Diabetes Mellitus: Diagnosis and Pathophysiology

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1. Goals

- To review the physiology of glucose and lipid metabolism, weight and energy regulation
- To appreciate the magnitude of the prevalence of diabetes and its effect on morbidity and mortality
- To understand the pathophysiology of type 1 and type 2 diabetes
- To be able to distinguish among diabetes mellitus, impaired fasting glucose and impaired glucose tolerance states and to become familiar with the Metabolic Syndrome

2. Learning Objectives

- Diabetes is a group of metabolic disorders characterized by abnormal fuel metabolism resulting chiefly in hyperglycemia and dyslipidemia.
- Diabetes is a common chronic disease affecting more than 1 in 10 adults in the US. It is more common in people who are older and socioeconomically disadvantaged.
- Diabetes is a serious disease associated with acute (due to hyperglycemia) and chronic (due to vascular damage) complications.
- Diabetes is clinically diagnosed if a fasting plasma glucose is ≥ 126 mg/dl more than once or when an individual has symptoms of diabetes and her casual plasma glucose is ≥ 200 mg/dl.
- Impaired fasting glucose and impaired glucose tolerance define intermediate dysmetabolic states (pre diabetes) with increased risk for cardiovascular disease and death.
- Type 1 diabetes is caused by an autoimmune destruction of the beta cells of the pancreas due to an interplay between genetic susceptibility and environmental modifiers.
- Type 2 diabetes, the most prevalent form of diabetes, is characterized by a combination of insulin resistance and insulin deficiency.
- The metabolic syndrome is characterized by insulin resistance, central obesity, hypertension, dyslipidemia, and increased risk for cardiovascular and disease death.
- Gestational diabetes develops secondary to the insulin resistant state of pregnancy and may be associated with fetal macrosomia, a higher rate of cesarean section and a high risk for developing type 2 diabetes in the future.

3. Definition of Diabetes Mellitus (DM)

Diabetes is a group of metabolic disorders characterized by abnormal fuel metabolism, which results most notably in hyperglycemia and dyslipidemia, due to defects in insulin secretion, insulin action, or both. Diabetes is a serious chronic disease without a cure, and it is associated with significant morbidity and mortality, both acute and chronic. Acute complications are due to severe hyperglycemia. Chronic complications are characterized by damage, dysfunction, and eventual failure of various organs, especially the eyes, kidneys, nerves, heart, and brain. The common denominator is vascular damage. See lecture on Complications of diabetes.

4. Epidemiology

Diabetes is one of the most common diseases in the US. It is estimated that 16.7 million US adults (about 7% of the total adult US population) have diagnosed diabetes (Figure 1). (Newly released statistics from the Centers for Disease Control and Prevention (CDC) illustrate that diabetes has risen by over 14 percent in the last two years. The CDC estimates that 20.8 million Americans -- 7 percent of the U.S. population -- have diabetes, up from 18.2 million in 2003. Nearly a third of these Americans are undiagnosed.) If undiagnosed diabetes is included, it is estimated that more than 1 in 10 adults in the US has diabetes. Over 93% of patients with diabetes have type 2 (see Classification of Diabetes).

Figure 1. Prevalence of Diabetes in US Adults in 1994 and 2001 based on self-reported data.

- About 1 million new cases of diabetes are diagnosed annually.
The prevalence of diagnosed diabetes increased 61% from 1990 to 2001 and 8.2% in just one year (2000 to 2001), mostly due to increased awareness, the aging of the population, and the increase in the prevalence of obesity (the major risk factor for type 2 diabetes).

The estimated lifetime risk of developing diabetes if born in 2000 is 35%, while a Hispanic female born in 2000 has a 50% chance of developing diabetes.

In addition to those with diagnosed or undiagnosed diabetes, close to 15 million people have glucose intolerance, which is considered a pre-diabetic state.

**Diabetes discriminates.** It afflicts those who can afford it the least (older [1 out of 5 individuals over 65 has diabetes], ethnic minorities [Hispanics, Non-Hispanic blacks and Asian-Americans], those in low socioeconomic status)

Diabetes is a serious disease. People with diabetes and its associated Metabolic Syndrome (see below) have an increased risk for macrovascular complications (stroke, ischemic heart disease, peripheral vascular disease) and microvascular complications (retinopathy, nephropathy and neuropathy).

