Diabetes Mellitus in children and adolescents

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Outline

- Classification
- Type 1 DM
- Epidemiology
- Risk factors
- Definition
- Clinical manifestations

Outline

- Insulin types
- Insulin treatment
- Follow up

Classification

- Type 1 DM
- Type 2 DM
- Gestational Diabetes
- Other types
- MODY (maturity-onset diabetes of youth)
- ……
- ….

Table 607.1 | Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
   A. Immune mediated
   B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
   A. Typical
   B. Atypical
III. Other specific types
   A. Genetic defects of β-cell function (monogenic diabetes)
      i. Neonatal diabetes
         1. Mutations leading to transient neonatal diabetes (*PLAGL1/HYMAI, ZFP57, ABCC8, KCNJ11, HNF1β*)
         2. Mutations leading to permanent neonatal diabetes (ABCC8, KCNJ11, GCK, IPF1, PTF1A, FOXP3, EIF2AK3, GATA6)
      ii. MODY (maturity-onset diabetes of the young) syndromes
         1. MODY 1 chromosome 20, *HNF4α*
         2. MODY 2 chromosome 7, *GCK*
         3. MODY 3 chromosome 12q24.2, *HNF1α, TCF-1*
         4. MODY 4 chromosome 13q12.1, *IPF-1 (PDX1)*
         5. MODY 5 chromosome 17, *HNF1β, TCF-2*
         6. MODY 6 chromosome 2q32, *neuro-D_1/β_2*
         7. MODY 7 chromosome 2p25, *KLF11*
         8. MODY 8 chromosome 9q34, *CEL*
         9. MODY 9 chromosome 7q32, *PAX4*
         10. MODY 10 chromosome 11p15.5, *INS*
         11. MODY 11 chromosome 8p23, *BLK*
      iii. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, and maternally inherited diabetes and deafness)
      iv. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness):
         1. WFS1-Wolframin—chromosome 4p
         2. Wolfram locus 2—chromosome 4q22-24
         3. Wolfram mitochondrial
      v. Thiamine responsive megaloblastic anemia and diabetes
   B. Genetic defects of insulin action
      i. Type A insulin resistance
      ii. Donohue syndrome
      iii. Rabson-Mendenhall syndrome
      iv. Lipoatrophic diabetes syndromes
   C. Other genetic syndromes associated with diabetes (insulin resistance or deficiency)
      i. Down syndrome
      ii. Turner syndrome
      iii. Klinefelter syndrome
      iv. Prader-Willi syndrome
      v. Bardet-Biedl syndrome
      vi. Alström syndrome
      vii. Werner syndrome
   D. Other autoimmune syndromes associated with diabetes
      i. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
      ii. Autoimmune polyendocrinopathy syndromes (APS)
         1. APS-1 (APCED)
         2. APS-2
      iii. Stiff person syndrome
      iv. Anti-insulin receptor antibodies
   E. Drug or chemical induced
      i. Antirejection—cyclosporine, sirolimus
      ii. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
      iii. L-Asparaginase
      iv. β-Adrenergic blockers
      v. Vacor (rodenticide)
      vi. Phenytoin (Dilantin)
      vii. α-Interferon
      viii. Diazoxide
      ix. Nicotinic acid
      x. Pentamidine
   F. Diseases of exocrine pancreas
      i. Cystic fibrosis
      ii. Trauma/pancreatectomy
      iii. Pancreatitis/ionizing radiation
      iv. Hemochromatosis
      v. Fibrocalculous pancreatopathy
   G. Infections
      i. Congenital rubella
      ii. Cytomegalovirus
      iii. Hemolytic-uremic syndrome
   H. Endocrinopathies associated with diabetes
      i. Cushing (hypercortisolism)
      ii. Acromegaly (growth hormone excess)
      iii. Pheochromocytoma
      iv. Glucagonoma
      v. Somatostatinoma
      vi. Aldosteronoma
IV. Gestational Diabetes

Type 1 DM

- T1DM accounts for approximately 10% of all cases of diabetes in all ages
- One of the most common chronic diseases in childhood
- DM1 is caused by insulin deficiency following destruction of pancreatic beta cells

Natural history

- 1- Preclinical β-cell autoimmunity with progressive defect of insulin secretion
- 2- Onset of clinical diabetes
- 3- Transient remission honeymoon period
- 4- Established diabetes

