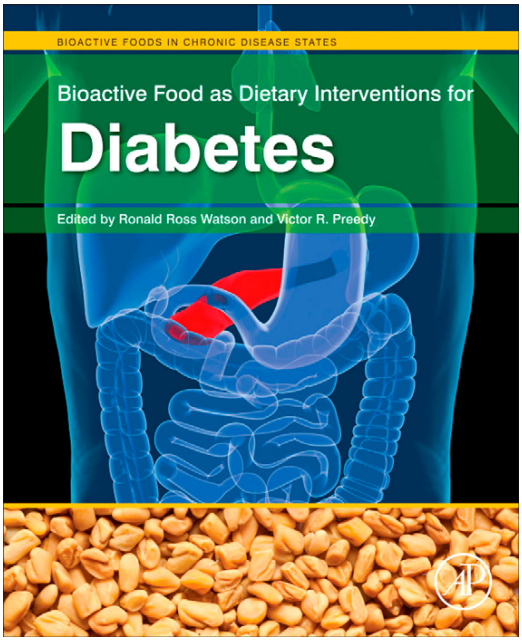

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CHAPTER 4

Diabetes as an Immune Dysfunction Syndrome

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Diabetes afflicts over 250 million people worldwide. Impaired glucose tolerance affects millions. This trend is projected to add an additional 220 millions before 2050. While diabetes kills too many and accounts for about half of disease care costs, it is a choice. Newly developed ultra-low glycemic balanced 200 calorie meals provide better options that can maintain healthier blood sugar levels for hours after consumption through higher fiber and nutrient dense ingredients.

1. DIAGNOSTIC LABORATORY TESTING

There have been more than 90 years of research and clinical experience related to the pathophysiology and management of diabetes since the first insulin products were released to physicians in 1923. However, there continue to be emerging insights into the dynamics of this condition, which has now reached pandemic proportions of global significance.

The clinical perception of diabetes has expanded far beyond simply blood sugar issues. Given the full physiologic impact of this condition, it is important to assess a number of other metabolic markers – to determine the full extent of disturbed insulin and glucose metabolism. Associated secondary pathologies are so widespread that they merit our full clinical attention.

1.1 First-Line Assessments

To confirm the diagnosis of diabetes, elevated blood sugar must be confirmed on at least two occasions to avoid a misdiagnosis of transient, stress-related hyperglycemia as diabetes (Table 4.1).

1.1.1 Glucose and insulin levels

Laboratory evaluations for plasma glucose and insulin levels are the basis of a diabetes diagnosis, providing clinically useful information on glycemic status and accompanying risks (Ferrannini, 1997). Glucose to insulin ratio, fasting insulin levels, and homeostatic model assessment (a method used to quantify insulin resistance and beta-cell function) are

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Table 4.1 Evaluations in the diagnosis of diabetes and sequella

First-line assessments
Primary measures
Glucose, insulin, and HgbA1c
Adjunctive functional tests
Delayed emptying/gastroparesis: C-Octanoci acid (OBT, breath test)
Inflammation/repair need: C reactive protein (hsCRP), intestinal permeability tests
Stress hormones: Free cortisol and Free DHEA + sleep evaluation
Delayed allergies: LRA tests
Methylation and detoxification: Homocysteine
Antioxidant and oxidative stress: Iron, ferritin, oxidized HDL/LDL
Metabolic acidosis: First AM urine pH, venous blood pH

common indices of insulin sensitivity in clinical practice. Elevated glucose levels are required for a formal diagnosis of diabetes. Yet blood glucose levels typically do not rise above the normal range until insulin resistance has been a factor for a period of months or even years.

The ADA guideline for plasma glucose is 70–100 mg dl^{-1} fasting and not more than 140 mg dl^{-1} two hours after a meal (Borai et al., 2007). Table 4.2 details the interpretation of blood glucose levels and reflects the often gradual onset of diabetes.

