Clinical Chemistry

Carbohydrate metabolism & related disorders

Lecture-3

1-Type 1 Diabetes Mellitus (T1DM)

Previously called insulin-dependent diabetes mellitus, this is the term used to describe the condition in patients for whom insulin therapy is essential because they are prone to develop ketoacidosis.

It usually presents during childhood or adolescence.

Most of these cases are due to immune-mediated processes and may be associated with other autoimmune disorders :-such as Addison's disease, vitiligo and Hashimoto's thyroiditis.

Practical markers of β-cell autoimmunity are circulating antibodies, which have been detected in the serum years before the onset of hyperglycemia

. **The best characterized antibodies are as follows :**

1. **Islet cell cytoplasmic antibodies (ICAs)**

(75 to 85% of patients with newly diagnosed type 1)

2-Insulin Autoantibodies (IAAs) are present in more than 90% of children who develop type 1 diabetes before age 5.

3-Antibodies to Glutamic Acid Decarboxylase GAD65 (GAD65 antibodies) found up to 10 years before the onset of clinical type 1 diabetes may be used to identify patients with apparent type 2 diabetes who will subsequently progress to type 1 diabetes.

4. Insulinoma-associated antigens (IA-2A and IA-2βA),detected in more than 50% of newly diagnosed type 1 diabetes patients.

5. Zinc transporter ZnT8 was identified recently as a found in type 1 diabetes, (60 to 80% of patients with new-onset type 1 diabetes) .

Idiopathic Type 1 Diabetes

- **Some forms of type 1 diabetes have no known etiologies.**
- **These patients have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity.**

- Only a minority of patients with type 1 diabetes fall into this category.

Type 2 Diabetes Mellitus (T2DM)

Previously called non-insulin-dependent diabetes mellitus, this is the most common variety worldwide (about 90 per cent of all diabetes mellitus cases). Patients are much less likely to develop ketoacidosis than those with type 1 diabetes, there is a familial tendency and an association with obesity.

Gestational Diabetes Mellitus (GDM)

It is first to be diagnosed during gestation , associated with increased fetal abnormalities, for example high birth weight, cardiac defects and polyhydramnios(excessive accumulation of amniotic fluid).

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Maternal Complications : birth complications ,maternal hypertension and the need for caesarean section may occur.

If maternal diet/life style factors fail to restore glucose levels, insulin is usually required to try to reduce the risk of these complications

Women with GDM are at significantly increased risk for the subsequent development of type 2 DM, and those whose GDM was diagnosed before (who have had GDM before), have previously given birth to a high-birthweight baby, are obese, have a family history of diabetes mellitus .

Other Specific Types Of Diabetes Mellitus

A variety of inherited disorders may be responsible for the syndrome, either by reducing insulin secretion or by causing relative insulin deficiency because of resistance to its action or of insulin receptor defects, despite high plasma insulin concentrations.

▪ Neonatal Diabetes

- **Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause .**

- **Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age.**

Maturity-Onset Diabetes of the Young MODY is characterized by:

- **Onset of hyperglycemia at an early age (<25 years, although diagnosis may occur at older ages).**
- **MODY associated with impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity).**
- **It is inherited as Autosomal Dominant AD pattern with abnormalities in at least 13 genes on different chromosomes identified to date.**

- **The most commonly reported forms are:**

- **MODY-1: HNF4A-MODY mutation of the hepatocyte nuclear factor(*HNF4A*) gene**

- **– MODY 2: GCK-MODY mutation of the Glucokinase gene,**

- **– MODY 3: HNF1AMODY mutation of the *HNF1A* gene.**

Metabolic Features of Diabetes Mellitus

I -Hyperglycaemia

If plasma glucose concentration exceeds about 10 mmol/L, glycosuria would be expected.

High urinary glucose concentrations produce an osmotic diuresis and therefore polyuria.

Cerebral cellular dehydration due to hyperosmolality, secondary to hyperglycaemia, causes thirst (polydipsia).

A prolonged osmotic diuresis may cause excessive urinary electrolyte loss.

These 'classic' symptoms are suggestive of diabetes mellitus.

Diabetic patients on insulin may show '**dawn' phenomenon** is the physiological response of the **elevation of blood glucose** concentration in the **early morning prior to breakfast** due to **nocturnal spikes in GH concentration** and a **rise in plasma cortisol concentration** that **increase hepatic gluconeogenesis**.

Conversely, in some diabetic patients **nocturnal hypoglycaemia** may **evoke a rebound counter-regulatory hyperglycaemia** called the **Somogyi phenomenon**.

Patient blood glucose checking at **02.00– 04.00** h, or continuous glucose monitoring if available, may distinguish these conditions, as the Somogyi phenomenon reveals hypoglycaemia.