Epidemiology

- Females and males are almost equally affected
- Modest male preponderance in some populations (Western European/U.S.)
- Female preponderance in others (Japanese)
- There is no apparent correlation with socioeconomic status

Epidemiology

- Peaks of presentation occur in 2 age groups:
- 5-7 yr of age and at the time of puberty
- The 1st peak : time of increased exposure to infectious agents

- 2nd peak : pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion

Epidemiology

- A growing number of cases are presenting between 1 and 2 yr of age, especially in high-risk groups
- Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country

GENETICS

- There is a clear familial clustering of T1DM
- Prevalence in siblings : 8%
- Prevalence in the general population in the United States is only 0.4%
- Risk of T1DM is also increased when a parent has T1DM
- The risk is 3–4% if the mother is affected but 5–6% when the father is affected
- In monozygotic twins, the concordance rate ranges from 30% to 65%
- Dizygotic twins have a concordance rate of 6–10%

GENETICS

- 85% of newly diagnosed type 1 diabetic patients do not have a family member with T1DM

HLA

- Overall, genetic variation in the HLA region can explain 40–50% of the genetic risk of T1DM
- Some of the known associations include the HLA DR3/4-DQ2/8

Viral Infections

- It is possible that various viruses do play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism

Congenital Rubella Syndrome

- Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children

- The time lag between infection and development of diabetes may be as high as 20 yr
- T1DM after congenital rubella is more likely in patients that carry the higher-risk genotypes

Enteroviruses

- Studies show an increase in evidence of enteroviral infection in patients with T1DM
- There are case reports of association between enteroviral infection and subsequent T1DM
- But the true significance of these infections remains unknown at this time

Mumps Virus

- It has been variably observed that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM
- Mumps alone is not a major causal factor in diabetes.

The Hygiene Hypothesis: Possible Protective Role of Infections

- Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes
- The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual's chances of developing autoimmune diseases, including T1DM

- Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed

Diet

- Dietary exposure may modify T1DM risk
- Early studies supported an association between early milk and/or gluten introduction and T1DM risk
- Subsequent studies have been inconsistent and in many cases refuted these findings

Diet

- A 2016 meta-analysis of both interventional and observational studies concluded that there was no association between early exposure of gluten or milk protein and risk of T1DM.

- Some, but not all, studies have suggested that breastfeeding lowers the risk of T1DM

- Early (before 4 mo of age) and late (after 6 mo of age) introduction of solid foods predicted development of T1DM

Diet

- Other dietary factors that have been suggested at various times as playing a role in T1DM risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E.

- Most observational studies have failed to find associations between vitamin D level or supplementation and T1DM risk
- Interventional studies to assess effect of vitamin D supplementation on T1DM risk are lacking

Psychologic Stress

- Several studies show an increased prevalence of stressful psychologic situations among children who subsequently developed T1DM.
- Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity through epigenetic mechanisms remains unknown

Presentations

- Classic new onset:
- Polyuria
- Polydipsia
- Weight loss

Presentations

- DKA
- Silent presentation

Diagnostic criteria

- FPG ≥**126** mg/dL (Fasting :no caloric intake for at least 8 h)
- Classic symptoms of hyperglycemia, a random plasma glucose ≥**200** mg/dL
- 2 hr plasma glucose ≥200 mg/dL during an OGTT.
- A1C ≥6.5 percent

Prediabetes

- FPG : 100-125 mg/dL → [IFG]
- OGTT : 140-199 mg/dL → [IGT]

Unique challenges in children

- Obvious differences in the size
- Unpredictability of a toddler's dietary intake and activity level
- Inability to communicate symptoms of hypoglycemia
- ↑ risk of hypoglycemia and DKA

Goals

- Balancing strict glycemic control
- Setting realistic goals for each child and family
- Maintaining normal growth, development, and emotional maturation.
- Training the patient and family

Initial management

- The diabetes team teaches :
- The cause and treatment of type 1 DM
- How to maintain a daily schedule
- Record of BG
- Insulin administration
- The timing and carbohydrate content of meals

Insulin types

- Regular(short act): Onset of action:0.5-1 hr
  Duration of action:6-8 hr
- NPH (intermediate): Onset of action:1-3 hr
  Duration of action: 10-20hr

Insulin types

- **Aspart,glulisine,Lispro (rapid act):Onset of action:5-15 min**

  Duration of action:3-5 hr
- **It is approved for injection <u>immediately after a meal.</u>**