- Diabetes is the leading cause of blindness, chronic kidney disease and non-traumatic limb amputation in the US.
- Compared to people without diabetes, persons with diabetes are 2 to 4 times more likely to develop heart disease or suffer a stroke.
- Diabetes during pregnancy is a principal cause of congenital malformations, perinatal mortality and premature mortality.

5. Clinical Presentation

Symptoms of diabetes can be either acute or chronic:

5.1. Acute Symptoms

Acute symptoms of diabetes are due to severe hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss and blurred vision. Patients may exhibit impaired growth and increased susceptibility to infections (e.g. recurrent vaginal candidiasis or urinary tract infections). Acute marked hyperglycemia may lead to diabetic ketoacidosis (DKA) in type 1 diabetes or to the hyperglycemic hyperosmolar nonketotic syndrome (HHNS) in type 2 diabetes. These conditions are covered further in the lecture on diabetic complications and discussed during the small group sessions.

5.2. Chronic Symptoms

Chronic symptoms of diabetes are due to vascular damage from persistent hyperglycemia. Vascular damage leads to end-organ damage. Other conditions associated with diabetes, such as hypertension, dyslipidemia (as well as smoking) accelerate the development of vascular damage and the chronic complications of diabetes, which are the following:

5.2.1. Microvascular

Microvascular complications are a significant cause of morbidity. Persistent hyperglycemia is the major cause for the microvascular complications which are highly specific for diabetes.

- retinopathy with potential loss of vision
- nephropathy leading to kidney failure
- peripheral neuropathy leading to pain, foot ulcers, and limb amputation
- autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction

5.2.2. Macrovascular

Macrovascular complications are the main cause of mortality. Although persistent hyperglycemia may contribute to macrovascular complications, it is the associated conditions (hypertension, dyslipidemia, smoking) that account for most of the burden of the macrovascular complications.

- coronary heart disease which is the major cause of death for patients with diabetes
- peripheral vascular disease
- cerebrovascular disease

Unfortunately, many patients with diabetes remain asymptomatic for long periods, so that the first presentation of the disease is frequently a chronic complication. Indeed, about 50% of newly diagnosed type 2 diabetes will already have developed a vascular complication.

6. Diagnosis of Diabetes and Glucose Intolerance

Diabetes is a dysmetabolic disorder affecting multiple bodily functions. Its diagnosis is based on the presence of hyperglycemia. The diagnostic criteria for diabetes were modified in 1997 and again in 2003 by the American Diabetes Association, as shown in Table 1. The criterion for FPG was derived from the strong association of FPG with retinopathy in various populations with a high prevalence of diabetes (such as the Pima Indians in Arizona). The cutoff value of FPG $\geq 126$ mg/dl was chosen to separate the bimodal distribution of the rate of chronic complications (figure will be shown in lecture).

**Table 1. Diagnosis of Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Glucose Intolerance</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$100 &lt; \text{Morning} &lt; 126$ mg/dL (IFG)</td>
<td>Classic symptoms of diabetes PLUS casual plasma glucose $\geq 200$ mg/dL or</td>
</tr>
<tr>
<td>$\geq 126$ mg/dL</td>
<td>Morning FPG $\geq 126$ mg/dL or</td>
</tr>
</tbody>
</table>
Glucose intolerance, denoted by Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT), is not a clinical entity on its own but rather an independent risk factor for progression to clinical diabetes and development of macrovascular complications. Individuals with glucose intolerance are at increased risk for cardiovascular disease and death indicating a continuing risk along glucose levels. However, persons with glucose intolerance do not exhibit an increased prevalence of microvascular, or diabetes-specific complications.

It is important to recognize that the impact of hyperglycemia as a risk factor for macrovascular disease and death is much less than other established risk factors (hypertension, dyslipidemia, smoking). It is therefore possible that mild pre-diabetic hyperglycemia is a marker of an underlying process that places people at risk for macrovascular complications, primarily because of the associated conditions such as hypertension and dyslipidemia which tend to cluster with hyperglycemia as part of the metabolic syndrome. People with glucose intolerance need to initiate nonpharmacologic lifestyle interventions (calorie restriction and increased physical activity leading to weight loss) to prevent progression to clinical diabetes and aggressively manage associated medical conditions (such as hypertension, dyslipidemia, smoking) to decrease vascular complications.

