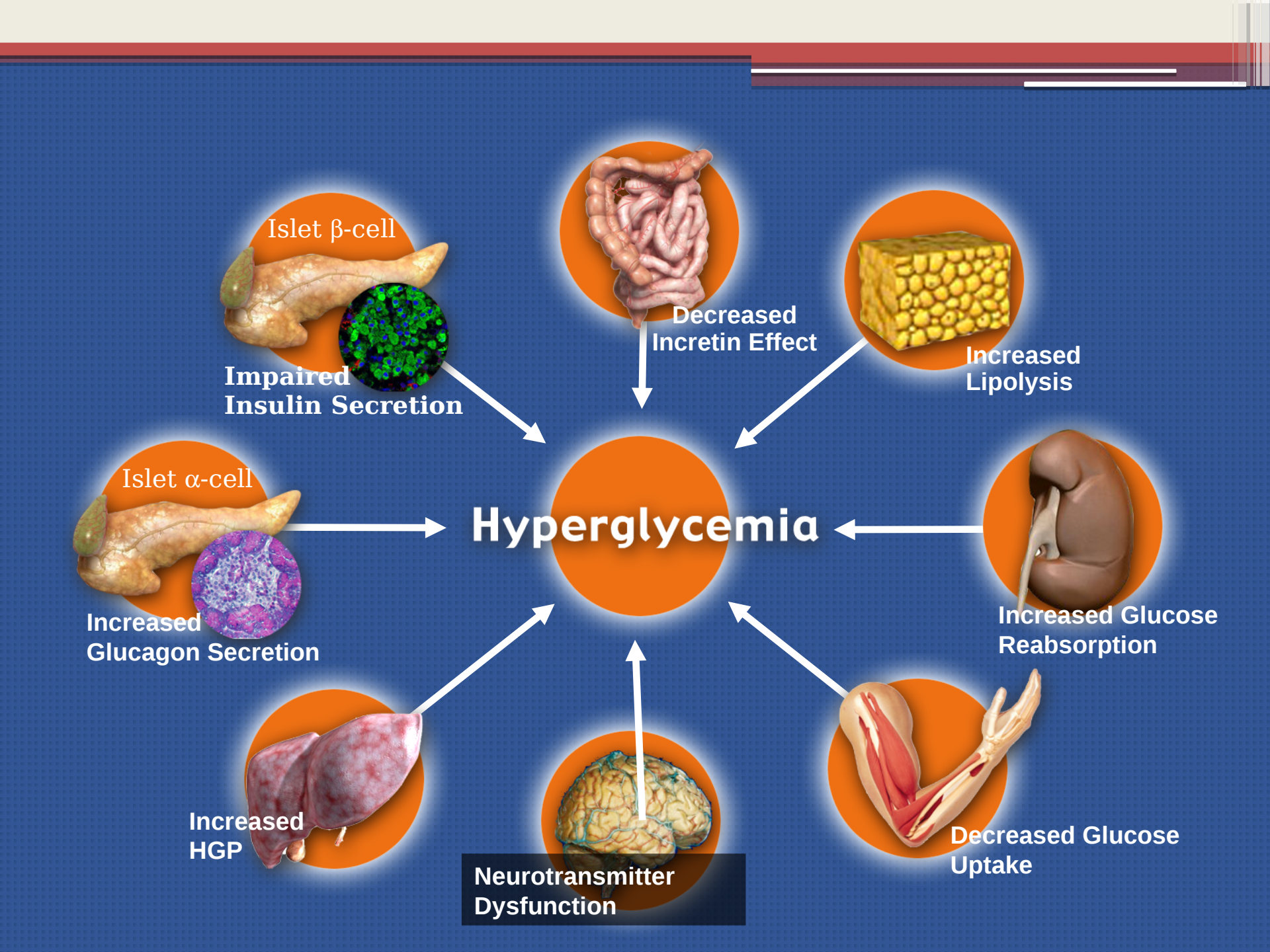
Diagnosis:

.Type 2 diabetes is defined according to the American Diabetes Association criteria, as

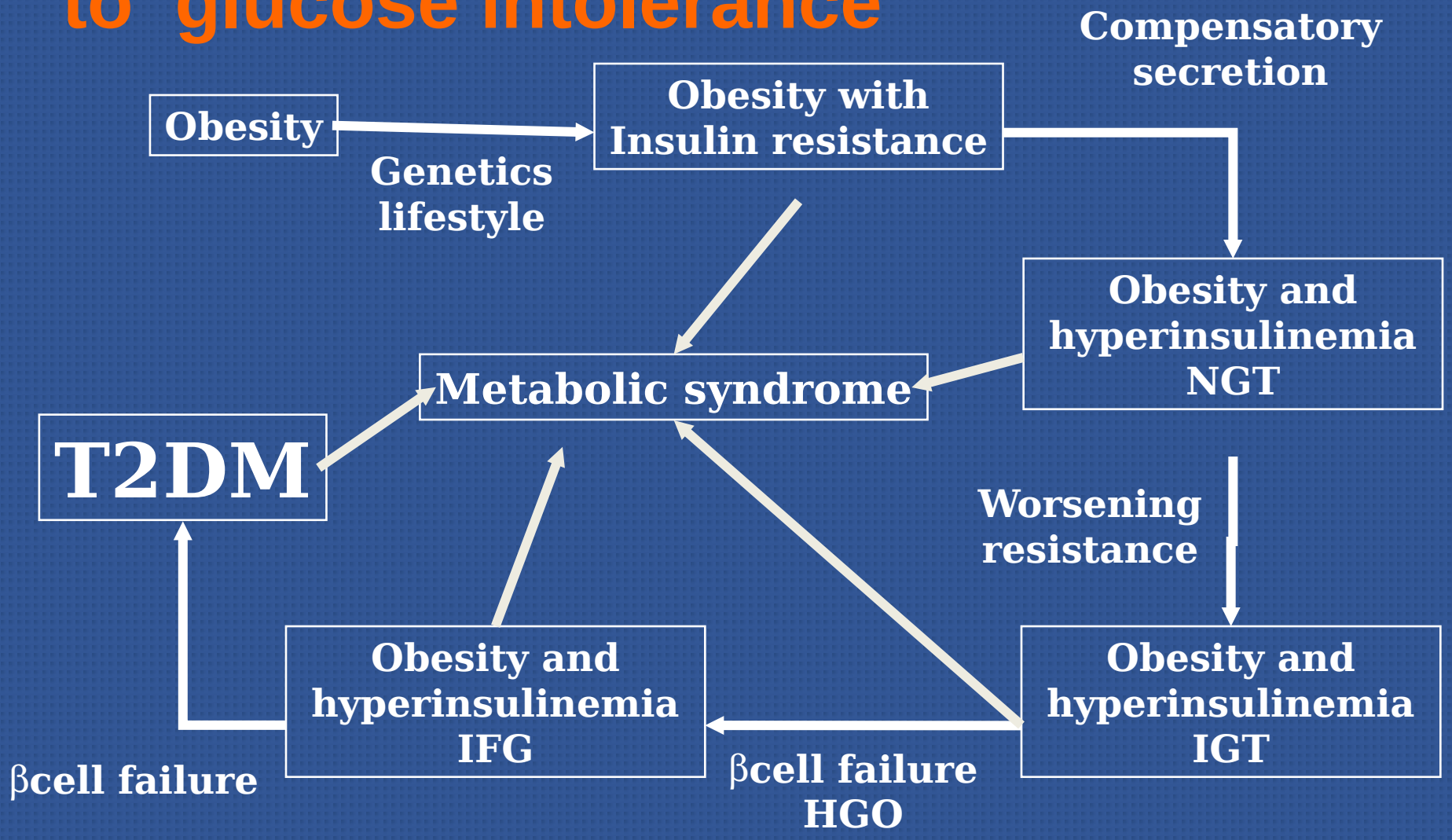
1. HbA1c ≥ 6.5% (test performed in an appropriately certified laboratory). or
2. Fasting (defined as no caloric intake for at least 8 hours) plasma glucose ≥126 mg/dL (7.0 mmol/L). or
3. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test performed as described by the World Health Organization by using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. or
4. A random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia.