Insulin types

- **Glargine,detemir, and degludec (long act): Onset of action:1-2 hr**

  Duration of action:24 hr
- **Glargine not be mixed in the same syringe with any another insulin** (alter its pH and affect its absorption)

Long acting insulin

- Long-acting insulin preparations are given once or twice a day.
- Insulin degludec has a longer duration of action but is still given once a day
- In general, if a single injection is used, it should be given in the evening in order to assure insulin availability during the night and counteract the counterregulatory hormone response in the early hours of the morning

Long acting insulin

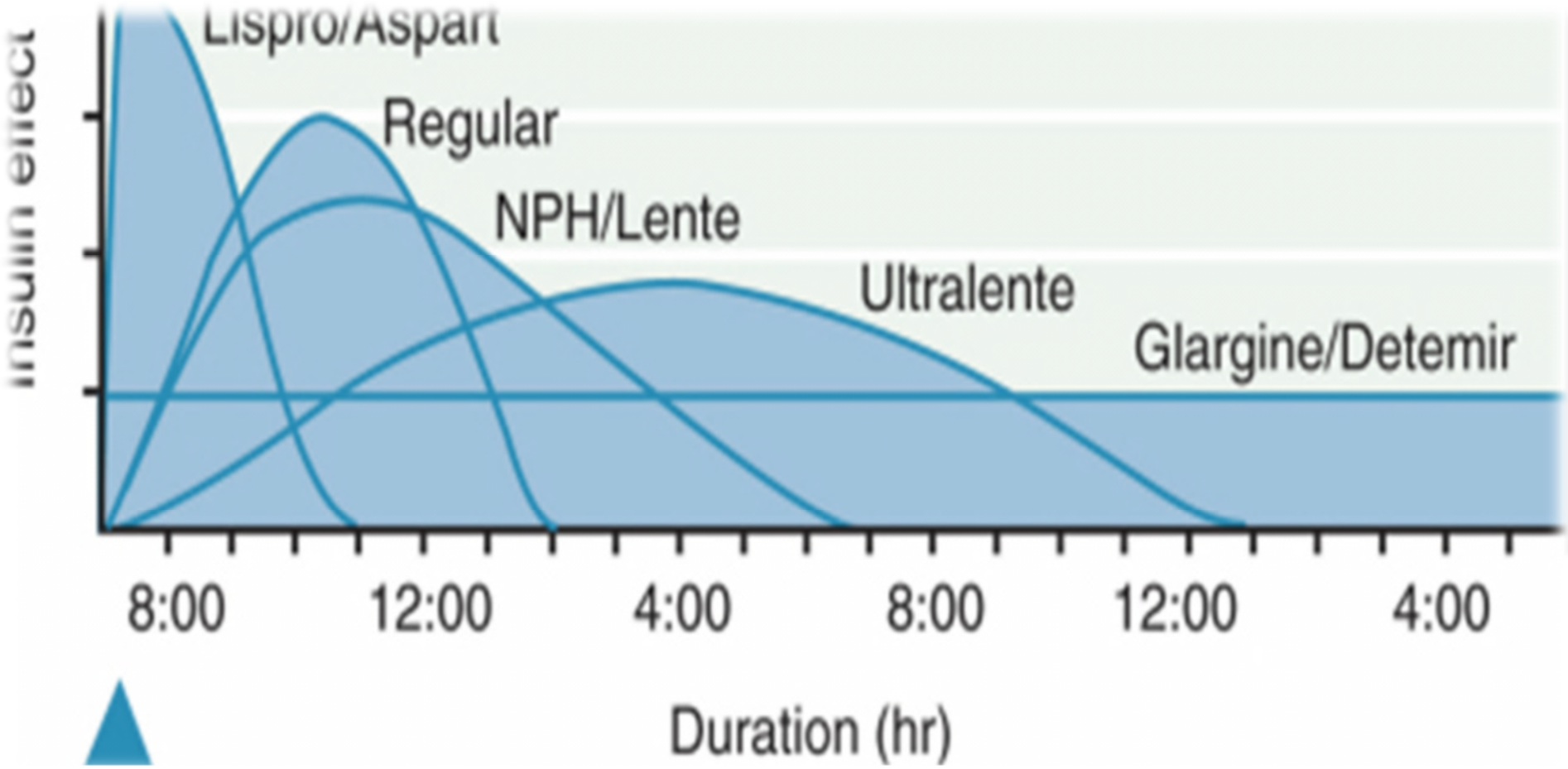
- Some very young children who are at greater risk of hypoglycemia do better with administration of long-acting insulin in the morning hours