7. Physiology of Insulin Release and Action

The endocrine pancreas consists of the islets of Langerhans, which are small endocrine glands scattered throughout the pancreas. The four different types of islets and its secretory products are shown in Table 2. We will review only insulin here.

<table>
<thead>
<tr>
<th>Table 2. Endocrine cell types in pancreatic islets of Langerhans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islet Cell Type</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>A cell (alpha)</td>
</tr>
<tr>
<td>B cell (beta)</td>
</tr>
<tr>
<td>D cell (delta)</td>
</tr>
<tr>
<td>F cell</td>
</tr>
</tbody>
</table>

7.1. Insulin Synthesis and Secretion

The beta cell synthesizes pro-insulin which is converted to insulin and C-peptide after proteolytic cleavage (figure 2). Both C-peptide and insulin are released in the circulation in equimolar amounts. This is the major site of regulation of circulating insulin. C-peptide has no known biological activity. A very small amount of pro-insulin is also secreted in the circulation. Insulin is a 51-amino acid peptide with 2 chains connected by a disulfide bond. Insulin’s half-life is 3-5 minutes and about 50% of it is cleared in a single pass through the liver.

Figure 2. Pro-insulin, Insulin and C-peptide

In the average individual, approximately 40-50 units of insulin are secreted daily into the portal circulation. Approximately 1/3-1/2 of total daily insulin is basal insulin, which is secreted in the fasting state. The rest is secreted as bolus (stimulated) insulin in response to exogenous stimuli. The main stimulus for insulin release is circulating glucose. Other stimuli for insulin release including: amino-acids, ketoacids, beta-catecholamines, and certain gut hormones (GLP-1). Glucose sensing by the beta islet cell is accomplished by glucose uptake via the receptor...
GLUT-2 and intracellular phosphorylation by glucokinase. Both GLUT-2 and glucokinase have a high affinity for glucose, so beta cell metabolism reflects extracellular glucose concentration. Intra-islet cell metabolism of glucose is essential for insulin release as the ratio of ATP/ADP closes K channels, which depolarize islet cell membrane, which leads to opening of Calcium channels and influx of Calcium. The latter causes release of insulin (see figure). Defects in the sensing of glucose that cause diabetes have been described.

7.2. Insulin Action

The main action of insulin is to promote storage of ingested nutrients as shown below:

<table>
<thead>
<tr>
<th>Anabolic Effects - require high insulin (e.g. post-prandial)</th>
<th>Anti-catabolic Effects - require low insulin (e.g. fasting)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>• stimulates glycolysis and glycogen storage</td>
<td>• inhibits gluconeogenesis and glycogen breakdown</td>
</tr>
<tr>
<td>• stimulates chylomicrons and VLDL uptake</td>
<td>• promotes triglycerids synthesis</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td></td>
</tr>
<tr>
<td>• stimulates glucose uptake (via GLUT-4 receptors) and glycogen synthesis</td>
<td>• inhibits gluconeogenesis and glycogen breakdown</td>
</tr>
<tr>
<td>• stimulates amino-acid uptake and protein synthesis</td>
<td></td>
</tr>
<tr>
<td><strong>Adipose</strong></td>
<td></td>
</tr>
<tr>
<td>• Increases glucose transport (via GLUT-4 receptors)</td>
<td>• Inhibits intracellular breakdown of triglycerides</td>
</tr>
<tr>
<td>• Induces activity of Lipoprotein Lipase which hydrolyzes circulating triglycerides leading to uptake of FFA and glycerol</td>
<td></td>
</tr>
</tbody>
</table>

Other actions of insulin include: cell growth regulation, beta cell survival and development, food intake regulation, reproduction.

Typical of other receptors, insulin receptors have an extracellular domain that binds insulin and a cytoplasmic domain that initiates the complex intracellular signal transduction pathway that gives rise to its various effects. Defects in the signal transduction pathway that cause diabetes have been described.

Clearance of insulin is achieved primarily via its receptors. About 50% of insulin is cleared in a single pass through the liver. Some clearance is via the kidney.