Pathophysiology

1) Insulin resistance.
2) Defective insulin secretion.
3) Increased glucose production by the liver.
4) Incretin hormone deficiency and resistance.
5) Increased renal tubular reabsorption of glucose.
6) Hyperglucogenemia.
7) Amylin deficiency.
8) Rule of CNS.

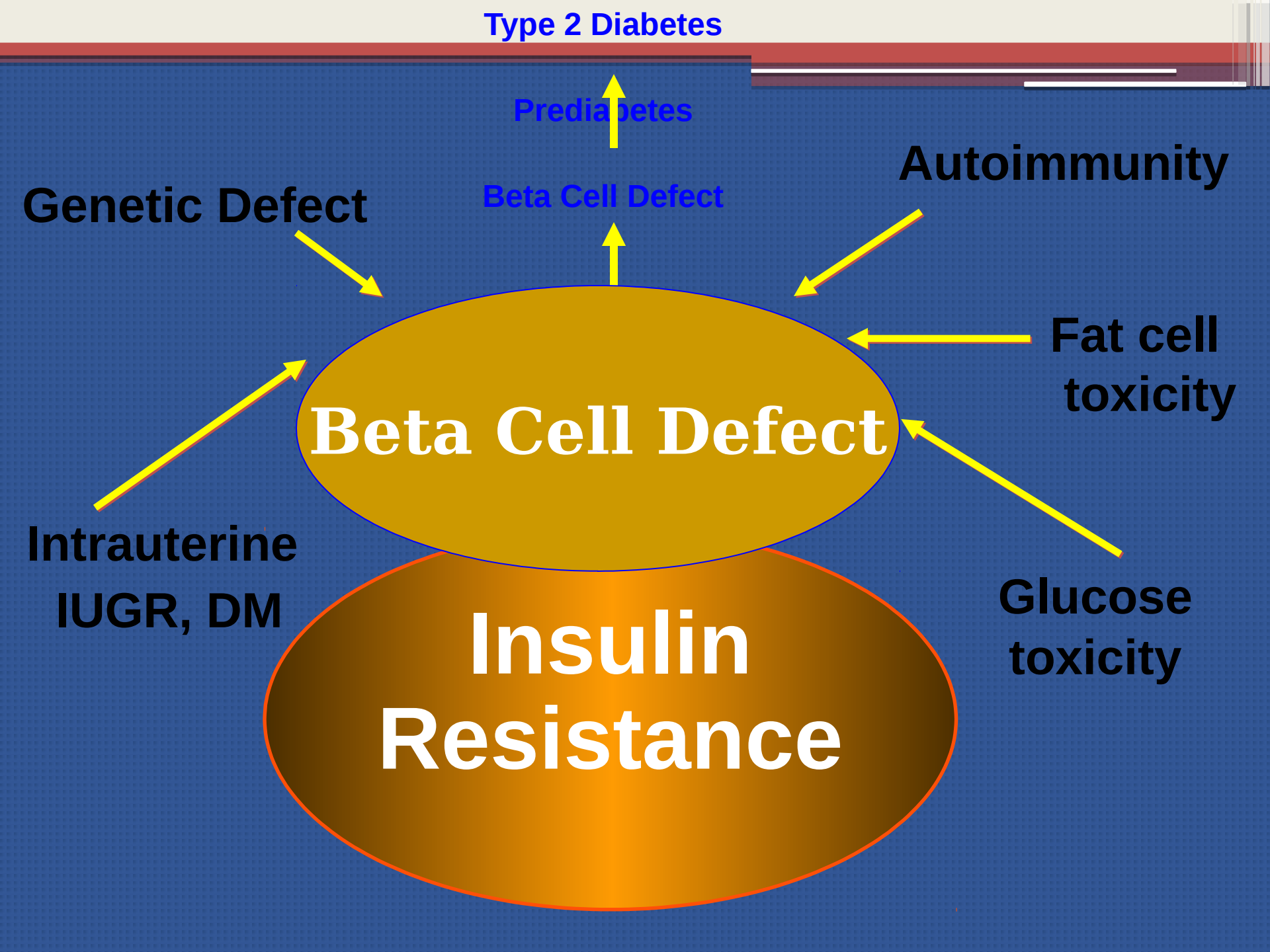

Islet β-cell
Impaired
Insulin Secretion
Decreased
Incretin Effect
Increased
Lipolysis
Islet α-cell
Increased
Glucagon Secretion
Hyperglycemia
Increased Glucose
Reabsorption
Increased
HGP
Neurotransmitter
Dysfunction
Decreased Glucose
Uptake