2-Abnormalities in lipid metabolism

These may be secondary to insulin deficiency. Lipolysis is enhanced and plasma NEFA concentrations rise . In liver, NEFAs are converted to acetyl CoA and ketones, or are re-esterified to form endogenous triglycerides and incorporated into VLDLs; which accumulate in plasma because lipoprotein lipase, which Is necessary for VLDL catabolism, requires insulin for optimal activity (hyperlipidemia).

- If insulin deficiency is very severe, there may also be chylomicronaemia.
- The rate of cholesterol synthesis is also increased, with an associated increase in plasmaLDL concentrations.
- Consequently, patients with diabetes may show :↑ plasma triglyceride, ↑ cholesterol and ↓HDL cholesterol concentrations.

Pathogenesis of Chronic Complications of Diabetes Mellitus

Patients with both type 1 and type 2 diabetes are at high risk for the development of chronic complications.

Diabetes-specific microvascular pathology in the retina, renal glomerulus, and peripheral nerve produces leading to retinopathy, nephropathy, and neuropathy.

As a result of these microvascular complications, diabetes is the most frequent cause of new cases of blindness in the industrialized world in persons between 25 and 74 years and the leading cause of end-stage renal disease.

Diabetes is also associated with a marked increase in atherosclerotic macrovascular disease involving cardiac, cerebral, and peripheral large vessels.

The consequence is that patients with diabetes have a high rate of myocardial infarction (the major cause of mortality in diabetes), stroke, and limb amputation.

Prospective clinical studies document a strong relationship between hyperglycemia and the development of microvascular complications.

Both hyperglycemia and insulin resistance appear to be important in the pathogenesis of macrovascular complications.

Progress has been made in our understanding of the molecular mechanisms underlying derangements produced by hyperglycemia.

Four main hypotheses to explain how hyperglycemia causes the neural and vascular pathology……..

These include:

1. **Increased aldose reductase (or polyol pathway) flux;**
2. **Enhanced formation of advanced glycation end products (AGE);**
3. **Activation of protein kinase C;**

4-Increased hexosamine pathway flux

Overproduction of superoxide by the mitochondrial ETC

integrates these four apparently disparate mechanisms.

Clinical trials are under way using novel therapies specifically directed at the signaling molecules or employing antioxidants to neutralize the effects of the oxidants.

Monitoring of Diabetes Mellitus

Glycosuria

Glycosuria can be defined as a concentration of urinary glucose detectable using relatively insensitive, but specific, screening tests. These tests often depend on the action of an enzyme, such as glucose oxidase, incorporated into a diagnostic strip. Glycosuria, , occurs only when the plasma, and therefore glomerular filtrate concentrations exceed the tubular reabsorptive capacity, i.e. When plasma and glomerular filtrate concentrations are more than 10 mmol/L, and therefore the normal tubular reabsorptive capacity is significantly exceeded.

Very rarely, if the GFR is much reduced, there may be no glycosuria despite plasma glucose concentrations more than 10 mmol/L. A diagnosis of diabetes mellitus should ***NEVER*** be made on the basis of glycosuria.

Blood glucose

Blood glucose concentrations may be measured using glucose testing reagent strips. The colour change of the strip can be assessed visually or by using a portable glucose meter and the reaction often involves an enzyme determination of glucose, for example glucose oxidase.

Glycated haemoglobin

Glycated haemoglobin (HbA1c) is formed by nonenzymatic glycation of haemoglobin and is dependent on the mean plasma glucose concentrations and on the lifespan of the red cell; falsely low values may be found in patients with haemolytic disease.