1.1.2 HbA1c

Hemoglobin A1c is a commonly used laboratory test for the assessment of blood sugar regulation status. Some labs also include a calculation based upon this value that predicts the patient's average daily blood sugar level over the past 3 months. This allows the

Table 4.2 Diabetes diagnostic criteria including suggested 'healthy' range values

Category	Routine tests (ranges) Fasting plasma glucose	Tests of diabetics 2-h plasma glucose
Usual	<100 mg dl^{-1} (<5.6 mmol l^{-1})	<140 mg dl^{-1} (<7.8 mmol l^{-1})
Healthy	<85 mg dl^{-1} (<5 mmol l^{-1})	<115 mg dl^{-1} (<6.3 mmol l^{-1})
Impaired fasting glucose (Prediabetes, metabolic syndrome)	100–125 mg dl^{-1} (5.6–6.9 mmol l^{-1})	
Impaired glucose tolerance (Prediabetes, Syndrome X)		140–199 mg dl^{-1} (7.8–11.0 mmol l^{-1})
Diabetes	≥126 mg dl^{-1} (≥7.0 mmol l^{-1})	≥200 mg dl^{-1} (≥11.1 mmol l^{-1})

Source: The Expert Committee on Diagnosis and Classification of Diabetes Mellitus. (2002). Report. *Diabetes Care* 25, S5–S20.

clinician to look beyond the glucose levels on the day of the test to gain a sense of the typical glucose load throughout the previous days.

1.2 Additional Testing

A range of evaluations are now available that can provide insight on the symptoms and processes affecting the individual patient.

1.2.1 C-octanoic acid breath test

The recently developed C-octanoic acid breath test (OBT) can be useful in detecting and studying gastric emptying (Nohara et al., 2006). Major symptoms of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, belching, or vague abdominal discomfort (Gentilcore et al., 2003).

1.2.2 C-peptide

This peptide serves as a marker of insulin secretion and in some cases is used to differentiate between type 1 and 2 diabetes. C-peptide also has effects on cellular health including that of endothelial cells, with implications for microcirculation.

1.2.3 C-reactive protein (hsCRP)

A common inflammatory marker of repair need that is frequently elevated in diabetes, C-reactive protein levels, suggests higher risk from associated pathology. High-sensitivity CRP has also been shown to be as predictive as LDL as an important cardiovascular risk indicator.

1.2.4 Cortisol and DHEA

An abnormal cortisol pattern (Miller et al., 1994) is associated with several factors: high-stress lifestyle, high-carbohydrate diet, insulin resistance, visceral obesity (Rosmond, 1991), and disrupted sleep and day–night rhythms. Saliva testing with four samples is currently considered the most clinically useful measurement, providing a window on the functionality of the hypothalamic–pituitary–adrenal axis.

1.2.5 Lymphocyte Response Assay (LRA) tests

Reduction of immune reactivity and inflammation is a primary clinical goal in diabetic patients. LRA tests for food sensitivities provide a practical strategy that can support improvement in diabetic and prediabetic patients by reducing antigen load. For example, cow's milk has been associated with the development of type 2 diabetes. Our research identified dairy antigens in 69% of patients with type 2 diabetes and 28% of those with type 1 (Jaffe et al., 2004, 2006). Clinical reports also indicate that the removal of reactive foods from the diet is often an important step in overcoming insulin resistance (Martin et al., 1991).

1.2.6 Fibrinogen

This is a common assessment to determine if there is a tendency to a coagulation disorder. While it does not indicate a clotting disorder per se, elevated fibrinogen suggests that inflammation and irritation of the endothelial blood vessel linings are affecting fibrin dynamics and microcirculation.

1.2.7 Homocysteine

Elevated homocysteine levels indicate impaired methylation and detoxification. High homocysteine predicts increased risk of cardiovascular disease, stroke, dementia, peripheral neuropathy, and microcirculation damage – and proposes the value of further evaluation of B12 and folic acid levels. This lab test is especially important in patients with hypochlorhydria, those on metformin or antacid medication (including proton pump inhibitors and H2 blockers), and any patient older than 65 years.

1.2.8 Insulin-like growth factor binding protein-1

This carrier protein for insulin-like growth factor (IGF-1) is emerging as a useful marker of insulin resistance.

1.2.9 Intestinal hyperpermeability test

Leaky gut has been associated with diabetes in a number of studies. A new test is now available for this condition, the intestinal antigenic permeability test. Emerging research suggests that managing a leaky gut is a critical step in improving systemic chronic illness. In the management of insulin resistance, secondary inflammation due to antigenic stimulation from leaky gut can significantly impede improvement. Foreign antigens of any kind increase immune defense work and reduce both repair and cancer surveillance.