8. Classification of Diabetes Based on Etiology

Knowledge of the physiology of insulin release and action helps us think about the pathophysiology of diabetes. Similar to other endocrine conditions, any defect along the pathway will result in abnormal fuel metabolism, which will be manifested primarily as hyperglycemia. In 1997, the American Diabetes Association revised the nomenclature for the major types of diabetes. The terms insulin dependent diabetes mellitus and non-insulin-dependent diabetes mellitus and their acronyms, IDDM and NIDDM, were eliminated. These terms had been confusing and had frequently resulted in classifying the patient based on treatment rather than etiology. The new classification of diabetes based on etiology is shown below:

- **Type 1 diabetes**: pancreatic beta islet cell destruction leading to absolute insulin deficiency
  - autoimmune (most common)
  - idiopathic (rare)
- **Type 1b** presents like type 1 (with DKA), then behaves like type 2
- **Type 2 diabetes**: varying degrees of insulin resistance and insulin deficiency
- **Gestational diabetes**
- **Other specific types**
  - **Maturity onset diabetes of the young (MODY)**
    - Currently 6 monogenic defects of beta cell function defined with defects in islet cell glucokinase or in various transcriptions factors such as HNF-1alpha, HNF-4alpha, IPF-1. The end result is impaired insulin release and hyperglycemia.
    - Autosomal dominant pattern. Onset of hyperglycemia generally before age 25
  - **Genetic defects in insulin action**
    - Mutant insulin gene, insulin exhibits impaired receptor binding (rare)
    - Mutation of insulin receptor. Often associated with acanthosis nigricans (thickening and discoloration of skin) and some forms of polycystic ovarian syndrome (uncommon)
  - **Diseases of the exocrine pancreas**
    - Need extensive damage to pancreas for diabetes to occur
    - Includes trauma, infection, chronic necrotizing pancreatitis and pancreatic carcinoma, cystic fibrosis and hemochromatosis
    - May be another mechanism besides simple beta cell reduction since cancers which involve a small part of the pancreas may lead to diabetes (?paracrine inhibition of insulin release)
  - **Endocrinopathies**
    - Includes acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma
    - Caused by excess secretion of hormones which antagonize insulin including growth hormone, cortisol, glucagon and epinephrine
  - **Drug/chemical induced diabetes**
Many drugs may impair insulin resistance or insulin secretion leading to diabetes in predisposed individuals. Major drugs include synthetic glucocorticoids, cyclosporin A, nicotinic acid, interferon, pentamidine, occasionally thiazide diuretics.

Infections
- Congenital rubella is the most common virus implicated in the development of diabetes.
- Coxsackievirus B, adenovirus, mumps and cytomegalovirus have all been implicated in inducing certain cases of the disease.

9. Type 1 Diabetes Mellitus

Type 1 diabetes (DM-1) was previously known as IDDM (insulin dependent diabetes mellitus) or juvenile-onset diabetes. About 5-10% of patients with diabetes have DM-1. Type 1 diabetes affects 3 in 1000 children and its incidence is increasing worldwide both in low and high prevalence populations.

9.1. Epidemiology/Pathogenesis of Type 1 Diabetes

Type 1 diabetes is primarily a disease of the young given its peak incidence at the age of 10 to 12 years for girls and 12 to 14 years for boys; however, the disease can occur at any age, but most patients are diagnosed before age 20. Type 1 diabetes refers to cell-mediated autoimmune destruction of pancreatic beta islet cells, which leads to absolute insulin deficiency and predisposes individuals to diabetic ketoacidosis (DKA). The etiology is most often autoimmune in origin, but idiopathic destruction of beta islet cells without evidence of autoimmunity is also classified under this group. Although the presentation and progression is variable, all patients with DM-1 require insulin for survival.

The autoimmune nature of DM-1 has been intensively investigated, and it has long been assumed that the pathogenesis of the disease can be explained by an interplay between genetics and environment. The pathogenesis can be summarized as follows: In a genetically predisposed individual, (currently not well-defined) environmental factors trigger an autoimmune process (activation of T lymphocytes reactive to islet cell antigens) that leads to destruction of islet cells and insulin deficiency (Figure 3).

