Introduction, Background and Various Types

MICHELLE RENEE CAMPBELL, MASIH SHOKRANI

LEARNING OBJECTIVES

1. Compare and contrast the causes, symptoms and pathophysiology of type 1 and type 2 diabetes mellitus.
2. Discuss diabetic ketoacidosis and its clinical presentation.
3. Describe the symptoms and pathophysiology of gestational diabetes
4. Recognize various other forms of diabetes

ABBREVIATIONS: DKA - Diabetic ketoacidosis, IA-2 - Islet antigen-2, IA-2B - Islet antigen-2B, IDDM - Insulin-dependent diabetes mellitus, MODY - Maturity-onset diabetes of the young

INDEX TERMS: History of Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gestational Diabetes, Causes and Types of Diabetes Mellitus

Clin Lab Sci 2016;29(2):106-110

Michelle Renee Campbell, MLS (ASCP), *Medical Laboratory Sciences Program, Northern Illinois University, DeKalb, IL*

Masih Shokrani, Ph.D. MT (ASCP), *Medical Laboratory Sciences Program, Northern Illinois University, DeKalb, IL*

Address for Correspondence: Masih Shokrani, Ph.D. MT (ASCP), *Associate Professor, Medical Laboratory Sciences Program, Northern Illinois University, DeKalb, IL, 60115-2828, 815-753-6323, mshokrani@niu.edu*

INTRODUCTION

An understanding of the various forms of diabetes mellitus is critical for healthcare workers. At least 29.1 million Americans have diabetes; with about 8.1 million of these individuals unaware they have the disease.[1] Worldwide, it is estimated that 150 million people live with diabetes mellitus.[2] In the United States, an additional 86 million individuals aged 20 years and older are believed to be prediabetic.[1] This figure does not take into account the growing number of prediabetic children across the globe.

Diabetes mellitus results in ineffective insulin utilization and hyperglycemia.[3] Healthy fasting blood glucose levels are between 70 and 100 mg/dL (~3.9-5.5 mmol/L). Diabetic individuals have chronic hyperglycemia, characterized as fasting blood glucose levels of 126 mg/dL (~6.9 mmol/L) and above.[4] Acute complications include severe elevations in blood sugar levels that, if occurring in a dehydrated patient, can lead to an increase in blood osmolality and coma.[5] Ketoacidosis, the accumulation of high levels of ketones in the blood, can also occur and be life threatening for diabetic individuals.[6] Chronic effects of uncontrolled blood glucose in diabetic patients include increased risk of complications involving the eyes, heart, kidneys, peripheral nerves and blood vessels.[7]

History of Diabetes Mellitus Treatment

While the history of diabetes mellitus spans several centuries, the use of insulin in the treatment of diabetes mellitus was not introduced until the 1920s. In the 1930's, Roger Hinsworth differentiated between type 1 and type 2 diabetes mellitus, describing them as "insulin sensitive" and "insulin insensitive".[8] Hemoglobin A1c testing came into use in the 1980's and dramatically improved the monitoring and treatment of diabetes mellitus.[9] In 1995, the Food and Drug Administration approved the use of metformin for blood glucose control,[10] which was followed shortly by the development of fast-acting insulin in 1996.[11] Advances in diabetes mellitus diagnosis and treatment continue to be improved upon today.

Types of Diabetes Mellitus

Type 1 Diabetes Mellitus

Type 1 diabetes, often referred to as juvenile-onset or insulin-dependent diabetes, is present in only 5% of individuals with diabetes, and is most frequently diagnosed in adolescents.[12] Type 1 diabetes is a chronic

condition with 80 people per day being diagnosed in the United States alone.[13]

Type 1 diabetes mellitus is diagnosed most often in children, although it may affect all age groups. Type 1 diabetes mellitus is usually characterized as a progressive autoimmune disorder wherein the insulin-producing β cells are destroyed by the body's own immune system. The β cells of the pancreatic islets are responsible for producing insulin, which in turn lowers blood glucose.[13] Type 1 diabetes mellitus occurs when these pancreatic β cells are destroyed through autoimmune attacks.[14] With the lack of insulin, glucose accumulates in the blood instead of being used for energy by the cells. This leads to many of the symptoms of type 1 diabetes mellitus, including hyperglycemia and fatigue.[13] It is commonly believed that viruses are a potential cause of type 1 diabetes mellitus. It has been postulated that infections with certain viruses, such as Coxsackieviruses, lead to β cell destruction.[15]

Hyperglycemia in type 1 diabetes is due to destruction of β cells in the pancreatic islet of Langerhans, resulting in a large or total loss of insulin production and subsequent secretion. Common features of type 1 diabetes mellitus include sudden onset and dependence on medicinal insulin. Pathogenesis of type 1 diabetes beyond β cell destruction includes the presence of autoantibodies such as glutamic acid decarboxylase, insulin, islet cell and tyrosine phosphatase IA-2 and IA-2B autoantibodies.[16]

