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Diabetes Mellitus
Lecture 2

Management of Hyperglycemia without Acidosis and Continuous Phase

Insulin

***Dose:** Starting dose of insulin is depend on the clinical presentation, weight, and pubertal stage. Post-DKA or hyperglycemia without DKA: U/kg/day, subcutaneous as follow: (للاطلاع)

	No DKA	**Post-DKA**
Prepubertal	0.25-0.5	0.75-1
Pubertal	0.5-0.75	1-1.2
Post-pubertal	0.25-0.5	0.8-1

If there is poor glycemic control with an insulin requirement > 1.5 U/kg/day, consider non-adherence with therapy.

***Types:**There are 3 types of insulin:

1. Animal insulin (from animal pancreas): no longer available as it is immunogenic.
2. Human insulin (rDNA insulin, structurally identical to human insulin): as lente and soluble insulin. It is less likely allergic than animal insulin. All human insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into circulation. Delayed absorption and prolonged action of human insulins contribute to problems of hyper and hypoglycemia, necessitating feeding the insulin with snacks and limiting the overall degree of blood glucose control.
3. Insulin analogs (a modification of human insulin): Modification of site of amino acids in insulin changed the pharmacokinetic properties of insulin, primarily affecting the absorption of drug from the subcutaneous tissue (rapid absorption for rapid analogs aspart and lispro and prolonged absorption for long acting analogs glargine and detemir).

***Regimens:** It includes:

- Conventional regimen; CR.
- Basal-bolus regimen; BBR:
    - Multiple Daily Injection (MDI).
    - Continuous Subcutaneous Insulin Infusion (CSII) by insulin pump.

CR

Two-third of total daily dose in the morning before breakfast and one-third in the evening before dinner, two-third NPH and one-third regular or rapid acting analog. It produces the least physiologic profile with substantial risk of hypoglycemia before lunch and during the early night combined with breakthrough hyperglycemia before supper and breakfast so requiring timing of injections, specific mealtimes, specific meal amounts, and snacks (rigid regimen), but has the advantage of twice-daily injection.

MDI

It Provides more physiologic insulin effects with more flexibility (no fixed mealtime, no fixed meal amount, extra snack can be added, meal may even be missed), and less likelihood of DKA if many bolus doses are missed, but has the disadvantage of at least four injection per day, including at school and education is complex as the patient or family must count carbohydrate in each meal consumed. It consist of**:**

Basal insulin dose (30-50 % of total insulin dose) that provide fasting insulin needs which achieved by long acting analog once usually at bedtime (glargine) or twice (detemir) daily, and

Bolus insulin doses (50-70 % of total insulin dose) that covers food requirements and correct hyperglycemia and achieved by rapid acting analog (aspart and lispro) before meals and snacks (anything containing ≥ 10g carbohydrate).

CSII

It use rapid acting analogues for both, basal and bolus infusion. Dosages calculation is the same as MDI regimen. It provides Less number of injections (infusion set must be changed every 2-3 days), but the disadvantage is that DKA will develop within hours if there is a problem in the infusion set, as there is no long acting insulin.

For determining the best insulin regimen for an individual the following factors should put in our minds:

- The availability of an adult parent/guardian to supervise insulin administration.
- The ability to count carbohydrates and monitor blood sugar (BS) levels, and
- The willingness to wear a pump or take four or more injections of insulin daily.

***Injection sites:** They include arms (lateral aspect), abdomen, thighs (front/lateral part), and buttocks (upper outer quadrant). subcutaneous injection in arm and abdomen in young children might result in intramuscular injection as they have less subcutaneous tissue in these sites (so should be avoided).

Monitoring

***Blood glucose monitoring**: The safety and success of any insulin regimen depend on frequent monitoring of blood glucose levels, which achieved by Home (self) monitoring and HbA1c.

Home monitoring: the targets are as close to metabolic normalcy and avoiding hyper or hypoglycemia. It is either by **Glucose meter (**accurate to within about 5%-10% of lab venous measurements) in which at least four tests per day (premeals and at bedtime), or **Continuous glucose monitoring (CGM)** which is available now.

Targets blood sugar according to the age:(للاطلاع)

Age (year)	Premeal mg/dl	Bedtime/overnight mg/dl
<5	100-200	110-200
5-11	80-150	100-180
12-15	80-130	90-150
16-18	70-120	90-150

HbA1c: It provides the gold standard by which to judge the adequacy of the insulin regimen. It represents the fraction of hemoglobin to which glucose has been non-enzymatically attached in the blood stream, and continue irreversibly throughout the RBC life span of approximately 120 days. So, HbA1c should be checked every 3 months. In children, based on International Society of Pediatric and Adolescent Diabetes (ISPAD) recommendations, our general goal is to keep all patients under 7.5% regardless of the patients age.