Progression of insulin resistance to glucose intolerance



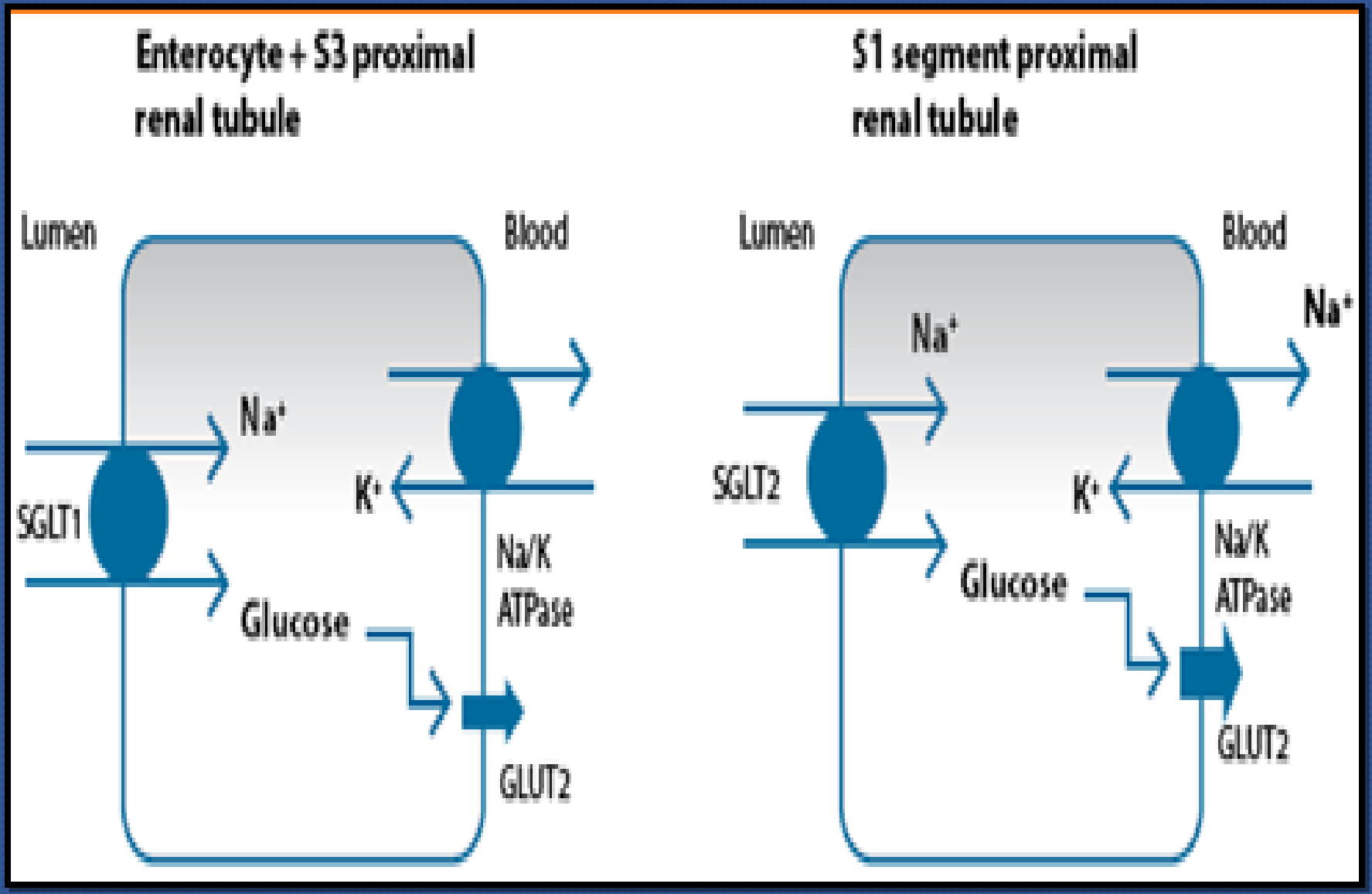
- 2- beta cell dysfunction:
- Causes

Type 2 Diabetes



- 3) RULES OF INCRETIN: **Incretins** are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, before blood glucose levels become elevated. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. As expected, they also inhibit glucagon release from the alpha cells of the Islets of Langerhans. The two main candidate molecules that fulfill criteria for an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (also known as: glucose-dependent insulinotropic polypeptide or GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

4) Rules of kidneys: Sodium-dependent glucose cotransporters (or sodium-glucose linked transporter, SGLT) are a family of glucose transporter found in the intestinal mucosa(enterocytes of the small intestine (SGLT1) and the proximal tubule of the nephron (SGLT2 in PCT and SGLT1 in DCT). They contribute to renal glucose reabsorption. In the kidneys, 100% of the filtered glucose in the glomerulus has to be reabsorbed along the nephron (98% in PCT, via SGLT2).


Enterocyte + S3 proximal renal tubule
Lumen
Blood
Na+
K+
SGLT1
Na/K ATPase
Glucose
GLUT2
S1 segment proximal renal tubule
Lumen
Blood
Na+
Na+
SGLT2
K+
Na/K ATPase
Glucose
GLUT2

Therapy

GOALS — The goals of managing a child or adolescent with type 2 diabetes mellitus (T2DM) include the following:

- To achieve and maintain near-normal glycemic control.
- To improve insulin sensitivity and secretion, which results in improved glycemic control.
- To identify and treat, if necessary, comorbidities, such as hypertension, dyslipidemia, and nonalcoholic fatty liver disease To prevent the vascular complications of T2DM.

- Target:
- Hemoglobin A1C (A1C) <7 percent **and** a
- Fasting plasma glucose (FPG) of <130 mg/dL (7.2 mmol/L).
- PPBS ≤180

Types:

- NONPHARMACOLOGIC THERAPY:

1- Weight reduction

Weight goals — In children and adolescents with T2DM, the optimal goal for body weight is a body mass index (BMI) <85th percentile for age and gender.

Advantages:

- Improve insulin sensitivity and resistance.
- To improve glycemic control.

Assessment and intervention should focus on the following:
Eating habits:
Reduce total dietary fat and calorically sweetened beverages.
Promote intake of vegetables and fruits.
Reduce consumption of food away from home.
Reduce portion sizes.
Do not skip breakfast.
Parental guidance:
Do not strictly restrict highly-palatable foods, because this is predicted to lead to covert consumption.
Do not pressure the child to eat or use food as a reward.
Energy intake goals:
Children 6 to 12 years: balanced macro-nutrient diet, no fewer than 900 kcal per day.
Adolescents 13 years and older: balanced macro-nutrient diet, no fewer than 1200 kcal per day.
For children and adolescents who are >120 percent of ideal body weight with serious medical complications that require rapid weight loss, a medically supervised Protein Sparing Modified Fast Diet (PSMF) may be utilized in a short-term intervention (typically 10 weeks).

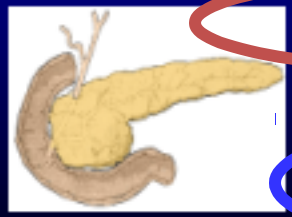
2- Physical activity — Increased physical activity, independent of its effect on body weight, improves insulin sensitivity. Youth with T2DM should be encouraged to engage in moderate to vigorous physical activity for at least one hour daily if possible, and to limit non-academic “screen time” (eg, television, video game, and computer) to less than two hours daily.

- PHARMACOLOGICAL THERAPY:
  - sites of action.

