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Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome

The Primary Care Guide to Diagnosis and Management

By

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This book is dedicated to the memory of my father, Salvatore Joseph Codario, World War II veteran, whose multiple hardships endured during the war were only appreciated by me after he died from the ravages of type 2 diabetes.
Series Editor’s Introduction

*Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management* is an important addition to the literature for primary care physicians. It covers concisely and with attention to clinical relevance the full spectrum of insulin resistance and diabetes. This book gives a practical, no-nonsense approach to understanding the basic pathophysiology of diabetes and the metabolic syndrome, an approach to treatment with oral agents and insulin, and an approach to risk factor management. By putting all this information in one readable text, Dr. Codario provides a service to us all, facilitating the understanding of a body of knowledge that cannot be obtained through any attempt to read portions of much larger textbooks in the field.

This textbook will serve as a resource for medical students, residents in family medicine and internal medicine, and attending physicians who wish to update and improve their knowledge in the field of diabetes and the newly emerging science of the metabolic syndrome. In addition, it allows attending physicians the opportunity to obtain Continuing Medical Education credits while performing self-directed learning. At the end of reading *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management*, the physician should feel comfortable and confident that they have acquired a solid understanding of the latest information in the field, and by so doing, should be better able to take excellent care of patients with diabetes and the metabolic syndrome.

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Diabetes has become an increasing problem throughout the world, with an estimated 300 million people expected to be diagnosed with the disease in the next 10 years. One hundred and fifty million people worldwide and 18.2 million people in the United States are currently afflicted, an additional 5.2 million are undiagnosed, and close to 16 million are insulin-resistant. More than 9 million women, 8 million men, and 120,000 children under 18 years of age currently have this disease (1).

Increasing obesity, dietary indiscretions, progressive physical inactivity, and advancing age of the population have all contributed to a sharp rise in the disease. In 1992, 2–4% of all newly diagnosed cases of diabetes in children were type 2 diabetes. By 1999, this number had risen to 45%. African Americans are more hyperinsulinemic and insulin-resistant at puberty with lower resting metabolic rates than white children (2).

According to statistics published by The American Diabetic Association, 15% of the US population has either impaired fasting glucose (6.9%), confirmed diabetes (5.9%), or undiagnosed diabetes (2.8%), including an alarming 22.7% of Mexican-Americans (9.3% confirmed, 4.5% undiagnosed, and 8.9% impaired fasting glucose), and 18.8% of African-American non-Hispanics (8.2% confirmed, 3.6% undiagnosed, and 7% impaired fasting glucose) (3).

Since 1980, the incidence rate of type 2 diabetes has increased by nearly 20%, with a fivefold increase in children and adolescents since 1994. Each year, more than 798,000 new cases are diagnosed in the United States alone, with close to 180,000 diabetics succumbing to the disease and its devastations. Since 1970, the occurrence rate of this disease has risen 700% in this country alone. According to the Centers for Disease Control and Prevention, 33% of men and 39% of women born in 2000 will develop diabetes. The highest lifetime risks are 45% for Hispanic men and 53% for Hispanic women. By the year 2025, nearly 22 million adults in the United States and 300 million adults worldwide will have diabetes! This disease is the leading cause of end-stage kidney disease and blindness in individuals between 20 and 74 years of age, and a major cause of peripheral neuropathy and peripheral vascular disease (4).

Clearly, diagnosing and managing the type 2 diabetic represents a tremendous challenge to the primary care provider already besieged with managed care issues, medication costs, liability concerns, and health access.

*Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management*, along with its Continuing Medical Education component, has been designed as a direct result of 5 years of lecturing throughout the country, listening, teaching, and empathizing with fellow primary care practitioners, and our ongoing fight with this killer disease. I have designed this as an easy-to-reference, state-of-the-art guide to all primary care practitioners, students, caregivers, and patients battling the ravages of this monster.

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INTENDED AUDIENCE
This activity is intended for internal medicine and family physicians, endocrinologists, diabetologists, physician assistants, and nurse practitioners.

OVERALL GOAL
The overall goal of this activity is to update the knowledge of clinicians on strategies and techniques needed to comprehensively manage patients with type 2 diabetes, pre-diabetes, and/or the metabolic syndrome.