***Monitoring for complications and associated autoimmune diseases** which include microvascular (retinopathy and nephropathy), macrovascular complications, neuropathy, cataract, and thyroid and celiac disease (as patients with T1DM are at increased risk for autoimmune diseases).

Other quite rarely noted complications now (as improvement in overall metabolic control) in diabetic children include:

- Mauriac syndrome: dwarfism associated with a glycogen-laden enlarged liver.
- Osteopenia, and
- Syndrome of limited joint mobility associated with tight, waxy skin; growth impairment; and maturational delay.

Nutrition

Appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development , and it not differ from that of non-diabetic children.

Heart-healthy diets are encouraged, which consist of 50% carbohydrate, 20% protein, and 30% fat (< 10% saturated fat). Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch and intake of sucrose and highly refined sugars should be limited. Dietary fats derived from animal sources (saturated) are reduced and replaced by polyunsaturated fats from vegetable sources. Substituting margarine for butter, vegetable oil for animal oils in cooking, and lean cuts of meat, poultry, and fish for

fatty meats is advisable. The intake of cholesterol is also reduced by these measures and by limiting the number of egg yolks consumed. These simple measures reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease.

Diet with high fiber content (grain, legumes, fruits and vegetables) are useful in improving glucose control. As vegetables and fruits are a natural source of antioxidants, as with other children, at least five portions are recommended in diabetics to provide some protection against long-term cardiovascular disease.

Regarding sweeteners, there is no available data to support an association of moderate amount of **saccharin** ingestion with bladder cancer in children. **Aspartame** is used in variety of products and it contraindicated in phenylketonuria, and **Fructose** in both diabetic and healthy populations increase LDL-cholesterol and may stimulate energy intake and promote weight gain. So adding large amount of fructose to the diet is undesirable. These concern should not extend to naturally occurring fructose in fruits and vegetables as they provide only modest amount of fructose.

Cakes and even candies are permissible on special occasions as long as insulin dose is adjusted to accommodate this increased caloric intake to not foster rebellion and stealth in obtaining desired food.

Meal plans should fit the child and family's food preference and provide satiety necessary for realistic adherence.

In a conventional regimen, constancy in timing and amount of carbohydrate meal is important to avoid hyper and hypoglycemia. Thus, the total daily caloric intake is divided to provide 20% at breakfast, 20% at lunch, 30% at dinner, leaving 10% for each of the midmorning, midafternoon, and evening snack (this strict divisions are not required in basal-bolus regimen). While in basal bolus regimen, near total flexibility in timing and amount of meals is possible provided that patients and families understand insulin dose calculation.

Exercise

Physical fitness and regular exercise are encouraged in all children with DMT1 as it improves glucoregulation by increasing insulin receptor number and no form of exercise is forbidden. However, it requires specific attention (blood glucose monitoring to assess the effect of exercise and then to determine an effective regimen for the individual child). Complications of exercise are:

- Hypoglycemia: It is a common complication and occurs during or after low-to-moderate-intensity exercise due to increased insulin absorption from its injection site. It may occur hours post-exercise reflecting depleted glycogen stores.
- Hyperglycemia: It occurs during or immediately after high-intensity exercise as a result of exercise-induced increase in the counterregulatory hormones, and so in patient with poor metabolic control vigorous exercise should not be performed as it may precipitate DKA.

HYPOGLYCEMIA

The ADA defines biochemical Hypoglycemia in diabetic patients (with or without symptoms) as any BS <70 mg/dl. Hypoglycemia is the major limitation to tight control of glucose levels and it occurs as a result of mismatching between insulin, food, and exercise, which may be due:

1. Taking too much insulin.
2. Missing or delaying a meal.
3. Vigorous exercise (may occur immediately or delayed by several hours).
4. Alcoholism (especially in excess).

Decreased BS values and decrease insulin requirement well after the time expected to span the honeymoon period might indicate the development of the followings:

1. Addison's disease.
2. Hypothyroidism.
3. Celiac disease.
4. Renal failure.

Hypoglycemia should be treated with oral glucose (5-10 g) as juice or a sugar-containing beverage or candy, and the blood glucose checked 15-20 min later and the administration of glucagon when the child cannot take glucose orally.

DAWN AND SOMOGYI PHENOMINA

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common **dawn phenomenon** which occurs as a result of combination of waning overnight insulin and early morning rise in counter-regulatory hormones and treated by increasing the evening dose of lente or long acting analog. Rarely, high morning glucose is caused by the **Somogyi phenomenon**, a theoretical rebound from late-night or early-morning hypoglycemia, thought to be from an exaggerated counterregulatory response and so treated by decreasing the evening dose. To distinguish between the two conditions ,we should measure the blood sugar at 3 am- 4 am and at 7 am-9 am. If blood sugar >80 mg/dl in the first sample and markedly high in the last one ,it means dawn phenomenon. If blood sugar <60mg/dl in the first sample followed by hyperglycemia at 7 am , this mean Somogyi phenomenon.