Therapy for Type 2 Diabetes: Sites of Action

Pancreas

Impaired Insulin Secretion = Insulin Deficiency



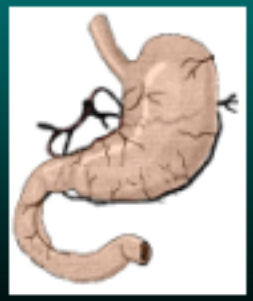
- ↑ Sulfonylurea
- ↑ Repaglinide/Nateglinide
- Exogenous Insulin Rx

GLP

Gut

Carbohydrate Metabolism

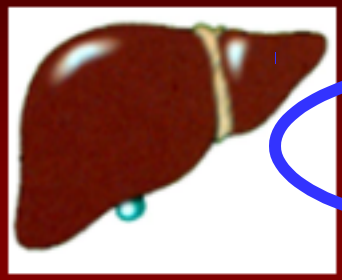
- ↓ Acarbose
- ↓ Miglitol



Hyperglycemia

Liver

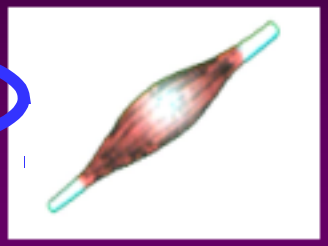
- ↑ Hepatic Glucose Production



- ↓ Metformin

Muscle

- ↓ Glucose Uptake = Insulin Resistance
- ↑ Rosiglitazone
- ↑ Pioglitazone



Types of therapy:

- 48% Treated with insulin alone.
- 44% With oral agents.
  - 71% Metformin.
  - 46% Sulfonylurea.
  - 9% TZD.
  - 4% Meglitinide.
- 8% Lifestyle.

- TYPES:

1- Metformin

Indication: its the first-line therapy for most patients, in conjunction with nonpharmacologic therapy.

Mechanism of action: It improves insulin responsiveness by increasing insulin-mediated glucose uptake in the peripheral tissues, and also by decreasing hepatic glucose production. Metformin has the additional benefit of producing modest weight loss; this is in contrast to the weight gain often associated with insulin, Thiazolidinedione, or Sulfonylurea therapy.

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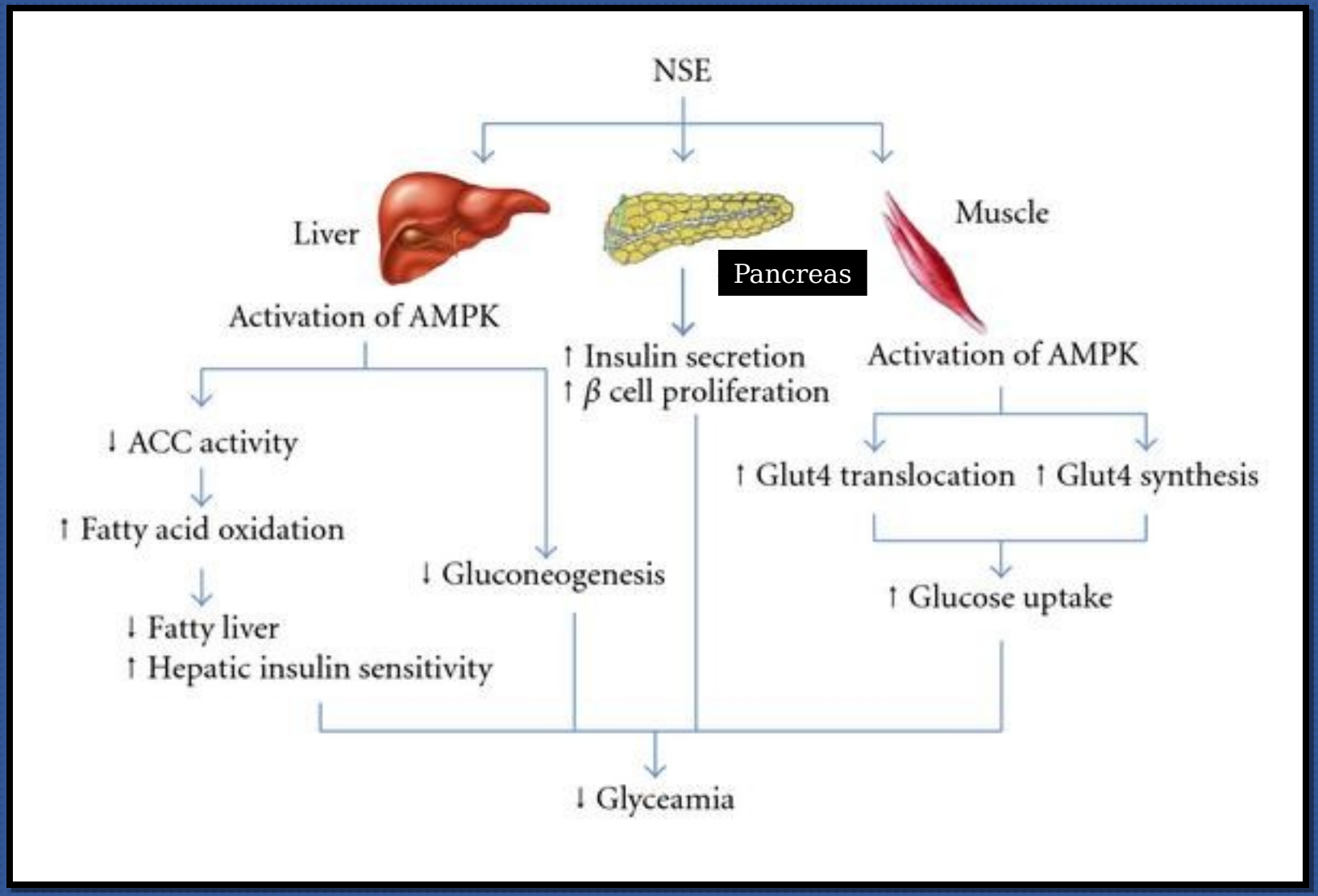
Activation of AMPK:



2- Thiazolidinediones: such as Rosiglitazone and Pioglitazone , increase insulin responsiveness and may also improve insulin secretion by preserving pancreatic beta-cell function. The use of Thiazolidinediones in pediatric patients was studied in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. However, these agents are not generally recommended for youth with type 2 diabetes, because of concerns about adverse effects (e.g., cardiovascular concerns with rosiglitazone, bladder cancer concerns with pioglitazone, and bone concerns with both). They are not approved by the FDA for use in pediatric patients with T2DM.

3- Insulin secretagogues (i.e. Sulfonylureas such as Glyburide and Glimepiride , or Meglitinides) increase insulin secretion. In adults, these agents have been shown to improve glycemic control, but also increase body weight and have moderate risks for hypoglycemia. In a randomized trial in 285 youth with T2DM, Glimepiride and Metformin improved hemoglobin A1C (A1C) levels to a similar degree (A1C reduced to <7 percent in 42 and 48 percent of subjects, respectively). However, Glimepiride caused weight gain, whereas metformin did not (0.26 kg/m^2 for glimepiride, versus -0.33 kg/m^2 for metformin, $p = 0.003$).