LEARNING OBJECTIVES
After completing this CME activity, participants should have improved their overall knowledge and attitudes in regard to treating type 2 diabetes, pre-diabetes, and/or the metabolic syndrome. Specifically, participants should be able to:

• Understand the pathophysiology of type 2 diabetes and metabolic syndrome
• Efficiently use oral agents, insulin and insulin/oral agent combinations to achieve glycemic goals
• Employ lipid lowering agents efficiently to achieve lipid goals
• Select antihypertensive agents effectively to achieve blood pressure goals
• Distinguish the importance of diet and exercise in preventing and controlling diabetes
• Appreciate, understand and apply a comprehensive strategy for risk reduction in diabetes and metabolic syndrome

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INTRODUCTION

Appropriate treatment of type 2 diabetes is dependent on the knowledge of the pathophysiology of the disease, the mechanisms underlying hyperglycemia, and the efficacy of various oral agents and insulins to improve fasting or postprandial hyperglycemia.

In the vast majority of patients with type 2 diabetes, no single genetic defect has been elucidated to explain the etiology of this process; thus, the disease may result from combined effects of multigenic, heterogeneous, complex, and related causes. In a small percentage of individuals with monogenic causes of type 2 diabetes, inheritance of two mutant genes from both parents or autosomal dominant inheritance are responsible (1).

These monogenic causes can effect:
1. β-Cell malfunction as immaturity onset diabetes of youth. Five different types of affected genes exist. All of these genes, except the glucokinase gene, which affects glycolysis, are transcription factors that affect development or gene expression at the β-cell level.
2. Insulin gene mutations demonstrating excessive proinsulin and defective insulin molecules with reduced function at the target tissues.
3. Insulin receptor mutations. More than 50 insulin receptor mutations exist, involving both production and function, including Leprechaunism, Rabson–Mendenhall syndrome, and type A severe insulin resistance syndrome.
4. Lipodystrophy with mutations in the LMNA gene and the seipin protein (1).

Despite this genetic heterogenicity, a consistent phenotype becomes manifested when the disease condition develops, characterized by the following (Table 1):

1. Impaired insulin secretion.
2. Insulin resistance.
3. Increased hepatic glucose production, caused by both increased glycogenolysis and gluconeogenesis.

Regulation of postprandial glucose depends on stimulation of insulin secretion with subsequent suppression of hepatic gluconeogenesis and glycogenolysis. Insulin release
Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome

Subsequently promotes glucose uptake in the muscle and the peripheral tissues. The effect of insulin in suppressing hepatic glucose production and muscle glucose uptake is more potent than the effect of hyperglycemia alone (2).

Fasting glucose levels are dependent on hepatic glucose production (hepatic glycogenolysis and gluconeogenesis), basal insulin levels, insulin sensitivity, and the level and duration of the previous prandial glucose. Elevated fasting glucose levels caused by excessive hepatic glucose production during the sleeping hours (midnight to 8 AM) may be responsible for the majority of the increments in day-long hyperglycemia (3).

After a meal or glucose load, elevated glucose levels stimulate insulin release from the β cell. This secreted insulin binds to the cell-surface receptors. Within the receptor site, two extracellular α subunits bind to the insulin, transmitting a signal to two identical β subunits via the cell membrane. Type 2 diabetic patients have either normal or slightly diminished insulin-receptor-binding affinity. After the binding process, the β subunit is phosphorylized, increasing tyrosine kinase activity and enhancing the phosphorylation of various endogenous protein substrates. This results in a cascading sequence of reactions responsible for the synthesis of RNA, DNA, protein, and intracellular enzymes. Hepatic glucose output is suppressed and glucose uptake by the peripheral tissues, notably skeletal muscle and adipose cells, is subsequently enhanced.

Patients with type 2 diabetes demonstrate excessive hepatic glucose production despite significantly elevated insulin levels. The combination of increased hepatic glucose production and fasting hyperinsulinemia illustrates the insulin resistance in these individuals. This is because hepatic glucose production is profoundly reduced with small increases in plasma insulin. In fact, the ability of insulin to suppress hepatic glucose production is diminished in type 2 diabetic patients across all plasma insulin concentrations, including both pharmacological and physiological levels (5).