1.2.10 Iron and ferritin

Iron levels are relevant to both insulin resistance and cardiovascular conditions, and are a routine measure included in the CBC. Elevated iron or ferritin is known to cause an increase in free radicals. High iron or ferritin can also be an obstacle to reducing insulin resistance. In terms of lab chemistry, the measurement of iron is a complex issue. To rule out iron as a factor in insulin resistance, it is recommended that a complete anemia panel be considered. Ferritin is one of the most useful measures of iron status and is often overlooked. Elevated iron, ferritin, and all inflammatory markers are linked to antioxidant deficits, particularly ascorbate, as well as metabolic acidosis.

1.2.11 Oxidized LDL (oxLDL)

It has long been understood that the major risk due to elevated total and LDL cholesterol is related to the degree of oxidation of LDL. A test is now available to directly measure levels of LDL, HDL, and cholesterol oxidation.

1.2.12 Metabolic acidosis risk

A first morning urine pH is a self-assessment monitoring tool that can be clinically useful. A urine pH of 6.5–7.5 suggests that the body's buffering systems are adequate and that there is no net acid excess. Acid-forming diets have been associated with increased hypertension, higher total and LDL cholesterol, and greater BMI and waist circumference. Six (6) or more hours of rest are needed for the urine in the bladder to equilibrate with cells lining the bladder.

1.2.13 Sleep survey or evaluation

Recent research findings on sleep and insulin resistance suggest that administering a brief sleep survey with diabetes is a useful diagnostic screening tool. Assessment of sleep is particularly important, given the association between increased waist circumference, abdominal adipose tissue, and both insulin resistance and obstructive sleep apnea. The recommendation of a sleep study may be warranted.

2. KEY CLINICAL ISSUES

Glucose dysregulation includes more than simple blood sugar-energy chemistry. Disturbed glucose–insulin interactions affect nearly all aspects of physiology including energy production, lipid chemistry, impact on protein requirements, autoimmune regulation, and gut function.

2.1 Energy Metabolism

Cells typically extract energy from food in the following order: (1) glucose, (2) fructose, (3) amino acids, and (4) fats. Generally, fat is metabolized only when sugar and amino acids are no longer available to sustain cell energy. The abundance of simple sugars and animal protein in the diet of industrialized nations forestalls fat metabolism. As long as patients are consuming high-glucose, high-fructose, or high-protein diets, they will not burn fat.

2.1.1 Glucose

As a constituent of whole foods, simple sugars are accompanied by the essential metabolic cofactors required for their effective use as fuel and energy. However, glucose that has been refined and purified is nutrient-depleted and therefore devoid of the nutritional cofactors essential for proper metabolism. White sugar and other refined sweeteners promote diabetes by depleting essential metabolic factors to metabolize the glucose.

2.1.2 Fructose

Fructose (i.e., isomerized glucose) occurs naturally as a component of whole fruit. Metabolized as part of a complete food, the accompanying fiber slows and modulates fructose

release. However, in many manufactured beverages and foods, refined fructose (without fiber) is used as the primary sweetener. Fructose is not regulated by insulin, so it is easily transported into the body's cells. Once inside the cells, fructose is rapidly converted back into glucose, compromising insulin receptors, and contributing to insulin resistance. This metabolic deception often has adverse consequences, and although high fructose foodstuffs such as agave and fruit concentrates are not considered 'high glycemic' foods, they ultimately contribute to glycemic load on the body.

2.1.3 Protein metabolism in diabetes

In the absence of effective energy metabolism from glucose, amino acids are catabolized from muscle tissue and converted into keto acids that increase the level of metabolic acids. As protein is directed to cellular energy production, less of it is available for repair functions when glucose metabolism is compromised. In a healthy state, muscle turnover is approximately 2% a day, but it decreases during metabolic dysregulation. Inflammatory repair deficit causes additional muscle damage and increases the need for increased immune system repair workload.