4- Incretin Mimetics (e.g. Exenatide, Liraglutide) act to increase glucose-dependent insulin secretion from beta cells and help to ensure an appropriate insulin response following ingestion of a meal. These agents are administered by subcutaneous injection. Exenatide and Liraglutide have the potential advantage of promoting modest weight loss, probably due to delayed gastric emptying and possibly through central affects on appetite. Small clinical trials report some weight loss benefit in obese adolescents with and without T2DM.

DPP-IV Inhibitors (e.g., Sitagliptin) increase insulin production and decrease the liver's production of glucose. They do not have significant effects on body weight and do not cause hypoglycemia.

5 – Amylin Analogs (e.g. Pramlintide acetate) are used to slow gastric emptying and suppress glucagon secretion, which leads to suppression of endogenous glucose output from the liver. They are administered by subcutaneous injection and are only approved for use in adult patients taking concomitant insulin. Pramlintide causes modest reductions in glycemia and body weight.

6 - Alpha-glucosidase Inhibitors (e.g. Acarbose) delay the absorption of carbohydrates; lipase inhibitors reduce the absorption of fat. They are less effective for hyperglycemia than metformin or sulfonylureas, and their use is limited by frequent gastrointestinal side effects.

7 - SGLT2 inhibitors for diabetes

Inhibition of SGLT2 leads to a reduction in blood glucose levels. Therefore, SGLT2 inhibitors have potential use in the treatment of type II diabetes. Several drug candidates have been developed or are currently undergoing clinical trials, including:

- Dapagliflozin, approval rejected by Food and Drug. Administration due to safety concerns, but marketed in Europe and Australia.
- Canagliflozin, approved in the United States.
- Ipragliflozin (ASP-1941), in Phase III clinical trials.
- Tofogliflozin, in Phase III clinical trials.
- Empagliflozin (BI-10773), in Phase III clinical trials.

Treatment regimens:

In general, the treatment of type 2 diabetes in children follows the same rationale as does treatment for the disease in adults. The safety and efficacy of oral hypoglycemic therapy in children and adolescents with type 2 diabetes have not been established; however, physicians have prescribed drugs typically used in adults to treat children and adolescents. Among all of the drugs currently in use to treat type 2 diabetes in adults, the US Food and Drug Administration (FDA) has approved only metformin and insulin for use in children.

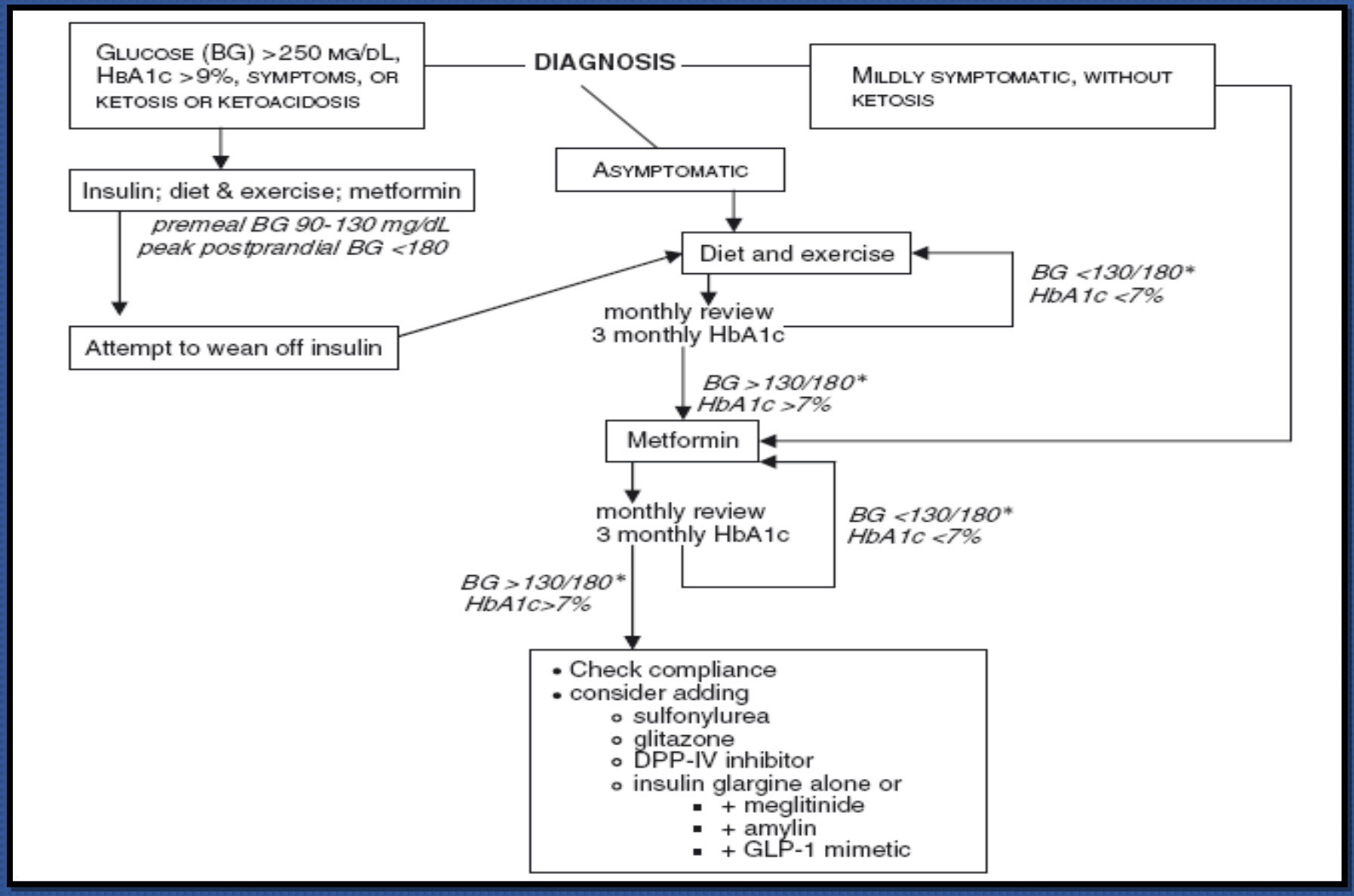
➢Proposed Management Algorithm

1. **Step 1: Life style modification:** If goals in step 1 not achieved after 3 months (fasting glucose level >126 mg/dL or HbA1c level >7%), change to step 2
2. **Step 2: Start drugs:**

- First-line therapy is metformin at 1000-2000 mg/d. Goals include a fasting glucose level goal of less than 126 mg/dL and/or an HbA1c level of less than 7%.If goals in step 2 are achieved, continue therapy.
- If goals in step 2 not achieved after 3 months (fasting glucose level >126 mg/dL or HbA1c level >7%), add another oral hypoglycemic drugs , if no response start step 3

3. **Step 3: Start insulin:**

- 0.4-0.6 U/kg of 24-hour insulin at bedtime (Glargine or Levemir). If combination therapy is adequate, continue therapy. If combination therapy is inadequate after 3 months, intensify insulin therapy until the fasting plasma glucose level is less than 126 mg/dL and the HbA1c level is less than 7%.