Figure 3. Pathogenesis of Type 1 Diabetes

Based on epidemiologic and genetic studies, it is well accepted that there is a strong genetic component for development of DM-1, although 90% of affected patients do not have a close relative with the disease. Multiple chromosomal loci associated with the disease have been identified; however, few true genes have been described. Loci associated with the development of DM-1 are found within the MHC-HLA class II region. These loci are known to harbor genes associated with presentation of antigens to T lymphocytes. There are also MHC haplotypes that provide protection and non-HLA loci that further contribute to the genetic variability of the disease.

The rising incidence of DM-1 suggests an important role of the environment in its pathogenesis. However, our understanding of the influence of the environment toward the pathogenesis of DM-1 is incomplete. It has long been thought that environmental triggers of the disease exist. These triggers may include infections agents (e.g. viruses- congenital rubella, enteroviruses), early life factors (early exposure to cow’s milk, vitamin D deficiency, rapid growth), toxins, vaccinations, stress and climatic influences. However, more recently, it is thought that environmental agents do not serve as triggers but as modifiers of genetic susceptibility to autoimmunity.

Immune dysregulation, caused by genetic susceptibility and environmental modifiers, leads to development of autoantibodies against various islet cell components, including glutamic acid decarboxylase antibodies (GAD-65), islet cell antibodies (ICA512/IA-2) and insulin antibodies (IAA). These antibodies serve as markers for DM-1 (see Table 3). Indeed, the best predictor for future development of DM-1 is the expression of multiple autoantibodies. Beta cell destruction is thought to be primarily a T-cell mediated process, as evidence by the presence of intense insulitis in newly diagnosed patients. Beta cell destruction is variable being more rapid in younger individuals and slower in older individuals. Type 1 diabetes is associated with other autoimmune disorders including Graves’ disease, Addison’s disease and autoimmune polyendocrine syndromes.

Table 3. Major islet-cell autoantigen-specific antibodies in type 1 diabetes

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Antibody</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD-65</td>
<td>GAD-65 Ab</td>
<td>80%</td>
<td>99%</td>
</tr>
<tr>
<td>ICA512/IA-2</td>
<td>ICA512/IA-2 Ab</td>
<td>50%</td>
<td>99%</td>
</tr>
<tr>
<td>Insulin</td>
<td>IAA</td>
<td>50%</td>
<td>99%</td>
</tr>
</tbody>
</table>
9.2. Clinical Findings

Diabetic ketoacidosis (see lecture on complications) may be the presenting clinical picture for DM-1 but more often, DM-1 presents with the classic symptoms of diabetes such as polyuria, polydipsia, polyphagia, blurry vision and unexplained weight loss. Upon presentation, DM-1 patients may also exhibit diabetic dyslipidemia, characterized by low HDL and high TG rich particles (such as VLDL, chylomicrons). Insulin deficiency, in type 1 diabetes, will lead to release of FFA from adipose tissue and transport to the liver where they re-esterified to VLDL and secreted back in the circulation. Additionally, in the absence of insulin, LPL will not function appropriately, and clearance of TG-rich particles will be deficient. Increased (hepatic) production and decreased clearance of TG-rich particles, therefore leads to the characteristic dyslipidemia of diabetes. In type 1 diabetes, the dyslipidemia is fully corrected with adequate insulin therapy.

10. Type 2 Diabetes Mellitus

Type 2 diabetes (DM-2), previously known as NIDDM or adult-onset diabetes, is the most prevalent form of diabetes, accounting for over 90% of all cases of diabetes.

10.1. Epidemiology/Pathogenesis

Type 2 diabetes (DM-2), previously known as NIDDM or adult-onset diabetes, is the most prevalent form of diabetes, accounting for over 90% of all cases of diabetes. Type 2 diabetes is characterized by varying degrees of insulin resistance and insulin deficiency. It is thought that the earliest defect in the pathogenesis of DM-2 is impaired insulin action or insulin resistance. Resistance to the action of insulin will result in impaired insulin mediated glucose uptake in the periphery (by muscle and fat), incomplete suppression of hepatic glucose output and impaired triglyceride uptake by fat. To overcome the insulin resistance (and therefore prevent abnormal fuel metabolism and maintain normal glucose and lipid levels), beta islet cells will increase the amount of insulin secreted. Higher circulating insulin levels will overcome the impedance to the action of insulin. This state of high insulin levels with euglycemia persists for many years. Abnormal fuel metabolism (hyperglycemia and dyslipidemia) occurs when there is a mismatch between insulin requirements, as dictated by insulin resistance, and insulin supply, as dictated by beta cell function. Therefore, for DM-2 to develop, two defects are necessary: insulin resistance and insulin deficiency relative to the resistance (figure 4).