Insulin types

Type	Onset (hours)	Peak (hours)	Duration (hours)	Comments
Ultra-rapid-acting				
Faster aspart*	0.1 to 0.2	1 to 3	3 to 5	Duration of action may be shorter.
Rapid-acting				
Lispro/aspart/glulisine	0.15 to 0.35	1 to 3	3 to 5	
Short-acting				
Regular	0.5 to 1	2 to 4	5 to 8	Longer action if larger dose (mass action effect).
Intermediate-acting				
Neutral protamine Hagedorn (NPH)	2 to 4	4 to 12	12 to 24	Peak and duration quite variable.
Neutral protamine lispro (NPL)	Approximately 2	6	15	Activity profile similar to NPH; can be mixed with insulin lispro. Not available in United States.

Insulin types

Type	Onset (hours)	Peak (hours)	Duration (hours)	Comments
Glargine Biosimilar glargine is approved in some countries	2 to 4	8 to 12 (not pronounced)	22 to 24	Half-life is shorter in some patients, requiring division of the daily dose into two injections per day. Cannot be mixed with other insulins because this alters pharmacokinetics. Insulin forms crystals at in vivo pH.
Detemir	1 to 2	4 to 7 (not pronounced)	20 to 24	Duration of action is dose-dependent. At higher doses (≥0.8 units/kg), mean duration of action is longer and less variable (22 to 23 hours). At lower doses, mean duration of action is shorter and twice daily injections are often needed. Cannot be mixed with other insulins because this alters pharmacokinetics.
Glargine U300	2 to 6	None	30 to 36	Cannot be mixed with other insulins because this alters pharmacokinetics.
Degludec	0.5 to 1.5	None	>42	Less day-to-day variation in glucose lowering effect at steady state (after 2 to 3 days' use) relative to glargine and detemir. Can be mixed with insulin aspart; coformulation with aspart available in some countries.


Lispro/Aspart
Regular
NPH/Lente
Ultralente
Glargine/Detemir
8:00
12:00
4:00
8:00
12:00
4:00
Duration (hr)

Insulin Dose

- Total daily insulin :0.3 to 0.7units/kg
- Dose in the newly diagnosed child :60-70%of the full replacement dose based on pubertal status.

Age	Starting Doses of SC insulin (U/Kg/d)
Prepubertal	0.25-0.50
Pubertal	0.5-0.75
Postpubertal	0.25-0.50

Conventional regimen

- Intermediate-acting insulin (NPH) at least twice a day (at breakfast and at dinner or bedtime)
- Rapid-acting or short-acting insulin two or three times a day(at breakfast and dinner, lunch)

Conventional regimen

- Before breakfast :1/2-2/3 total 2/3 NPH ,1/3 rapid/short
- Before lunch:1/4
- Before dinner or at bedtime:1/3-1/4 2/3 to 1/2NPH 1/3 to 1/2 R/S

Conventional regimen

- Control of BS is important
- With twice a day insulin injection we can’t control BG

Intensive regimen

- Multiple daily injections
- A long-acting insulin analog (40-50% of total dose)
- Premeal/snack boluses of rapid- or short-acting insulin

Insulin pump

- Recurrent severe hypoglycemia
- Wide fluctuations in blood glucose (regardless of A1C)
- Suboptimal diabetes control (A1C exceeds target range for age)