One of the most critical effects of insulin is its effect on glucose disposal. Because of impaired muscle glucose uptake, glucose disposal is significantly reduced, resulting in impaired glycogen synthesis glucose oxidation and tissue glucose uptake. Glucose transport is rate-limiting for overall disposal under most normal physiological conditions. Of the five types of glucose transporters identified, the GLUT4 protein is referred to as the insulin-sensitive glucose transporter. This transporter is found in high concentrations in adipose cells, skeletal muscle, and cardiac muscle, and is primarily responsible for glucose uptake and its effects. The GLUT4 proteins are housed in intracellular vesicles and, upon insulin stimulation, they translocate to the cell surface and are inserted into the plasma membrane. This causes glucose to enter the cell. Type 2 diabetic patients usually have normal GLUT4 levels but impaired glucose transport. This may indicate that a flaw exists in the insulin-influenced translocation of GLUT4 to the cell surface. This defective signaling pathway between the receptor and the transport stimulation results in insulin resistance in these patients (3).

Table 1
Classic Metabolic Disturbances in Type 2 Diabetes

- Increased hepatic gluconeogenesis and glycogenolysis
- Impaired insulin secretion
- Insulin resistance

From ref. 4.
Type 2 diabetic patients have multiple intracellular deficiencies in insulin activity. The most conspicuous deficiency is impaired activation of the insulin receptor by stimulating insulin receptor tyrosine phosphorylation. Other deficiencies include the following:

1. Impaired ability to phosphorylate and to stimulate the association of insulin receptor stimulator-1 with the P85 subunit of PI-3 kinase.
2. Impaired phosphorylation of PI-3 kinase.
3. Impaired induction of GLUT4 translocation by PI-3 kinase.

It remains unclear which defects result from the diabetic state and which defects cause the condition (6).

Thus, the impaired ability of endogenous insulin to enhance tissue glucose uptake (primarily in muscle) and suppress hepatic glucose output account for the postprandial rises in plasma glucose that are typical of the diabetic state.

The release of free fatty acids from adipose cells resulting from enhanced lipolysis may also contribute to insulin resistance by inhibiting glucose transport and phosphorylation, followed by reduced rates of glucose oxidation and glycogen synthesis, increased apolipoprotein B secretion, and increased hepatic lipase activity. Chronically elevated free fatty acid levels inhibit insulin secretion from the \( \beta \) cell and decrease insulin sensitivity in the muscle and the liver (7).

Thus, it is no small wonder that insulin resistance has been associated with a wide range of clinical maladies, including polycystic ovaries, hyperuricemia, acanthosis nigricans, decreased fibrolytic activity, dyslipidemia, arteriosclerotic vascular disease, obesity, hypertension, and impaired glucose tolerance.

**THE NATURAL HISTORY OF TYPE 2 DIABETES**

Although both insulin resistance and impaired insulin secretion precede the development of postprandial hyperglycemia and the subsequent type 2 diabetic phenotype, insulin resistance is more prominent in the prediabetic state and plays an important role in the pathogenesis of macrovascular disease. Insulin resistance is commonly the earliest manifestation in the development of type 2 diabetes, typically originating 5–10 years before postprandial glucose levels in the diabetic range (200 mg/dL). As long as the \( \beta \) cell is able to compensate by increased insulin production, normal glucose tolerance is maintained. Thus, not all patients with insulin resistance will develop diabetes (8).

Insulin resistance can be worsened by genetic factors, elevated free fatty acids, hyperglycemia, pregnancy, obesity, sedentary lifestyle, aging, and various medications (i.e., steroids, \( \text{cis} \)-retinoic acid, estrogens, nicotinic acid, oral contraceptives, phenothiazines, and antipsychotic agents). Insulin resistance is characterized by impaired responses to the physiologic effects of this hormone on glucose, lipid, and protein metabolism, and by affecting vascular endothelial function. The endogenous insulin that is secreted is inefficiently capable of suppressing hepatic gluconeogenesis or stimulating glucose use in the muscle and fat (9).