2.1.4 Fat metabolism

Obesity, particularly abdominal 'belly fat,' is a primary marker of insulin resistance with the release of nonesterified fatty acids, glycerol, hormones, fibrinogen, pro-inflammatory cytokines, and C-reactive protein, together with a wide range of adverse sequella (Haffner, 2007). The metabolic dynamics of this adipose tissue can cause extreme blood sugar highs and lows, driving food cravings and subsequent weight gain. Clinically, the measurement of waist girth is one of the five primary markers of metabolic syndrome. Estrogens, particularly estrone, produced in adipose tissue can also significantly increase cancer risk.

2.2 Autonomic Neuropathy

Systemic insulin resistance contributes to the likelihood of energy-linked issues. Over 90% of brain activity is directed to regions of the brain that control autonomic regulation, including every aspect of digestive function. Insulin-glucose dysregulation problems slow the firing of the brain due to inflammation, oxygen deficit, microcirculation changes, and the inability of brain cells to produce consistent energy. All these conditions contribute to a reduction in activity in the ponto medullary region of the brain, specifically the vagal (parasympathetic) nervous system. Reduced stimulation of vagal nuclei, in turn, decreases intestinal blood flow, suppresses intestinal immune activation, and alters intestinal motility. These changes contribute to the increased likelihood of maldigestion and long transit time favoring intestinal yeast or bacterial overgrowth and increased intestinal hyperpermeability (leaky gut). Activation of leaky gut causes not only the activation of the gut immune system and antigen release but also intestinal inflammation. Autonomic neuropathy, mentioned earlier, can be a contributing cause of any of these maldigestion issues.

2.3 Immune Dysregulation and Increased Permeability

Loss of immune tolerance, for example, in conditions such as hyperpermeability (Vaarala et al., 2008) in the gut is now believed to potentiate diabetes (Bosi et al., 2006). Improvement in permeability and gut immune tolerance improves glucose status (Jaffe et al., 2006). Diabetes includes immune system dysregulation with reduction of protective immunity, activation of cytokine cascades, increase in free radical-injury, and impaired healing and repair (Jaffe et al., 2004). Protein glycation (alteration in protein structures, due to insulin resistance and related glucose regulatory disorders) depletes antioxidant scavengers and enzymes. Alterations in protein structure potentially cause cross-linking in the arteries and in tissues and fascia throughout the body, contributing to the subtle tissue effects of impaired function sometimes linked to aging.

This altered redox equilibrium is due to antioxidant depletion and this accentuates inflammatory injury. Low antioxidant levels leave the body more vulnerable to injury. Oxidative stress plays a major role in the pathogenesis of diabetic macro- and microvascular complications by contributing to damage of the endothelial lining of the vasculature. The clinical consequences of these deficits are inflammation, as measured by elevated C-reactive protein, tumor necrosis factor (TNF), fibrinogen, ferritin, and inflammatory cytokines.

2.4 Maldigestion

Major issues in digestive compromise include gastroesophageal reflux, dyspepsia, dysbiosis, malabsorption, and unhealthy delayed transit times (Kuo et al., 2007).

2.4.1 Reflux

Research has shown a higher prevalence of abnormal gastroesophageal reflux among asymptomatic diabetic patients than among the general population (Wang et al., 2008). The presence of abnormal reflux in diabetic patients has been reported at 38.7% in patients with cardiovascular autonomic neuropathy (CVAN), compared with a prevalence of 10.5% in diabetic patients who test negative for CVAN (Lluch et al., 1999).

2.4.2 Dyspepsia

Diabetic patients may present vague discomfort in the upper digestive tract that could be described with the catch-all term dyspepsia. Underlying issues can include abnormal motility, decreased enzyme production, and hypochlorhydria secondary to vitamin B12 deficiency.

2.4.3 Dysbiosis

These conditions include bacterial overgrowth such as SIBO (small intestinal bacterial overgrowth), yeast overgrowth, parasitic infection, and chronic latent viral infection.

These infectious processes can influence motility, enzyme and HCl secretion, B12 levels, digestion, absorption, levels of inflammation, gut immune function, and their sequella.

2.4.4 Malabsorption

Impaired uptake of nutrients from the GI tract as a result of numerous causes, with a seemingly endless array of potential symptoms, foremost including fatigue, low HCl output, B12 deficiency and, in some cases, intrinsic factor or autoimmune issues, hypervitaminosis D, failure to thrive, and even some dementias.