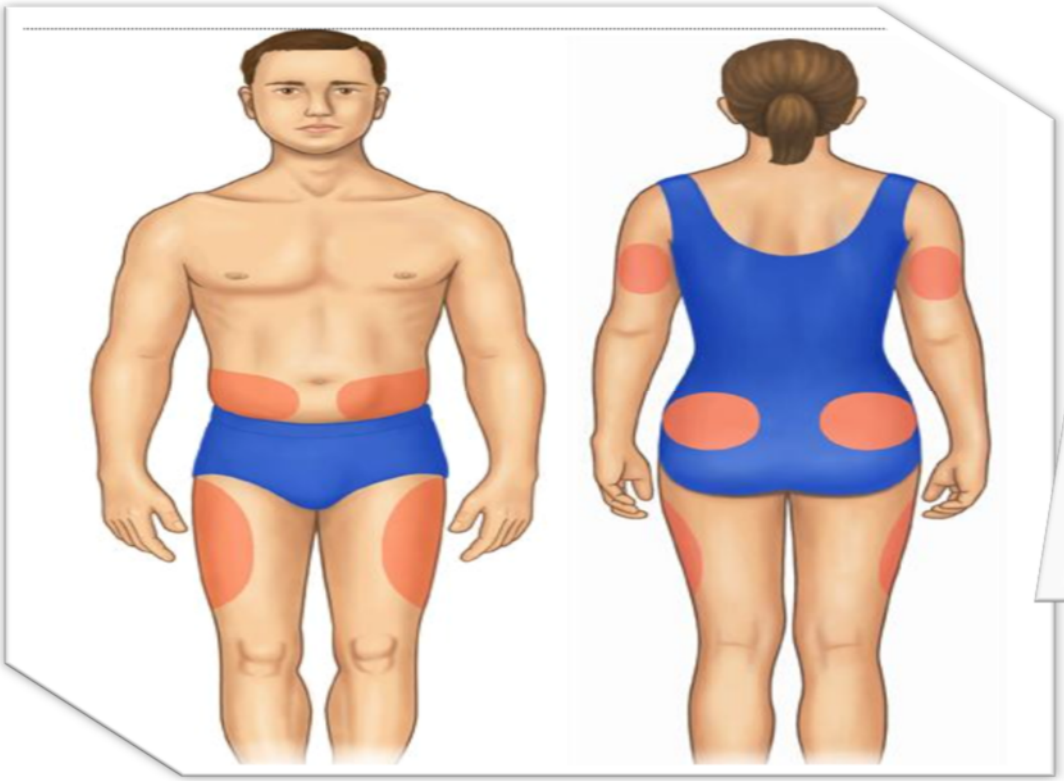
Insulin pump

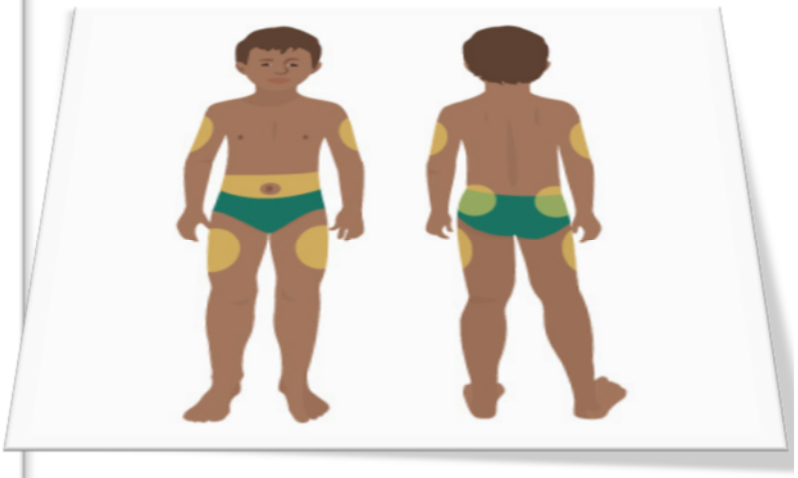
- Microvascular complications and/or risk factors for macrovascular complications
- Good metabolic control, but insulin regimen that compromises lifestyle