Increases in plasma glucose concentrations by 50–100 mg/dL for as little as 24 hours can cause downregulation of the glucose transport system in the muscle (GLUT4), significantly increasing insulin resistance. Over time, insulin resistance peaks and then plateaus as increases in plasma insulin compensate to maintain the glycemic state.
Fasting hepatic glucose production is increased in both obese and nonobese diabetic patients, compared with normal individuals and those with impaired glucose tolerance that have not met the criteria for diabetes. This increase in hepatic glucose output, owing to increases in glycogenolysis and gluconeogenesis, results in fasting hyperglycemia in type 2 diabetic patients. At some point, usually approximately 10 years after insulin resistance and hyperinsulinemia develop, postprandial hyperglycemia begins to develop, resulting from β-cell dysfunction and/or depletion. Postprandial hyperglycemia is characterized by a delay in first-phase insulin release and blunted second-phase output. This first-phase response plays an important role in the suppression of hepatic glucose production. This progressive deterioration leads to fasting hyperglycemia when insulin levels begin to decline although insulin resistance remains elevated. The progressive nature of the disease and the progressive lack of glycemic control are predominantly caused by this ongoing deterioration of β-cell function with subsequent decreased production of insulin (10).

There is a small subset of patients with type 2 diabetes in whom β-cell dysfunction develops with minimal insulin resistance, but the progressive hyperglycemia induces subsequent insulin resistance. Even those individuals with absolute increases of serum insulin (i.e., higher than normal) have a relative insulin deficiency given their levels of hyperglycemia and severity of insulin resistance.

Although the triple disturbance of insulin resistance, increased hepatic glucose production, and impaired insulin secretion critical to the development of type 2 diabetes has received a great deal of attention in research, the etiological sequence of events resulting in the diabetic state is also of compelling interest. Accelerated hepatic gluconeogenesis and glycogenolysis do not seem to exist in the state of impaired glucose tolerance, where insulin resistance and impaired insulin secretion predominate; in fact, these two abnormalities precede the onset of hyperglycemia in the diabetic type 2 phenotype. Prediabetic individuals have severe insulin resistance, whereas insulin secretion tends to be normal or increased in the prediabetic or impaired glucose tolerant state, including first-phase insulin responses to intravenous challenges. Thus, the type 2 diabetic phenotype evolves from the individual with impaired glucose tolerance and insulin resistance. Although the genetic factors previously mentioned play a key role, acquired factors are also important in susceptible individuals, including sedentary lifestyle, high-fat diet, central visceral obesity, and progressive aging (5).

The body’s response to insulin resistance is to enhance the β cell’s secretion of insulin to maintain normal glucose tolerance. The development of type 2 diabetes from the impaired glucose-tolerant state occurs as the result of an organized sequence of events.

Initially, hepatic glycogenolysis and gluconeogenesis increase, resulting in enhanced basal hepatic glucose production. This is common in all type 2 diabetic patients with fasting hyperglycemia. Insulin resistance tends to become more severe and peak when fasting hyperglycemia develops, because of the degree of glycemic load, aging, sedentary life style, obesity, and any other concomitant factors that can affect insulin sensitivity and resistance. Normalization of hepatic glucose production and improvement in insulin resistance can be achieved through antidiabetic treatment, resulting in significant amelioration of this particular state. The final sequence of events is a progressive deterioration in β-cell function with subsequent decline in insulin-secreting ability (11).
Several factors can be involved in the deterioration in β-cell function, including progressive β-cell exhaustion owing to dietary indiscretion, prolonged glucose toxicity, and preprogrammed genetic abnormalities in β-cell function. Nonetheless, it is the progressive β-cell deterioration that results in a worsening of the hyperglycemic state in the type 2 diabetic patient. The majority of type 2 diabetic patients are overweight and hyperinsulinemic at the time of diagnosis. The subsequent conversion from the impaired glucose-tolerant state to type 2 diabetes is influenced by concomitant medical conditions, distributions of body fat, degree of obesity, ethnicity, sedentary lifestyle, and aging. Thus, one can see that the type 2 diabetic patient is at the end of a progressive triad of metabolic defects whose interrelationships directly affect the natural history and progress of the disease (see Fig. 1) (12).

The impaired glucose-tolerant state is characterized by mild postprandial hyperglycemia, compensatory hyperinsulinemia, and insulin resistance. Clearly, insulin resistance can be present for many years before an individual becomes diabetic. Even at these stages, blood sugar levels are not necessarily elevated.