2.4.5 Delayed gastric emptying

Delayed gastric emptying is observed in 40% of patients with long-standing type 1 and type 2 diabetes. Accelerated gastric emptying, on the other hand, is manifested in about 20% of recently diagnosed patients. Hyperglycemia slows gastric emptying, whereas hypoglycemia may accelerate it. Optimizing glycemic control is the key.

2.5 Autacoids: Profound Biochemical Effects

Dysregulation from diabetes includes a wide range of potential effects, including those mediated by the autacoids. Autacoids are non-blood-borne biochemical factors with brief localized effects, which take forms that can be either stimulating or inhibitory, such as vasoconstrictors and vasodilators. The autacoids include

- Eicosanoids, inflammatory messengers derived from Omega 6 fats
- Angiotensin excess that increases blood pressure
- Endothelins that induce small vessel vasoconstriction and increase blood pressure
- Histamine, an amplifier or immediate type 1 allergic reactions
- Nitric oxide (NO) that increases with repair need
- Serotonin, affected by carbohydrate loading and regulation

The interaction of autacoids with insulin and insulin-like growth factor hormones includes effects on IGF-1, 2, 3, 4, and other growth inducers. Monitoring and management of these factors may become more relevant in clinical practice as increasingly subtle lab tests are found outcome predictive.

3. DIAGNOSES AND COMORBIDITIES

The following conditions reflect current, established categories of insulin–blood sugar dysregulation.

3.1 Prevalent Comorbidities

Due to diabetes, macrovascular and microvascular pathologies are prominent in every major physiologic system in the body. When blood flow is impaired and/or blood pressure increases, so do risks and complications.

3.1.1 Vascular sequella and neurodegeneration

Atherosclerosis accelerates in poorly controlled diabetes and manifests as endothelial and phagocytic immune cell injury due to incomplete repair. People with diabetes also are at risk of neurodegeneration. The risk of Alzheimer's and stroke is 2–4 times higher in diabetics than in the general population (American Diabetes Association, 2011). Vascular consequences related to carotid and cerebrovascular disease, hypertension, and changes in the blood–brain barrier are common. Metabolic consequences that arise are related to alternating hypoglycemic and hyperglycemic episodes, hyperosmolarity, metabolic cellular acidosis, ketosis, uremia, neuroendocrine, or neurochemical changes (Mooradian, 1997). Diets high in fat (especially trans and saturated fats) (Morris et al., 2006), processed foods, and high glycemic index foods (Greenwood et al., 2003) adversely affect cognition, whereas those high in fruits, vegetables, cereals, and fish are associated with better cognitive function and lower risk of dementia (Parrott and Greenwood, 2007).

In these neurological conditions, the hippocampus, frontal cortex, hypothalamus, and other regions of the brain responsible for memory have measurably lower levels of insulin and insulin-like growth factor in patients with Alzheimer's type dementia. Several lines of research now indicate that Alzheimer's senility is diabetes on the other side of the blood–brain barrier (van Elderen et al., 2010). Symptoms of cognitive decline have also been documented in patients with prediabetes and early type 2 diabetes (Baker et al., 2011). In some cases, elevated copper, lead, or mercury may also be a factor.

3.1.2 Hyperlipidemia and hypertension

Poorly controlled diabetes contributes to hyperlipidemia and hypertension, which can become increasingly more involved, elevating the risk of myocardial infarction, strokes, and aortic aneurysms. Organ specific microvascular complications include macular degeneration, optic neuritis, nephropathy, peripheral neuropathy, and autonomic neuropathy including gastrointestinal, genitourinary, or cardiovascular symptoms, as well as sexual dysfunction. It is important to remember that a high-carbohydrate diet can cause lipid dysregulation just as a high-fat diet appears to affect lipid levels.

3.1.3 Kidney disease

Diabetes frequently involves renal compromise. Since the kidneys aid the regulation of blood pH, when individuals with nephropathy eat a diet high in acidifying foods such as sugars, starches, and meat, the kidneys may be slow to adapt. An extensive body of research has linked metabolic acidosis with chronic kidney disease (Souto et al., 2011). Avoiding excess dietary protein is one way to slow the progression of diabetic renal disease (Robertson et al., 2007). Reduction in protein intake typically improves insulin sensitivity and has beneficial influences on different steps in carbohydrate metabolism. Consumption of low glycemic index foods and a low-phosphate diet is also recommended for these patients.