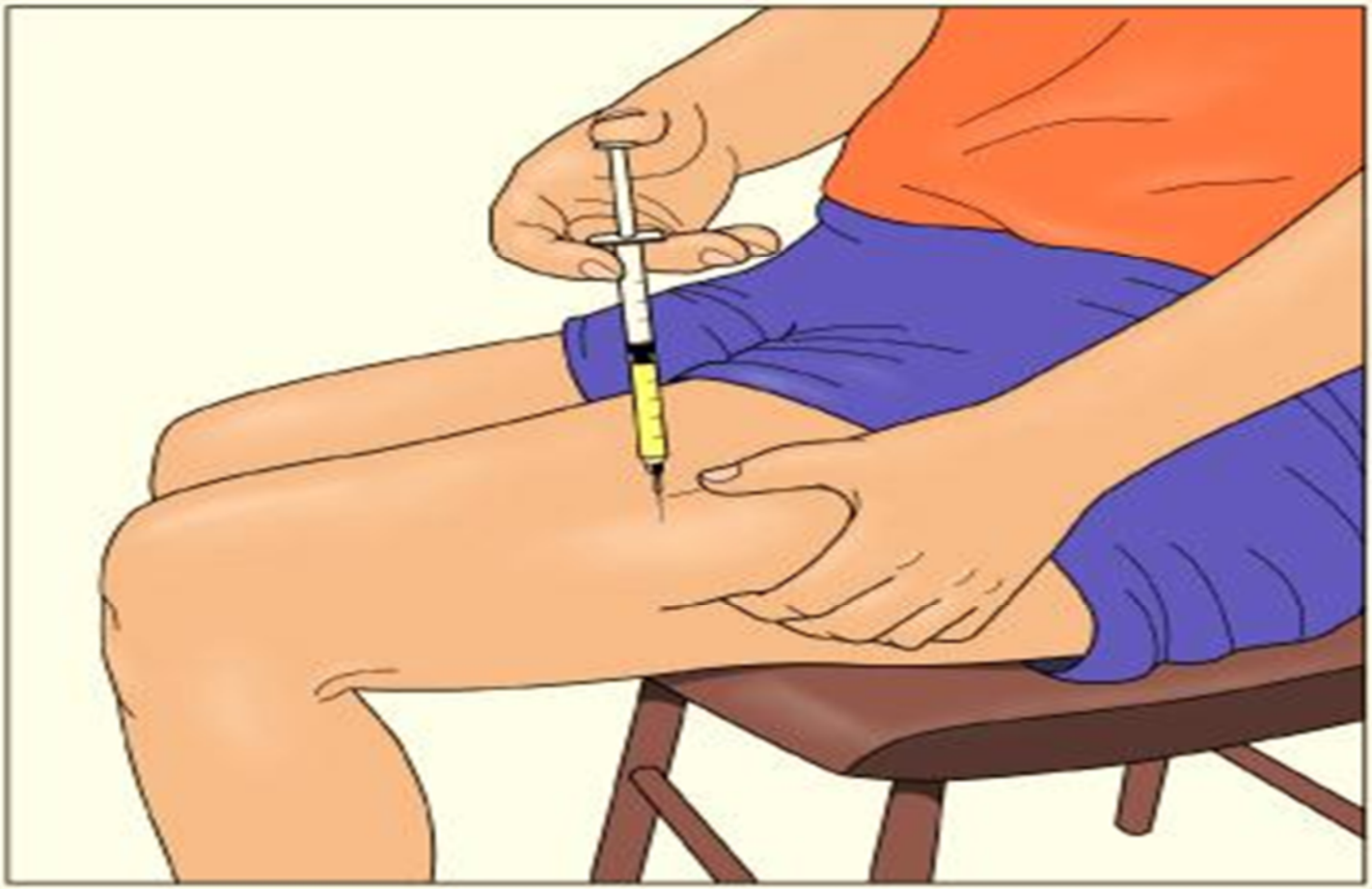
Insulin syringe

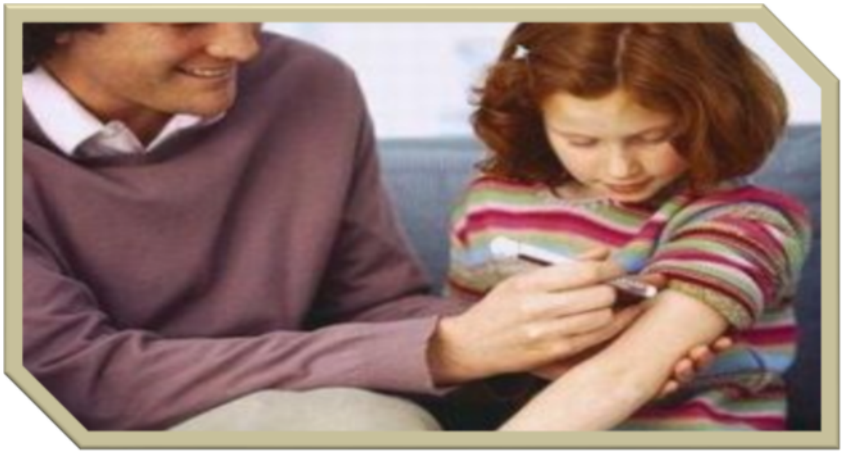
- 100 unit
- 50 unit
- 30 unit

Sites of injections









Blood glucose goals

- Before meals:80-130 mg/dl
- Bedtime:80-140 mg/dl

Target blood glucose

- The ADA emphasizes that glycemic targets should be further tailored to the individual patient