Glucose (BG) >250 mg/dL, HbA1c >9%, symptoms, or ketosis or ketoacidosis
DIAGNOSIS
Mildly symptomatic, without ketosis
Asymptomatic
Insulin; diet & exercise; metformin
premeal BG 90-130 mg/dL
peak postprandial BG <180
Diet and exercise
BG <130/180*
HbA1c <7%
monthly review
3 monthly HbA1c
Attempt to wean off insulin
BG >130/180*
HbA1c >7%
Metformin
monthly review
3 monthly HbA1c
BG <130/180*
HbA1c <7%
BG >130/180*
HbA1c>7%
• Check compliance
• consider adding
◦ sulfonylurea
◦ glitazone
◦ DPP-IV inhibitor
◦ insulin glargine alone or
▪ + meglitinide
▪ + amylin
▪ + GLP-1 mimetic

Beginning Insulin Therapy

- Insulin:

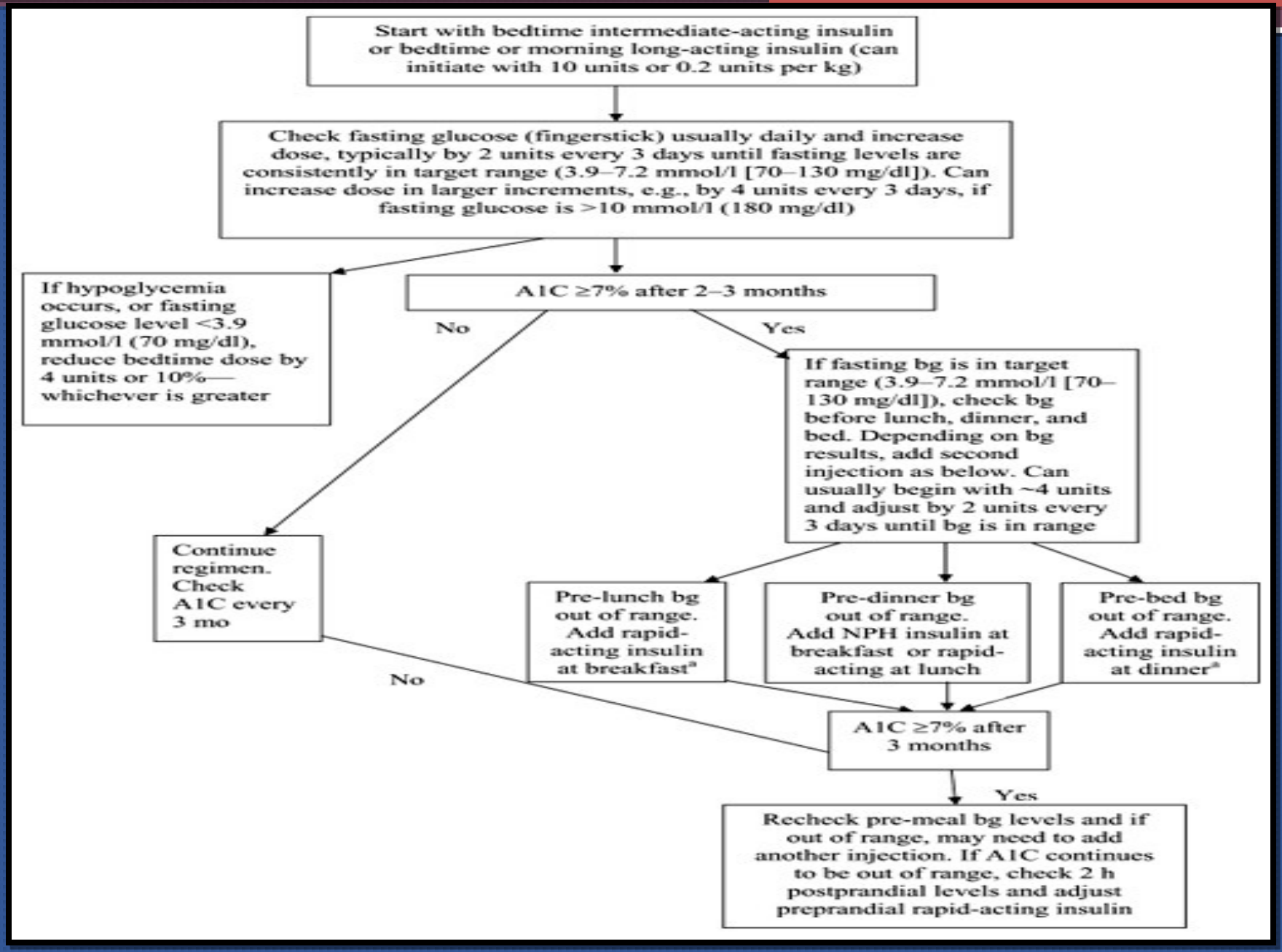
Indication for use:

- Patient presented with DKA.
- Severe metabolic decompensation.
- No response to oral agents.

25-30% of adolescent type 2 patients are being treated with insulin alone.

Initiating Insulin Therapy in Type 2 Diabetes

- **Let blood glucose levels guide choice of insulin:**
  - Select type(s) of insulin and timing of injection(s) based on pattern of patient's sugar (fasting, lunch, dinner, bedtime).
- **Choose from currently available insulin preparations:**
  - **Rapid-acting (mealtime):** lispro, aspart.
  - **Short-acting (mealtime):** regular insulin.
  - **Intermediate-acting (background):** NPH, lente.
  - **Long-acting (background):** ultralente, glargine.
  - **Insulin mixtures.**
- **Provide long-acting or intermediate-acting as basal and rapid-acting as bolus.**
- **Titrate every week.**


Start with bedtime intermediate-acting insulin or bedtime or morning long-acting insulin (can initiate with 10 units or 0.2 units per kg)
Check fasting glucose (fingerstick) usually daily and increase dose, typically by 2 units every 3 days until fasting levels are consistently in target range (3.9–7.2 mmol/l [70–130 mg/dl]). Can increase dose in larger increments, e.g., by 4 units every 3 days, if fasting glucose is >10 mmol/l (180 mg/dl)
If hypoglycemia occurs, or fasting glucose level <3.9 mmol/l (70 mg/dl), reduce bedtime dose by 4 units or 10%—whichever is greater
A1C ≥7% after 2–3 months
No
Yes
If fasting bg is in target range (3.9–7.2 mmol/l [70–130 mg/dl]), check bg before lunch, dinner, and bed. Depending on bg results, add second injection as below. Can usually begin with ~4 units and adjust by 2 units every 3 days until bg is in range
Continue regimen. Check A1C every 3 mo
Pre-lunch bg out of range. Add rapid-acting insulin at breakfast[a]
Pre-dinner bg out of range. Add NPH insulin at breakfast or rapid-acting at lunch
Pre-bed bg out of range. Add rapid-acting insulin at dinner[a]
No
A1C ≥7% after 3 months
Yes
Recheck pre-meal bg levels and if out of range, may need to add another injection. If A1C continues to be out of range, check 2 h postprandial levels and adjust preprandial rapid-acting insulin

Initiating and Adjusting Insulin

Hypoglycemia
or FG >3.89 mmol/l (70 mg/dl):
Reduce bedtime dose by ≥4 units
(or 10% if dose >60 units)

Bedtime intermediate-acting insulin, or
bedtime or morning long-acting insulin
(initiate with 10 units or 0.2 units per kg)

Check FG and increase dose until in target range.