Type 1 diabetes often leads to the formation of ketone bodies, known as diabetic ketoacidosis (DKA).[16] DKA is more common in type 1 diabetes mellitus; however, it can also occur with type 2 diabetes mellitus.[17] Roughly 30% of children with type 1 diabetes mellitus present with acute DKA.[18] Patients with DKA display acidosis, electrolyte imbalances, and are often dehydrated. The oxidation of fatty acids generates acetoacetate, acetone and β-hydroxybutyrate. Acetoacetate and β-hydroxybutyrate are ketone bodies that often lead to the development of ketoacidosis. Minor factors leading to the development of ketoacidosis include the presence of fatty acids, lactate and a variety of organic acids.[19]

Various symptoms are associated with the occurrence of DKA. Deep breathing at an increased rate with a stereotypical "fruity" smelling breath is commonly noted, as well as dry, flushed skin. Patients also may experience nausea, abdominal upset, difficulty breathing, and mental confusion.[19]

Several methods of treatment exist for DKA, most of which utilize three steps. Physicians often will order intravenous fluid replacement to replenish fluid lost from additional urination often associated with DKA. Fluid replacements will also dilute the blood, which has increased concentration of glucose. To protect cardiac, muscular and nervous functions, electrolyte therapy also may be used. In order to increase blood pH from acidic levels, insulin will be delivered intravenously to patients in DKA to lower blood sugar to safe levels.[20]

A hallmark feature often noticed in type 1 diabetics is Kussmaul-Kien respiration. Kussmaul-Kien respirations are a pattern of deep breathing used by the body to rid itself of accumulated hydrogen ions by exhalation of carbon dioxide. Additional lab findings in type 1 diabetics include anion gaps often above 16 mmol/L, high serum osmolality and hyperkalemia.[16]

Some controversy exists within the medical community regarding the exact cause of type 1 diabetes mellitus. Arguments exist for both genetic predisposition and viral infections as causes of β cell destruction. Researchers have discovered at least 18 genetic markers (IDDM1-IDDM18) that have relevance to type 1 diabetes mellitus. Inheritance of type 1 diabetes mellitus is possible. There is only a 10% odds of being affected when a first degree relative has type 1 diabetes mellitus. Furthermore, if an identical twin has type 1 diabetes mellitus, there is only a 33% chance that the other twin will be affected as well.[15]

Complications from type 1 diabetes mellitus include increased risk of heart and blood vessel problems, such as myocardial infarction, stroke and coronary artery disease. Neuropathy is also common, as excess sugar in the blood can damage vessel walls in capillaries that feed the nerves. Nerve damage can be widespread and affect areas such as the arms, legs, feet, hands and even the gastrointestinal tract. Nerve damage in the eyes may lead to retinopathy and eventually blindness. Diabetes can lead to low mineral density, thus causing osteoporosis and an increased risk for bone damage. Risk of deafness is also increased in those with uncontrolled diabetes. Keeping blood sugar within the normal range is vital to prevent serious complications.[21]

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is the most prevalent form of diabetes and is seen in over 90% of diabetic patients. Similar to type 1 diabetes mellitus, type 2 diabetes mellitus presents with characteristic hyperglycemia. Insulin is required for the proper uptake of glucose into the cells within the body. In type 2 diabetes mellitus, however, there is a lack of sufficient insulin or the body no longer responds to insulin. Insulin resistance is the most common manifestation of type 2 diabetes mellitus.[22]

Type 2 diabetes mellitus develops gradually. Overweight and inactive individuals are the most likely to be diagnosed with type 2 diabetes mellitus, although it is encountered in individuals of average body weight, especially geriatric individuals. The most significant risk factors for developing type 2 diabetes mellitus include a family history of type 2 diabetes mellitus, physical inactivity and having a diet high in carbohydrates and sugars. Symptoms of type 2 diabetes mellitus include fatigue and lethargy, polydipsia and polyuria.[23]

Ketoacidosis does not occur as frequently in type 2 diabetes, but hyperosmolar comas are a more common occurrence. Glucose being produced in excess quantities, in combination with an imbalance of urine production and excretion, contribute to the hyperosmolar state. Frequently, hyperosmolar states are followed by pancreatitis, heart disease and strokes and could lead to death. Glucose values can rise to levels exceeding 300-500 mg/dL (~16.5-27.5 mmol/L). Dehydration occurs, causing a lack of the urine output required to rid the body of excess glucose. In contrast to the case with type 1 diabetes, ketone bodies usually are not seen in hyperosmolar states, as the conditions do not allow glucagon to stimulate the breakdown of fats. Laboratory findings seen in hyperosmolar states include high glucose levels (300 to above 1000 mg/dL or ~16.5-27.5 mmol/L), increased osmolality, elevated blood urea nitrogen, marginally decreased bicarbonate and normal or high levels of sodium and potassium.[16]