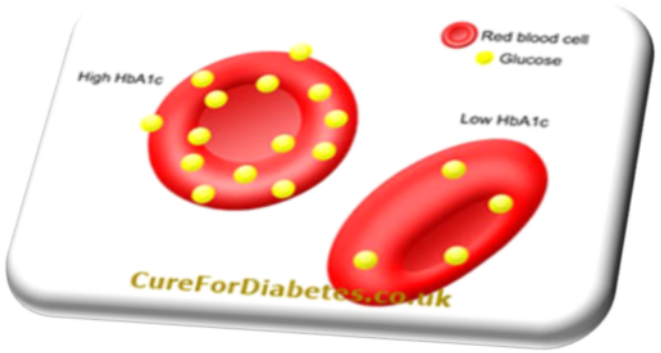
Table 607.10	Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for Each Age Group		
AGE GROUP (yr)	**TARGET PREMEAL BG RANGE (mg/dL)**	**30-DAY AVERAGE BG RANGE (mg/dL)**	**TARGET HbA_{1c} (%)**
<5	100-200	180-250	7.5–9.0
5-11	80-150	150-200	6.5–8.0
12-15	80-130	120-180	6.0–7.5
16-18	70-120	100-150	5.5–7.0

Blood glucose monitoring

- ADA recommends testing of blood glucose at least four times a day
- (Fasting & before meals & bed time)
- 2 hr after meals
- At 3 AM: 3-4×mo

HbA1C

- HbA1C :at least every 3 mo



Target HbA1C

- We suggest a target A1C of <7 percent for children and adolescents

A1C

- Less stringent goal of A1C <7.5 percent may be appropriate for :
- Younger patients
- Underlying conditions that limit their ability to articulate symptoms of hypoglycemia
- Hypoglycemia unawareness

A1C

- Those without access to analog insulin formulations,a continuous glucose monitor, or advanced insulin delivery technology
- Those with known micro- and macrovascular complications or lifestyle or psychosocial considerations

HbA1c

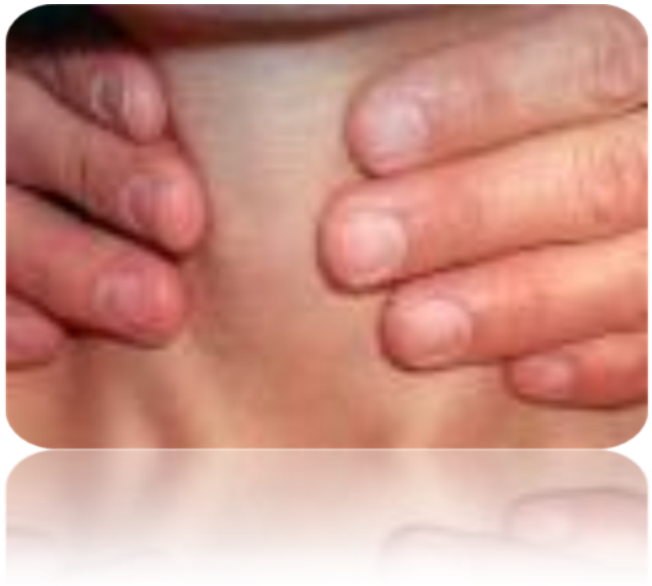
- HbA1c may be spuriously elevated in thalassemia(or other conditions with elevated hemoglobin F)
- Lower in sickle cell disease (or other conditions with high red blood cell turnover)
- Fructosamine can be used instead of HbA1c in these patients.

Physical examination

- Height and weight
- Blood pressure

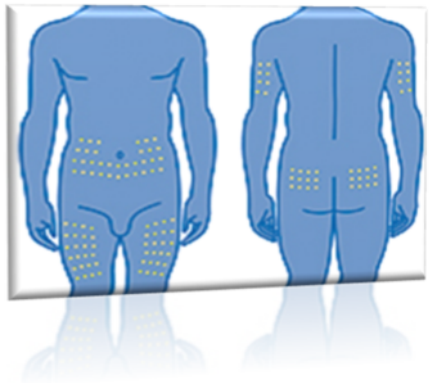
Physical examination

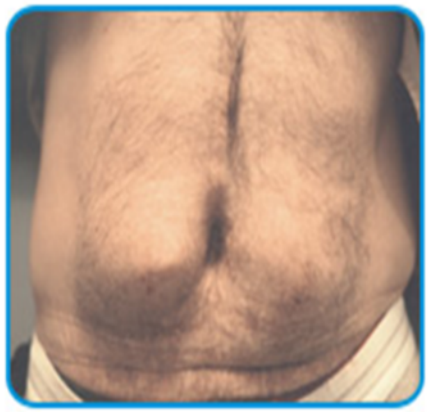
- Pubertal assessment
- Thyroid examination