Target range:
3.89-7.22 mmol/L
(70-130 mg/dL

If HbA_{1c} ≤7%...

If HbA_{1c} ≥7%...

Continue regimen; check HbA_{1c} every 3 months

If fasting BG in target range, check BG before lunch, dinner, and bed.
Depending on BG results, add second injection
(can usually begin with ~4 units and adjust by 2 units every 3 days until BG in range)

Pre-lunch BG out of range: add rapid-acting insulin at breakfast

Pre-dinner BG out of range: add NPH insulin at breakfast or rapid-acting insulin at lunch

Pre-bed BG out of range: add rapid-acting insulin at dinner

If HbA_{1c} ≤7%...

If HbA_{1c} ≥7%...

Continue regimen; check HbA_{1c} every 3 months

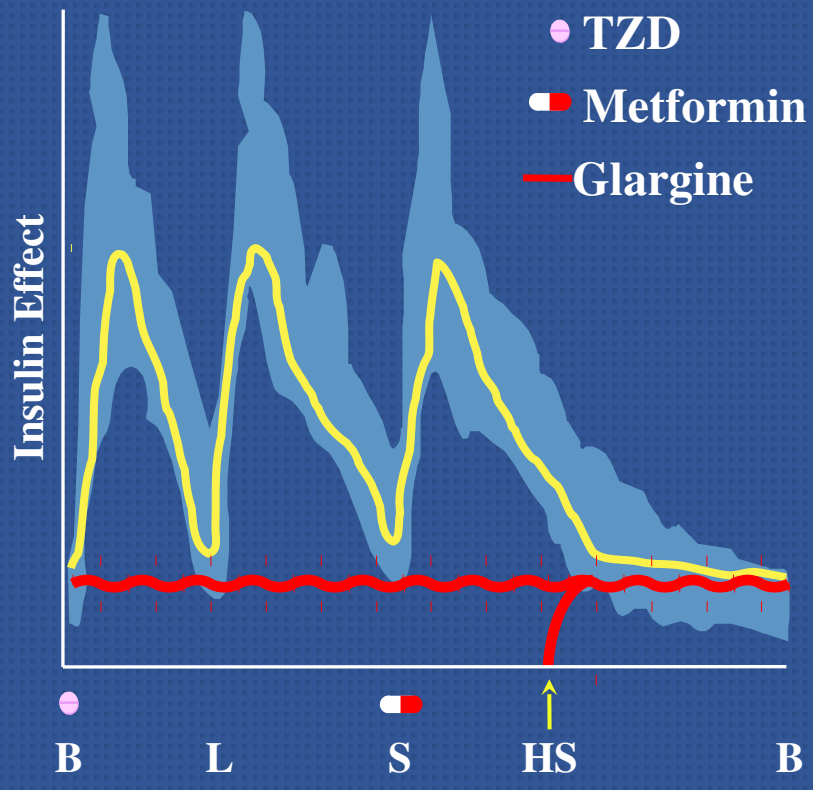
Recheck pre-meal BG levels and if out of range, may need to add another injection; if HbA_{1c} continues to be out of range, check 2-hr postprandial levels and adjust preprandial rapid-acting insulin

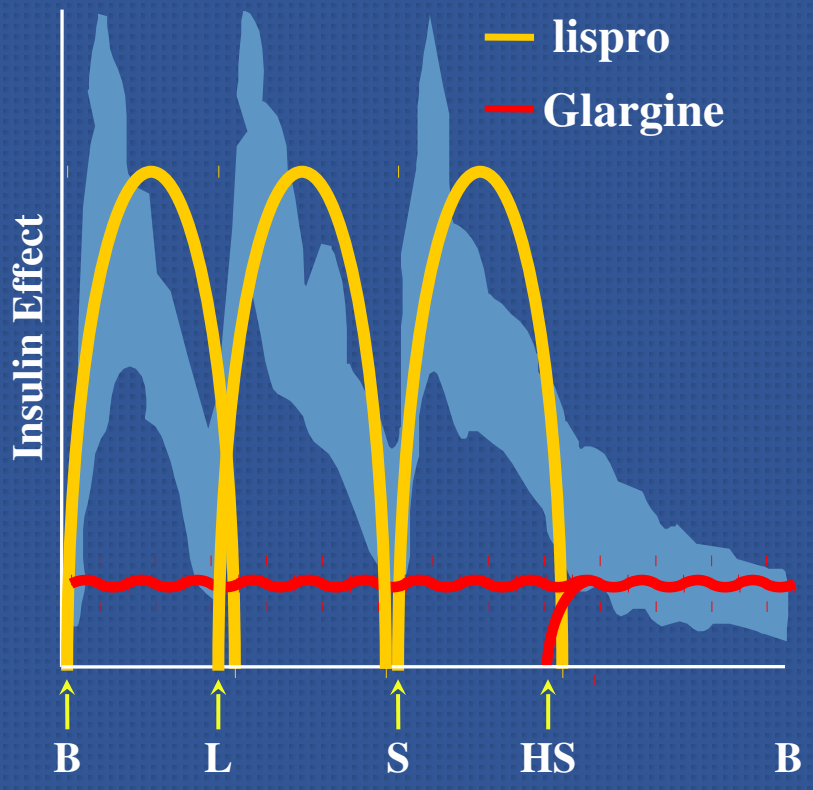
Nathan DM et al. *Diabetes Care.* 2006;29(8):1963-72.

Starting With Basal Insulin: Advantages

- 1 injection with no mixing.
- Slow, safe, and simple titration.
- Low dosage.
- Limited weight gain.
- Effective improvement in glycemic control.