![Figure 4. Pathogenesis of type 2 Diabetes and the Metabolic Syndrome](image)

The dual defect of insulin deficiency and insulin resistance in DM-2 is caused by an interplay between genetic and environmental factors.

10.1.1. Genetics

Epidemiologic and genetic studies suggest a strong genetic basis for development of type 2 diabetes. (~90% concordance rate in monozygotic twins). The concordance rate in monozygotic twins is much higher compared to fraternal twins highlighting the importance of genetics over a common intrauterine environment. However, candidate genes that account for the majority of cases have not yet been identified. Type 2 diabetes appears to be a genetically heterogeneous disorder and different genes may be implicated in different populations.

10.1.2. Environment

Despite its strong genetic basis, the rising incidences of DM-2 over the past few decades strongly suggest that important environmental contributions to its pathogenesis exist. The role of genetics and environment for each component of the pathophysiology of DM-2 is discussed below.

10.1.3. Insulin deficiency

Although insulin resistance may be thought as the central defect in the pathogenesis of DM-2, and most patients with the disease have insulin resistance, it is the health of the beta islet cell that determines the development of hyperglycemia which defines clinical diabetes. This concept is supported by data from the UK Prospective Diabetes Study showing that in patients with DM-2, β islet cell function is already reduced by approximately 50% at time of presentation. The importance of the β islet cell dysfunction in the pathogenesis of diabetes is further highlighted by the fact that insulin resistance in highly prevalent in the U.S. (approximately 25% of the population) but only 7% of the population has clinical diabetes.

10.1.3.1. Genetics
The capacity of the β islet cell to produce insulin and to adapt to the increasing demands of the insulin resistance state is genetically predetermined to a great extent. Rare monogenetic defects in insulin synthesis or secretion have been described:

- Mutant insulin gene (resulting in dysfunctional insulin)
- Abnormal processing of pro-insulin
- Defects in glucose-mediated insulin secretion by the beta islet cell. These autosomal dominant conditions are known as Maturity Onset Diabetes of the Young (MODY) syndromes. The following genetic defects have been described:
  - MODY1 - Mutant transcription factor, Hepatic Nuclear Factor-4alpha (HNF-4a)
  - MODY2 - Impaired beta cell Glucokinase activity
  - MODY3 - HNF-1a
  - MODY4 - IPF1 (necessary for normal beta cell development and function).

Although these defects provide us with important insight into the physiology of β cell function, these candidate genes only account for a small number of adult diabetes (1-2%).

10.1.3.2. Environment

There are no well-characterized acquired/environmental factors that contribute to the decline of the β islet function with the exception of certain medications (e.g. pentamidine), although certain factors have been implicated (congenital rubella).

Although the decline in β islet cell function is slowly progressive in most patients with DM-2, some patients (lean, elderly) may have extensive insulin deficiency very early in the course of their disease (probably due to genetics). This group of patients may have a condition closely related to type 1 diabetes. This difference contributes to the heterogeneity in the metabolic expression of clinical DM-2 and has implications for therapy as this subgroup may require insulin therapy at an early stage.

10.1.4. Insulin Resistance

Insulin resistance has both inherited and acquired etiologies.

10.1.4.1. Genetics

Offspring of patients with DM-2 show signs of insulin resistance at an early age, suggesting a strong genetic contribution to insulin resistance. However, despite intense investigations into the hereditary causes of insulin resistance, specific gene mutation account only for a minority (less than 5%) of insulin resistance. Most genes remain to be identified.

10.1.4.2. Environment

Much more is known about acquired causes of insulin resistance. These include obesity, nutrition, and physical activity, which are closely associated with each other.

10.1.4.2.1. Obesity

The association of obesity and insulin resistance is well documented and accepted. From cross sectional data, we can see that the increase in the prevalence of diabetes over the last 10 years (up by 61%) is paralleled by an increased in the prevalence of obesity (up by 74%) as shown in figure 5.