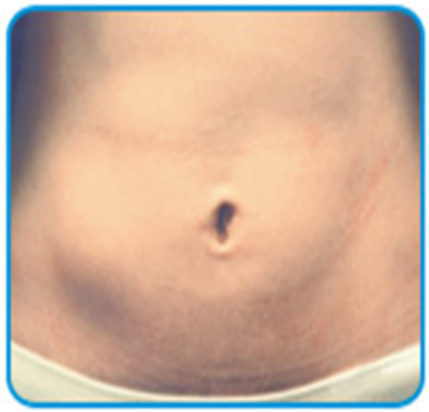


Physical examination

- Skin (injection sites)
- Extremities (limited joint mobility) or peripheral neuropathy







Physical examination

- Annual foot examination in children ≥10 yr

Table 607.13	Screening Guidelines		
	INITIAL TESTING	**FREQUENCY**	**TEST**
Thyroid disease	At diagnosis	Every 1-2 yr or sooner if symptoms	TSH, thyroid antibodies
Celiac	At diagnosis	Within 2 yr and again at 5 yr or sooner if symptoms	IgA and TTG
Hypertension	At diagnosis	Each visit	Elevated BP based on ≥ 90th% for age, sex, height on 3 separate occasions
Dyslipidemia	≥10 yr of age at diagnosis once glucose control established	If abnormal annually; every 5 yr if initially normal	Goal LDL-C < 100 mg/dL
Nephropathy	At puberty or age ≥ 10 yr whichever comes first, if T1DM ≥ 5 yr	Annually	Albuminuria; urine albumin to creatinine ratio
Retinopathy	T1DM ≥ 3-5 yr when ≥ 10 yr or puberty, whichever comes first	Annually	Dilated eye exam
Neuropathy	At puberty or ≥ 10 year, whichever earlier if T1DM > 5 yr	Annually	Foot exam

Albuminuria

- A value of albumin to creatinine ratio ≥ 30 mg/g or µg/mg.

False positive test

- UTI
- Hematuria
- Acute febrile illness
- Vigorous exercise
- Short-term pronounced hyperglycemia
- Uncontrolled HTN
- Heart failure

Albuminuria

- Abnormal results should be confirmed with a second random sample
- If the albumin/creatinine ratio is persistently elevated: confirmation of albuminuria with a or 24-hour urine sample

Albuminuria

- Elevated albumin/creatinine ratio on two occasions, should be sufficient to trigger treatment with an ACE inhibitor.
- Annual assessment of renal function (serum creatinine and computing creatinine clearance)

Case

- کودک 8 ساله مورد جدید دیابت نوع یک می باشد .چگونه انسولین را شروع می کنید ؟
- Weight =25 kg

Intensive therapy

- ٠,٣×٢٥=7.5 ~8 unit
- 4 unit insulin glargine
- Aspart insulin:
- 1 unit before breakfast
- 2 unit before lunch
- 1 unit before dinner

Conventional

- Morning NPH 3 unit
  Reg 2 unit
- Lunch : Reg 1 unit
- Dinner : NPH 2 unit
  Reg 1 unit

Summary

- T1DM is the result of insulin deficiency caused by destruction of the pancreatic beta cells
- T1DM is one of the most common chronic diseases of childhood
- The risk of T1DM is moderately increased in children with an affected close relative
- Although exposure to an environmental agent(s) in genetically susceptible individuals appears to trigger the destruction of the insulin-producing pancreatic beta cell, no factor(s) has been definitively identified.

Summary

- Childhood T1DM usually presents with the classic signs and symptoms
- Other presentations: DKA , silent
- Diabetes education and self-management training by a pediatric diabetes multidisciplinary team provides the ideal setting to acquire the knowledge and skills needed for care

References

- Nelson text book of pediatrics2020
- Up To Date 2022