Understanding the natural history of the disease is important both for the early identification of patients at risk for developing diabetes, and for developing an effective treatment plan including diet and exercise with weight reduction to prevent or delay the development of the disease. Additionally, because insulin resistance is one of the major factors in the prediabetic state and persists in the frankly diabetic individual, improvements in insulin sensitivity with medications like thiazolidinediones and biguanides may be invaluable as first-line agents in early treatment. As we will see in Chapter 6, the glitazones can be invaluable not only in preserving β-cell function but also in regenerating β-cell tissue (13).

Early recognition and treatment is of tremendous advantage because macrovascular disease begins with impaired glucose tolerance and microvascular disease begins with diabetic levels of hyperglycemia. Clearly, patients will die from their macrovascular disease but suffer from their microvascular disease.

Of critical importance is an understanding of how damaging the hyperglycemic state is at the tissue level. At the cellular level, various critical and damaging signaling pathways can be affected by abnormal glucose tolerance. These damaging pathways can be
activated by the direct toxic effects of the hyperglycemic state, or by the metabolic
derivatives of the hyperglycemic state and their by-products, or by the continuous effects
on special signaling pathways at the cellular level caused by glucose metabolites.

Several of these pathways have been characterized. They include the following:

1. Increased formation of advanced glycation endproducts (AGE).
2. Accelerated oxidative stress resulting from reactive oxygen intermediates.
3. Activation of protein kinase C (PKC) isoforms.
4. Increases in the polyol pathway flux.
5. Enhanced aldose reductase activity.
6. Increased flow through the hexosamine pathway, because of overproduction of super-
oxide anions induced by the electron transport chain in the mitochondria.

Aldose reductase is an enzyme that causes accumulation of sorbitol at the cellular
level in various diabetic conditions. Sorbitol accumulation directly leads to tissue
damage and promotes the macro- and microvascular complications of diabetes because
excess intracellular sorbitol levels decrease the concentration of various protective
organic osmolytes. This is seen in the animal model of cataracts that contain decreased
levels of taurine, a potent antioxidant and free-radical scavenger. Interestingly, inhibitors of aldose reductase have restored levels of protective osmolites and prevented
diabetic complications by diminishing sorbitol reduction (13).

In many cellular models, progressive elevations of intracellular sorbitol disrupt the
signal transduction in related cellular functions, and the elevations are usually associ-
ated with the depletion of protective osmolytes, such as taurine and myoinositol. A
deficiency of myoinositol correlates with the clinical neuropathy responsible for the
impaired nerve fiber regeneration and neurological damage associated with diabetes.
Myoinositol deficiencies impair prostaglandin metabolism and nitric oxide synthetase,
disrupting cyclo-oxygenase pathways and nitric oxide production, and resulting in
various defects in the peripheral nerves, the ganglia, and the endoneurium. Some myo-
inositol deficiencies have been improved with the addition of prostaglandin E1 analogs
and other substances.

Sorbitol accumulation may also destroy pericytes, thereby accelerating retinopathy
and neuropathy. The destruction of the pericytes in the nervous tissue and the retina alters
the microcirculation, resulting in tissue ischemia and increased capillary permeability,
which decreases the ability of the tissues to produce vasodilatory nitric oxide, which
enhances angiotensin II production, increases acetylcholine release, and augments symp-
thetic tone. This diminution in nitric oxide, with enhanced polyol pathway flux, slows
nerve conduction, diminishes blood flow within the endoneurium, and depletes protec-
tive intracellular osmolytes (14).

Nitric oxide maintains sodium–potassium adenosine triphosphatase activity, which is
critical to nerve metabolism and impulse transmission and to taurine and myoinositol
uptake. Thus, disruption in nitric oxide production contributes to many vascular and
metabolic defects in the peripheral nerves, endoneurium, and sympathetic ganglia.