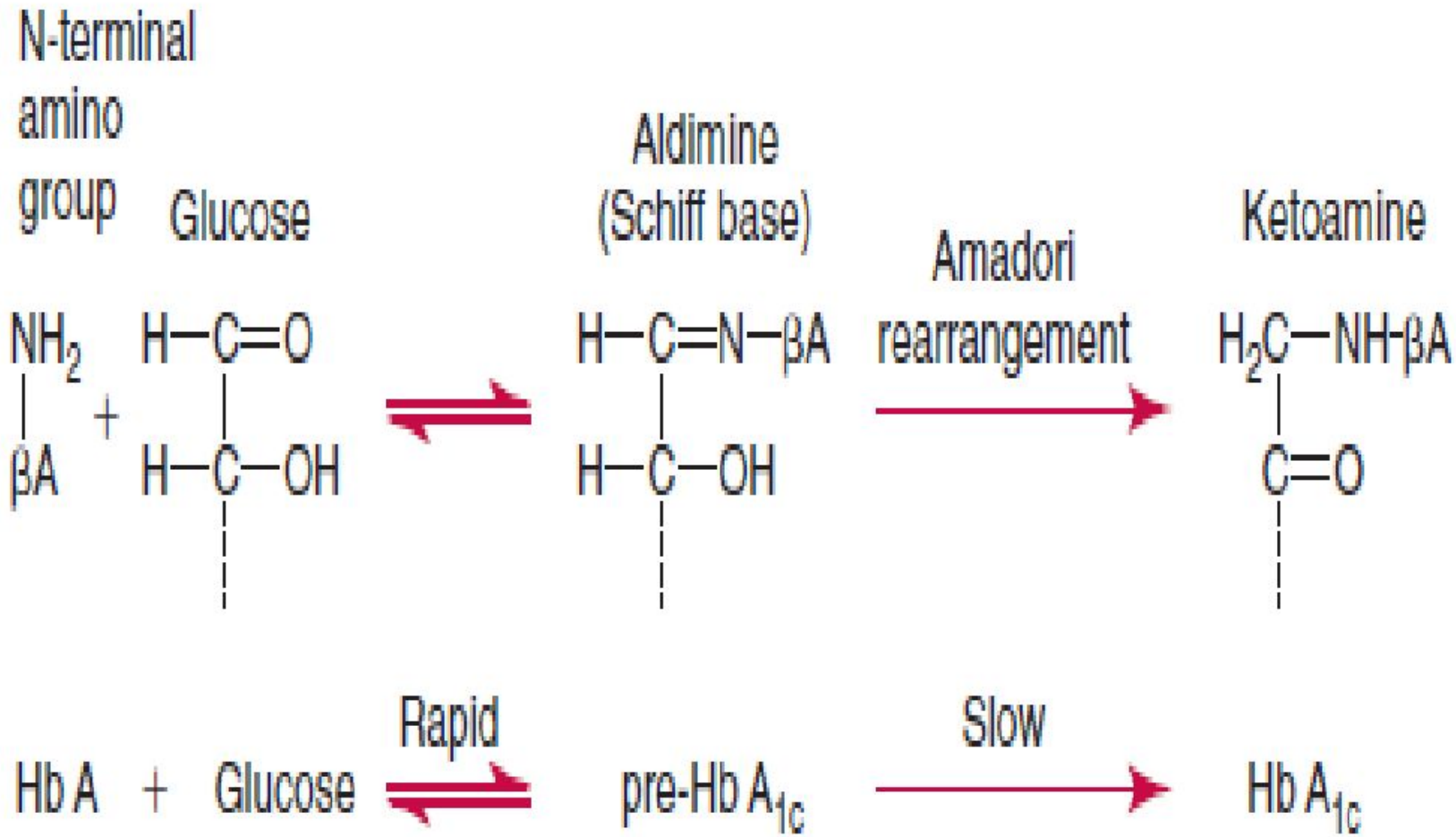

Figure 46-6 Formation of hemoglobin A_{1c}.

Measurement of blood HbA1c may not reveal potentially dangerous short-term swings and nor does HbA1c detect hypoglycaemic episodes and thus plasma glucose estimations may also be useful.

AIC is expressed as a percentage of total blood haemoglobin concentration and gives a retrospective assessment of the mean plasma glucose concentration during the preceding **6–8 weeks**.

AIC now is expressed as mmol/mol

The higher the glycated haemoglobin, the poorer glycaemic control.

Intervention trials for type 1 and type 2 diabetes have shown that trying to optimize glycaemic control, as judged by HbA1c < 6.5 % reduces the risk of microvascular diabetic complications.

Estimated Average Glucose eAG (mg/dl)

$$= 28.7 \times \text{HbAIC (\%)} - 46.7$$

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Conditions Altering the Relationshipof A1C and Glycemia

- In conditions associated with increased red blood cell turnover, (sickle cell disease)
- Pregnancy (second and third trimesters)
- Glucose-6-phosphate dehydrogenase deficiency
- Hemodialysis,
- Recent blood loss or transfusion, or erythropoietin therapy

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In All Above Conditions

Only plasma blood glucose criteria should be used to diagnose diabetes

A1C is less reliable than blood glucose measurement in other conditions such as:

The postpartum state , HIV treated with certain drugs , and iron-deficient anemia .

Fructosamine

The measurement of plasma fructosamine concentrations may be used to assess glucose control over a shorter time course than that of HbA1c (about 2–4 weeks), but the assay has

Fructosamine reflects glucose bound to plasma proteins, predominantly albumin, which has a plasma half-life of about 20 days but is problematic in patients with hypoalbuminaemia, for example due to severe proteinuria.

This assay may sometimes be useful in pregnancy and also if haemoglobin variants, for example HbS or HbC, exist that may interfere with certain HbA1c assays.