Figure 5. Prevalence of Obesity and Diabetes in US Adults 1991 and 2001 based on self-reported data.

Even small increases in body weight result in increased risk of diabetes. For every one kilogram increase in weight, the risk of diabetes increases by 4.5 — 9%. The mechanisms by which obesity contributes to insulin resistance are incompletely understood. It has been postulated that adipose tissue in obese individuals preferentially secretes substances that interfere with insulin action in other tissues (skeletal muscle and liver). Several substances have been identified, including tumor necrosis factor alpha, leptin, adiponectin, resistin and plasma free fatty acids (FFA). Among those substances, the most convincing data exists for FFA which are thought to directly promote insulin resistance in skeletal muscle and liver by promoting TG uptake and deposition in these two tissues. High circulating levels of FFA may also directly alter
insulin secretion by the beta cells. Central (omental) adipose tissue is more metabolically active and contributes more to the dysmetabolic state of DM-2 compared to other fat depots.

The observation that most obese people do not develop diabetes raises certain important points. These will be discussed during small group sessions.

### 10.1.4.2.2. Nutrition

A significant factor contributing to the development of obesity, insulin resistance and DM-2, is nutrition. It is well documented and accepted that increased total caloric intake leads to obesity. However, beyond caloric intake, which components of diet are important is not clear. There is evidence that refined carbohydrates (increase risk), saturated and trans fat (increase risk), fiber intake (decrease risk) and alcohol intake (decrease risk) are all important in the development of DM-2.

### 10.1.4.2.3. Physical Activity

It is well documented that physical activity improves insulin sensitivity. Part of the benefit of exercise is mediated through weight loss, but effects independent of weight loss also exist. The latter is evident after a single bout of exercise but is transient and dissipates after a few days without exercise. The mechanism of the beneficial effect of exercise on insulin sensitivity is, at least in part, mediated by an increase in the number of glucose transporters in skeletal muscle.

### 10.1.4.3. Summary

In summary, type 2 diabetes is a genetically heterogeneous disorder with a strong environmental component, characterized by varying degrees of insulin resistance and insulin deficiency.

### 10.2. Clinical Findings

Type 2 diabetes was primarily a disease seen in adults but recently more and more young people are diagnosed with type 2 diabetes because of obesity in childhood and young adulthood. Unlike patients with type 1 diabetes, most patients with type 2 diabetes do not present with the typical symptoms of severe hyperglycemia. Often they are found to have diabetes on screening or after they present with a chronic complications (myocardial infarction, stroke).

Similar to type 1, type 2 diabetes is also characterized by low HDL and high TG rich particles (such as VLDL, chylomicrons) as well as small LDL particles (thought to be highly atherogenic). In contrast to type 1 diabetes, the dyslipidemia of type 2 diabetes is due to insulin resistance (which leads to increased hepatic production of VLDL and decreased clearance by LPL).

### 11. Metabolic Syndrome

In addition to hyperglycemia, type 2 diabetes is thought to be related to a cluster of metabolic abnormalities such as central obesity, hypertension, dyslipidemia and increased risk for cardiovascular disease, collectively known as the Metabolic Syndrome. Recently, specific criteria for the metabolic syndrome were defined, as shown in table 4.

#### Table 4. Adult Treatment Panel III Diagnostic Criteria for the Metabolic Syndrome

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal Obesity</strong></td>
<td>Waist circumference &gt; 102 cm in men and &gt; 88 cm in women</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td><strong>Low HDL</strong></td>
<td>&lt; 40 mg/dL in men and &lt; 50 mg/dL in women</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>≥ 130/85 mmHg</td>
</tr>
<tr>
<td><strong>High Fasting Glucose</strong></td>
<td>≥ 110 mg/dL</td>
</tr>
</tbody>
</table>

Insulin resistance is thought to be the unifying characteristic of the metabolic syndrome. Individuals with the metabolic syndrome (irrespective of glycemic status) are at increased risk of mortality from all causes. The importance of recognizing the metabolic syndrome underscores the design of an appropriate treatment regimen which constitutes an integrative approach to treating all components for improved outcomes.

### 12. References


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