3.1.4 Liver diseases

Fatty liver disease and steatohepatitis (Yeh and Brunt, 2007) are associated with obesity and diabetes. The hepatitis C virus (HCV) also induces insulin resistance because of the increased production of TNF by the HCV core antigen. Routine glucose tolerance testing has been suggested in patients with chronic hepatitis C (Lonardo et al., 2007).

3.1.5 Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a complex disorder affecting up to 10% of all American women. It is the leading cause of female infertility and comprises both hormonal and metabolic abnormalities, which can include impaired glucose tolerance, type 2 diabetes, vascular disease, dyslipidemia, and obstructive sleep apnea (Hoffman and Ehrmann, 2008).

4. CONCLUSION

Improved glycemic control is the goal of modern diabetes management and translates to better long-term outcomes. Half of the overall morbidity and mortality in industrial societies are due to diabetes and its complications. Each year, this adds over half a million avoidable deaths at high cost and suffering. Our research has shown that comprehensive care using functional interventions in a patient-specific treatment plan can be more cost and outcome effective than current conventional diabetes care alone.

Diabetes Diagnoses

Type 1 diabetes (5–10% of cases) is deficiency of insulin production usually following an autoimmune destruction of pancreatic islets – 'insulinitis.'

Type 2 diabetes (90–95% of cases) is usually due to insulin resistance and inadequate compensatory insulin secretion from the pancreas, with high levels of insulin in the bloodstream.

Gestational diabetes is a variant of type 2 diabetes occurring in approximately 4% of all pregnancies, which increases the risk of the offspring developing diabetes (American Diabetes Association, 2007).

Latent autoimmune diabetes of the adult (LADA) occurs in nonobese, anti-insulin antibody-positive patients and can be diagnosed decades before an individual becomes frankly diabetic (Palmer and Hirsch, 2003). People with metabolic syndrome, prediabetes, and syndrome X are usually LADA positive. In contrast, people who are not insulin resistant are rarely LADA positive.

Type 1.5 diabetes is an emerging syndrome that includes symptoms of autoimmune type 1 diabetes, anti-insulin antibodies, and phenotypic type 2 diabetes. These patients are usually obese and insulin resistant.

Type 3 diabetes is another emerging syndrome, characterized by insulin resistance and neurodegeneration. Insulin resistance in the brain results in accelerated nerve cell oxidative stress, cell damage, poor function, and early death (de la Monte et al., 2006).

REFERENCES

American Diabetes Association, 2007. Diagnosis and classification of diabetes mellitus. Diabetes Care 30, S42–S47.

American Diabetes Association, 2011. Diabetes Statistics. Available at: http://www.diabetes.org/diabetes-basics/diabetes-statics/. Accessed 03-25-2011.

Baker, L.D., Cross, D.J., Minoshima, S., et al., 2011. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Archives of Neurology 68, 51–57.

Borai, A., Livingstone, C., Ferns, G.A., 2007. The biochemical assessment of insulin resistance. Annals of Clinical Biochemistry 44, 324–342.

Bosi, E., Molteni, L., Radaelli, M.G., et al., 2006. Increased intestinal permeability precedes clinical onset of type 1 diabetes. Diabetologia 49, 2824–2827.

de la Monte, S.M., Tong, M., Lester–Coll, N., Plater Jr., M., Wands, J.R., 2006. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: Relevance to Alzheimer's disease. Journal of Alzheimer's Disease 10, 89–109.

Ferrannini, E., 1997. Insulin resistance is central to the burden of diabetes. Diabetes Metabolism Research and Reviews 13, 81–86.

Gentilcore, D., O'Donovan, D., Jones, K.L., Horowitz, M., 2003. Nutrition therapy for diabetic gastroparesis. Current Diabetes Reports 3, 418–426.

Greenwood, C.E., Kaplan, R.J., Hebblethwaite, S., Jenkins, D.J., 2003. Carbohydrate-induced memory impairment in adults with type 2 diabetes. Diabetes Care 26, 1961–1966.