Aldose reductase inhibitors prevent many of the microvascular complications of dis-
eease and preserve nerve conduction velocity in animals. However, they have not been
effective in treating or preventing microvascular disease in humans or in relieving symp-
toms. Therefore, mere suppression of aldose reductase pathway flux may be inadequate,
perhaps because of the many avenues of hyperglycemic tissue damage.
The modification or the glycation of lipoproteins or proteins by sugars result in the formation of AGE. Intracellular and extracellular AGE are primarily the result of intracellular hyperglycemia. AGE are formed by the intracellular oxidation of glucose, the fragmentation of phosphate compounds, and the decomposition of glucose-derived deoxyfructose lysine adducts (Amadori product), which react with amino groups from various cellular proteins. This irreversible formation of AGE accelerates with aging and with the diabetic state (15).

Impaired cellular function seen in the various diabetic complications results from the crosslinkage and covalent modification of proteins by intracellular glucose, enhancing abnormal matrix–cell interactions, which reduce neurite outgrowth and impair endothelial cell adhesion, decreasing vascular elasticity.

The glycosylated hemoglobin commonly measured to indicate the average blood sugar over 60 days is the best-known example of an AGE. Enhanced atherogenicity and accelerated atherosclerosis in diabetes is related to the glycosylation of low-density lipoproteins (LDL), phospholipids, and apolipoprotein B. This glycation decreases the clearance of LDL and enhances its deposition within the intima of the blood vessels. The formation of intracellular and extracellular AGE products is promoted by intracellular hyperglycemia (16). These end products are irreversibly formed and tend to accumulate with aging as the result of the auto-oxidation of glucose to form glyoxal in association with fragmentation of various phosphate compounds, which subsequently react with the amino groups of various cellular proteins.

Impaired cellular functioning in diabetes results in alteration of intracellular proteins and abnormal reactions between various matrix components within the cell. This results in false linkages and covalent modification of proteins.

The critical phenomenon of extracellular matrix-cell impairment can explain the Depuytren contractures found in patients with diabetes and other disorders. These contractures result from adhesive capsulitis and the stiffening of periarticular structures with impairment in full extension associated with flexion contractures and the “prayer sign” in advanced diabetes.

Advanced glycosylation end products are also responsible for enhanced permeability of the renal glomerular basement membrane. This permeability results in microalbuminuria and then macroalbuminuria. Inflammatory responses, apoptosis, and mediators of various immune functions are also enhanced by the glycosylation end products, which bind to their receptor for advanced glycation endproducts (RAGE). The binding of AGE to their receptor sites enhances the expression of proinflammatory and procoagulant molecules, enhancing vascular adhesion and thrombogenesis. This could explain the impaired wound healing and enhanced susceptibility to infection that is prominent in diabetic patients (17).

Various AGE inhibitors and RAGE blockade substances have been successful in inhibiting many of the detrimental effects of these substances, including diminished arterial elasticity, decreased nerve conduction velocity, enhanced urinary albumin excretion, and periodontal inflammation.

The hyperglycemic state induces the formation of harmful free radicals, increasing oxidative stress through nonenzymatic reactions and enzymatic processes. This oxidative stress results from a chemical imbalance between the reactive oxygen species known as free radicals and the endogenous cellular defenses against them. The presence of oxidative stress enhances diabetic vascular disease by inhibiting barrier function within
the endothelium, promoting leukocytic adhesion, and reducing circulating levels of nitric oxide. The subsequent accelerated production of prothrombin by the hyperglycemic state helps to explain diabetic hypercoagulation (18).

Free radicals are produced within the mitochondria by oxidative phosphorylation, synthesizing adenosine triphosphate during glucose metabolism and subsequent oxidation. This generates free radicals that can exist independently and contain at least one unpaired electron. These free radicals can combine with hydrogen, forming a hydroxy radical, contributing to the atherogenic process by initiating lipid peroxidation and subsequent foam cell formation. Unless these free radicals are neutralized by antioxidants, they can cause direct cellular damage by oxidation of intracellular mitochondrial DNA, lipids, proteins, and vital cellular structures. These radicals can wreak havoc by indirectly activating the signaling pathways that increase the expression of various gene products responsible for the diabetic microvascular complications of retinopathy, nephropathy, and neuropathy.

By diminishing the bioavailable nitric oxide, oxidative stress enhances inflammatory cell adhesion to the endothelial surface, impairing endothelial barrier function and enhancing diabetic and arteriosclerotic vascular disease and endothelial dysfunction (19).