Glargine at HS + Oral Agents or Mealtime Lispro



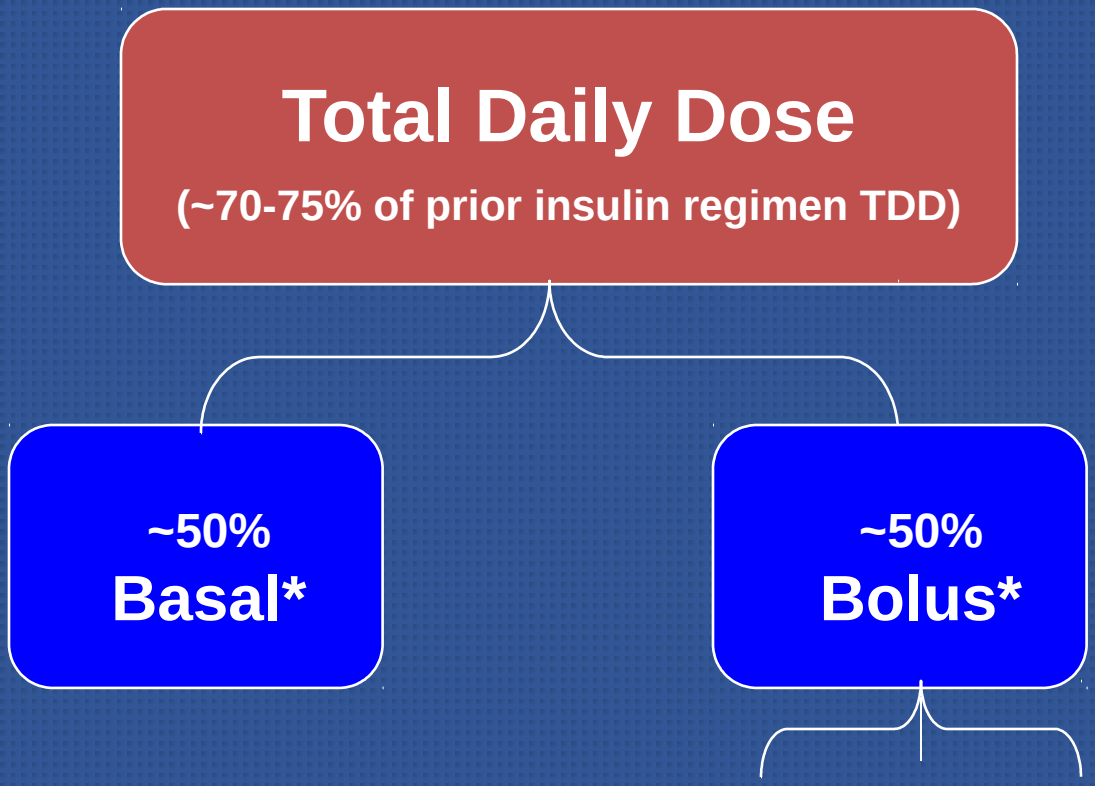


- Who to start:
- Failure to maintain A1c <6.5
- Add-on insulin
  - Once-daily basal insulin (glargine or detemir) – start at 10–20 units a day:
    - Given whenever adherence and supervision are most likely.
    - Titrate as needed to maintain A1c <6.5
  - Addition of short-acting insulin:
    - Inability to maintain A1c in target despite 1 unit/kg long-acting insulin.
    - Evidence for postprandial hyperglycemia.

Advancing Bolus/ Adding Bolus Insulin

- **Indicated when FBG acceptable but:**
  - HbA_{1c} not at goal. and/or
  - Postprandial BG not at goal (<140mg/dl).
- **Insulin options:**
  - To Glargine, add mealtime Regular or Lispro.
  - To bedtime NPH, add morning NPH and mealtime Regular or Lispro.
  - To suppertime 70/30 or 75/25, add morning 70/30 or 75/25.
- **Oral agent considerations:**
  - Usually stop secretagogue (it is redundant to be on insulin and secretagogue).
  - Continue metformin and TZD for additional glycemic and other benefits.

Changing from Other regimens to Basal/Bolus Insulin



*Range: 40 to 60%

Table 3 RECOMMENDATIONS FOR MONITORING COMPLICATIONS OF TYPE 2 DIABETES

Annual screening

- Random spot urine for microalbumin-to-creatinine ratio
- Ophthalmologic exam
- Fasting lipid panel

Monitoring goals

Glycemia	Hb A1c at each visit
	Hb A1c target <7.5% (ages 13-19)
	Fasting glucose <126 mg/dl
Lipid disorders	LDL <100 mg/dl
	TG <150 mg/dl
	HDL >35 mg/dl
Hypertension	Blood pressure check at each visit
	Diagnose and treat if ≥95th percentile for age, sex, height

Complications:

- Although the natural history of type 2 diabetes mellitus in children is not well studied, the experience accumulated over years of treating adults may help to minimize the occurrence of complications in children. (See Prognosis and Clinical).
- Acute complications of type 2 diabetes include hyperglycemia, diabetic ketoacidosis, hyperglycemic-hyperosmolar state,[8] and hypoglycemia. Complications from insulin resistance include hypertension, dyslipidemia, and polycystic ovarian syndrome (PCOS).
- As many as 4% of patients with type 2 diabetes initially present in a hyperglycemic-hyperosmolar coma, which can lead to cerebral edema and death if not promptly recognized and treated.

- Long-term complications of type 2 diabetes mellitus include the following:
- Nephropathy.
- Neuropathy.
- Retinopathy.
- Coronary artery disease.

- **Evaluation for Diabetic Nephropathy:**
- Microalbuminuria is said to be present if urinary albumin excretion is 30 mg/24 h (equivalent to 20 µg/min with a timed specimen or 30 mg of albumin per gram creatinine with a random sample). Testing for albuminuria can be performed using 1 of 3 methods, as follows:

1. Measurement of the ACR in a random spot collection.
2. A 24–hour collection for albumin and creatinine determinations, which allows for simultaneous measurement of creatinine clearance.
3. Timed (eg, 4-h or overnight) collection.

- **Evaluation for Dyslipidemia:**
- Obtain fasting lipid profile after stable glycemia has been achieved and every 2 years thereafter if normal. Optimal lipid levels for children with type 2 diabetes are as follows:

1. Triglycerides optimal level - Less than 150 mg/dL.
2. Low-density lipoprotein (LDL) optimal level - Less than 100 mg/dL.
3. High-density lipoprotein (HDL) optimal level - More than 35 mg/dL.

- Treatments:
- Same as in Adults
  - Efficacy in lipid lowering similar.
  - No evidence for (or against) cardioprotective effect with any intervention.
- Statins.
- Fish Oil/Omega 3 Fatty acids.
- Ezetimibe.
- Nicotinic acid.
- Fibrates.

- Blood pressure.
- Goal < 95%ile for age
  - pharmacologic therapy may be appropriate if > 95%ile AND
    - No improvement with lifestyle modification.
    - Evidence of target organ damage (microalbuminuria).
  - ACE or ARB first line drug.
  - Titrate ACE until BP < 90th %ile.

THANK YOU