Haffner, S.M., 2007. Abdominal adiposity and cardiometabolic risk: Do we have all the answers? American Journal of Medicine 120, S10–S17.

Hoffman, L.K., Ehrmann, D.A., 2008. Cardiometabolic features of polycystic ovary syndrome. Nature Clinical Practice Endocrinology and Metabolism 4, 215–222.

Jaffe, R., Mani, J., Trocki, T., Mehl-Madrona, L., 2004. First line comprehensive care. The diabetes continuum of insulin, glucose, energy dysregulation: Better clinical management of causes improves outcomes, reduces risks and vascular complications. Original Internist 11, 11–27.

Jaffe, R., Mani, J., DeVane, J., Mani, H., 2006. Tolerance loss in diabetics: Association with foreign antigen exposure. Diabetic Medicine 23, 924–925.

Kuo, P., Rayner, C.K., Jones, K.L., Horowitz, M., 2007. Pathophysiology and management of diabetic gastropathy: A guide for endocrinologists. Drugs 67, 1671–1687.

Lluch, I., Ascaso, J.F., Mora, F., et al., 1999. Gastroesophageal reflux in diabetes mellitus. American Journal of Gastroenterology 94, 919–924.

Lonardo, A., Carulli, N., Loria, P., 2007. HCV and diabetes. A two-question-based reappraisal. Digestive and Liver Disease 39, 753–761.

Martin, J.M., Trink, B., Daneman, B., Dosch, H.M., Robinson, B., 1991. Milk proteins in the etiology of insulin dependent diabetes mellitus (IDDM). Annals of Internal Medicine 23, 447–452.

Miller, J.E., Bray, M.A., Faiman, C., Reyes, F.I., 1994. Characterization of 24-h cortisol release in obese and non-obese hyperandrogenic women. Gynecological Endocrinology 8, 247–254.

Mooradian, A.D., 1997. Pathophysiology of central nervous system complication in diabetes mellitus. Journal of Clinical Neurosciences 4, 322–326.

Morris, M.C., Evans, D.A., Tangney, C.C., et al., 2006. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Archives of Neurology 63, 1085–1088.

Nohara, S., Iwase, M., Imoto, H., et al., 2006. Gastric emptying in patients with type 2 diabetes mellitus and diabetes associated with mitochondrial DNA 3243 mutation using 13C-octanoic acid breath test. Journal of Diabetes and its Complications 20, 295–301.

Palmer, J.P., Hirsch, I.B., 2003. What's in a name? Latent autoimmune diabetes of adults, type 1.5, adult-onset, and type 1 diabetes. Diabetes Care 26, 536–553.

Parrott, M.D., Greenwood, C.E., 2007. Dietary influences on cognitive function with aging: From high-fat diets to healthful eating. Annals of the New York Academy of Sciences 1114, 389–397.

Robertson, L., Waugh, N., Robertson, A., 2007. Protein restriction for diabetic renal disease. Cochrane Database of Systematic Reviews CD002181 Oct 17.
Rosmond, R., 1991. Stress induced disturbances of the HPA axis: A pathway to type 2 diabetes? Medical Science Monitor 9, RA35–RA39.
Souto, G., Donapetry, C., Calviño, J., Adeva, M.M., 2011. Metabolic acidosis-induced insulin resistance and cardiovascular risk. Metabolic Syndrome and Related Disorders 9, 247–253.
Vaarala, O., Atkinson, M.A., Neu, J., 2008. The "perfect storm" for type 1 diabetes: The complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. Diabetes 57, 2555–2562.
van Elderen, S.G., de Roos, A., de Craen, A.J., et al., 2010. Progression of brain atrophy and cognitive decline in diabetes mellitus: A 3-year follow-up. Neurology 75, 997–1002.
Wang, S., Pitchumoni, C.S., Chandrarana, K., Shah, N., 2008. Increased prevalence of symptoms of gastroesophageal reflux diseases in type 2 diabetics with neuropathy. World Journal of Gastroenterology 14, 709–712.
Yeh, M.M., Brunt, E.M., 2007. Pathology of nonalcoholic fatty liver disease. American Journal of Clinical Pathology 128, 837–847.

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