Eating foods high in AGE and various lipid peroxides enhances a predisposition to postprandial hyperglycemia, impairing endothelial function, increasing lipid peroxidation, and decreasing radical trapping activity. Thus, increased levels of oxidized LDL and decreased levels of antioxidant vitamins, such as C and E, are present in diabetic patients, predisposing these patients to macrovascular disease.

The PKC family is a group of phospholipid-dependent protein kinases. These substances mediate various cellular responses to hormones, neurotransmitters, and growth factors; thus, play a key role in regulating vasodilator release, in endothelial activation and in other important cellular functions. The hyperglycemic state increases PKC levels to pathological ranges, increasing the PKC levels directly and enhancing the production of diacylglycerol (20).

PKC is a proinflammatory substance that stimulates the release of growth factors such as vascular endothelial growth factor (VEGF) which enhances endothelial permeability. The activation of PKC contributes to cardiovascular complications by activating nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidases, accelerating the production of plasminogen activator inhibitor-1. Inhibitors of PKC have reversed or prevented impaired angiogenesis in diabetic retinopathy but the responses seemed to vary depending on the patient’s genetic background.

PKC-activated NF-κB (a nuclear transcription factor) is responsible for signal transduction, thereby exerting proinflammatory effects. The protein kinase family also induces the transcription of various growth factors including the following:

1. Platelet-derived growth factor-β, which induces vascular wall growth.
2. Transforming growth factor, which promotes matrix expansion.
3. Endothelin 1, which is a vasoconstrictor.
4. VEGF, which increases endothelial permeability and may increase neovascularization.

Tissue damage in the diabetic state also involves a shunting of excess intracellular glucose by the hexosamine pathway (3). This diverts fructose phosphate from glycolysis to provide substrates for the formation of O-linked glycoproteins and syntheses of various proteoglycans. Pancreatic β cells may be especially sensitive to activation of
the hexosamine pathway, resulting in increased intracellular hydrogen peroxide levels impairing insulin release and promoting β-cell dysfunction. N-acetyl-L-cysteine, an antioxidant, suppresses many of the pathological changes associated with activation of the hexosamine pathway.

The hyperglycemic state is also responsible for the overproduction of superoxide anions by the electron transport system in the mitochondria. This may be the central mechanism that underlies all of the destructive pathways responsible for the diabetic paradigm. This central mechanism has been offered by some as an explanation underlying the mechanism whereby retinopathy may continue to progress long after normoglycemia has been regained. Hyperglycemia can induce mitochondrial DNA mutations resulting from monocyte adhesion and inhibition of peroxisome proliferator-activated receptor activation. The subsequently defective subunits in the electron transport system caused by these mutations may be responsible for increases in the superoxide anion production, continuing to activate tissue damage despite normoglycemic states (18).

Aberrant regulation of the well-studied NF-κB pathway is associated with arthritis and diabetes and may be among the initial mechanisms in the tissue damage seen in these states. Bovine endothelial cell data have demonstrated that this pathway regulates numerous genes, including those that express VEGF and RAGE.

When abnormally stimulated, this system can generate an ongoing cycle of dysregulatory metabolic derangements.

Diabetic patients may be prone to an enhanced effect of glucosamine on the plasminogen activator inhibitor-1 promoter, which subsequently activates PKC isoforms. Because of this potential complication, patients with type 2 diabetes should be cautioned about using glucosamine. The activation of the hexosamine pathway decreases insulin resistance and promotes β-cell dysfunction, increasing the stress on pancreatic β cells.

Other kinase pathways in the body enhance insulin resistance, worsening hyperglycemia and related tissue damage, and subsequently resulting in a vicious cycle of worsening hyperglycemia and enhanced insulin-activity resistance. Inhibition of various detrimental kinase pathways has been experimentally reversed with the antioxidant α-lipoic acid. In some studies, this has lowered fructosamine levels in patients with type 2 diabetes. The subsequent activation of these various detrimental biochemical pathways is responsible for the cellular damage and the systemic disease characterized by type 2 diabetes (10).

**SUMMARY**

A trio of metabolic defects contributes to the etiology of type 2 diabetes: resistance to insulin, impaired insulin production and secretion caused by deficient nonautoimmune β-cell function, and increased hepatic glucose production. An appreciation of these pathophysiological mechanisms and the natural history of the disease are crucial to understanding the therapeutic maneuvers, treatment plans, outcome data, and risk reduction strategies for the diabetic patient.

**REFERENCES**

CME Questions

1. Which of the following is not true concerning type 2 diabetes?
   a. A single genetic defect can explain the etiology of most cases of type 2 diabetes.
   b. Most type 2 diabetic patients are insulin resistant.
   c. Insulin levels can be low, normal, or high with type 2 diabetes.
   d. Type 2 diabetic patients have impaired insulin secretion.
   e. Insulin secretion suppresses hepatic gluconeogenesis.

2. On which of the following are fasting glucose concentrations not dependent?
   a. Hepatic glucose production.
   b. Basal insulin levels.
   c. Insulin sensitivity.
   d. Level and duration of previous prandial glucose.
   e. Blood pressure.

3. Which of the following is not true regarding insulin resistance?
   a. All patients with insulin resistance are diabetic.
   b. Insulin resistance plays an important role in macrovascular disease.
   c. Insulin resistance is generally increased in obese individuals.
   d. Insulin resistance plateaus when fasting hyperglycemia develops in type 2 diabetic patients.
   e. Insulin resistance is likely to be the earliest manifestation of type 2 diabetes.

4. Which of the following can play a role in decreasing insulin resistance?
   a. Tight glycemic control.
   b. Nicotinic acid.
   c. Antipsychotic drugs.
   d. Obesity.
   e. Sedentary lifestyle.

5. Maintenance of normal glucose tolerance after glucose ingestion does not depend on which of the following?
   a. Insulin secretion.
   b. Suppression of hepatic gluconeogenesis.
   c. Stimulation of glucose uptake by muscle.
   d. Stimulation of glucose uptake in adipose tissue.
   e. Absolute plasma insulin levels.

6. Which of the following statements about the GLUT-4 transporter is true?
   a. It is the only glucose transport unit.
   b. It is independent of insulin.
   c. It is located extracellularly.
   d. It is located mainly in adipose cells.
   e. It is located in vesicles within muscle cells.

7. Which of the following is not a cause of increase in postprandial glucose in type 2 diabetic patients?
   a. Preprandial glucose may be elevated.
   b. There is a loss of first-phase insulin release.
   c. There is blunting of second-phase insulin release.
   d. There is impaired glucose uptake in muscle.
   e. There is increased hepatic glucose production.
8. Which of the following acquired factors does not underlie the etiology of type 2 diabetes?
   a. Sedentary lifestyle.
   b. High-fat diet.
   c. Central obesity.
   d. Visceral obesity.
   e. Menopause.

9. True or false? Fasting hepatic glucose output is increased in nonobese diabetic patients compared with patients who have impaired glucose tolerance.
   a. True.
   b. False.

10. True or false? The first step in the action of insulin at the cellular level is to bind to cell surface receptors.
    a. True.
    b. False.
INTRODUCTION

The American Diabetes Association lists five classes within the group of disorders that represent the diabetic syndrome. These include:

1. Type 1 diabetes.
2. Type 2 diabetes.
3. Diabetes associated with contributing clinical states, diseases, drugs, and/or chemicals.
5. Malnutrition-associated diabetes (1).

TYPE 1 DIABETES (INSULIN-DEPENDENT DIABETES)

This autoimmune disease is the result of genetic environmental triggers. These patients demonstrate CD8-cell infiltration of the islet cells that likely are involved with subsequent β-cell destruction. A long prodrome is usually present from genetic predisposition to onset of disease. These patients may demonstrate various antibodies to islet antigens including insulin, glutamic acid decarboxylase, and tyrosine phosphotase 1A-2. Thus, a combination of markers rather than a single test should be used for predictive and diagnostic testing to enhance sensitivity without losing specificity.

A curious form of autoimmune diabetes is found in Autoimmune Polyglandular Syndrome—Type I. This syndrome results from a mutation of the autoimmune regulator gene, resulting in a wide array of endocrine disturbances.

The environmental trigger in development of type 1 diabetes in genetically susceptible individuals is believed to be the Coxsackie virus. This may be because of the anti-