Several severe complications from type 2 diabetes mellitus may arise that can affect numerous body systems. Hospitalizations due to myocardial infarctions in previously diagnosed adult diabetics 20 years old or over were 1.8 times more common and strokes rates 1.5 times higher than in those without diabetes.[24] Kidney damage is also common in diabetics, frequently leading to the need for dialysis or kidney transplantation.[25] Neuropathy and other nerve disorders affecting the extremities are commonly encountered in diabetic patients. Due to loss of feeling and an inability to notice pain from injuries, amputations are common, particularly those of toes and feet. Infections may develop at sites of unnoticed sores or injuries. If infections are left untreated for prolonged periods of time, they may spread to areas such as the bone and require amputation of the extremity.[26] Complications of type 2 diabetes mellitus involving vision, such as retinopathy and blindness, also are increased.[27] According to the Center for Disease Control and Prevention "a person with diabetes has a shorter life expectancy and about twice the risk of dying on any given day as a person of similar age without diabetes" with medical bills doubling that of their non-diabetes counterparts.[28] Complications may be prevented or reduced through adequate monitoring of blood glucose levels.[29]

The incidence of type 2 diabetes mellitus continues to increase in the young population of America. As of May 2011, type 2 diabetes mellitus accounted for 45% of "new onset" cases of diabetes in children.[30] This increase in type 2 diabetes mellitus is due to an increase in inactivity and obesity in American children and adolescents. African American, Hispanic/Latino, Pacific Islander and Native Americans are at increased risk for developing type 2 diabetes mellitus. In all individuals, it is important to take note of common symptoms of diabetes mellitus, including increased thirst, frequent urination, blurry vision or an unusual amount of fatigue.[31]

Gestational Diabetes

Gestational diabetes occurs in pregnant women who do not exhibit hyperglycemia prior to pregnancy, but develop high blood glucose levels during pregnancy.[32] Gestational diabetes affects an estimated 1-14% of pregnancies in the United States.[33] During pregnancy, the placenta produces numerous hormones that diminish the effects of insulin on cells, resulting in increased blood sugar levels during pregnancy. In some women, the effects of these placental hormones cause blood sugar levels to rise to an unhealthy level leading to gestational diabetes.[34]

Women with gestational diabetes rarely notice

symptoms, although polyuria and excessive thirst are occasionally noted. Several risk factors for gestational diabetes exist and include being older than 25, having a family history of type 2 diabetes or being prediabetic before becoming pregnant, having a body mass index of 30 or higher and being of African American, Hispanic, Asian or Native American decent. [35]

If properly diagnosed and managed, babies born to mothers with gestational diabetes can be healthy. If inadequately managed, however, gestational diabetes' complications may be encountered that would affect both mother and baby. Infants may suffer from excessive birth weight, preterm birth with respiratory distress syndrome, jaundice and type 2 diabetes mellitus later in life. Infants born to mothers with gestational diabetes are accustomed to high glucose levels. After birth, the infants must adjust to normal glucose levels, and are also at risk for complications such as high blood pressure, preeclampsia and eclampsia and an increased risk for diabetes in the future.[35]

Other Causes and Types of Diabetes Mellitus

There are types of diabetes other than the aforementioned. In addition to type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes, other forms of diabetes may be caused by genetic conditions, infections, medical treatment, surgery and several other medical conditions. Overall, these additional forms of diabetes comprise 1-5% of all forms of diabetes.[36] Systemic corticosteroids (often abbreviated 'steroids') are an example of a medication that can lead to the development of diabetes.[37] Steroids often are prescribed to counteract inflammation.[38] Steroids often are prescribed to counteract inflammation and some steroids have been linked to the onset of diabetes. Prolonged use of steroids can lead to increased average blood glucose levels, with the potential for diabetes. Hyperglycemia developed during steroid use may remain after steroid use ceases.[39]

Mutations in various genes can lead to a unique type of monogenic diabetes termed "maturity-onset diabetes of the young," often abbreviated as MODY. MODY typically is diagnosed during adolescence. MODY is known to have strong genetic associations. A variety of genetic mutations can cause MODY, but the most common mutations occur in the *HNF1A* and *GCK* genes. The *HNF1A* gene decreases quantities of insulin produced in the pancreas while mutations in the *GCK* gene result in a balanced hyperglycemia. [40] Those with MODY may not suffer the usual symptoms of diabetes and states of hyperglycemia may not be noted until present in routine blood work. Additionally, MODY is not characterized as either type 1 or type 2 diabetes mellitus. Also, MODY is not related to increased blood pressure or obesity. MODY differs from type 1 diabetes mellitus in that individuals with MODY often are successfully treated with oral medications and do not always require insulin therapy.[41]

REFERENCES

1. American Diabetes Association [Internet]. [2014, June 10. cited 2015 January 11] Statistics About Diabetes. Available from: http://www.diabetes.org/diabetes-basics/statistics/
2. World Health Organization [Internet]. [2014, November. cited 2015 April 28] Diabetes. Available from: http://www.who.int/mediacentre/factsheets/fs138/en/
3. World Health Organization [Internet]. [2013, October. cited 2014September 24] Diabetes. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/
4. Medline Plus [Internet] [2014, August 5. 2015 cited January 11] Blood sugar test- blood. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/003482.htm.
5. American Diabetes Association. Hyperglycemic crises in diabetes. Diabetes Care, 2004;27,S94-102.
6. Medline Plus [Internet] [2014, August 5. cited 2015 January 11] Diabetic ketoacidosis. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/000320.htm
7. Mayo Clinic [Internet]. Davidson NK, Moreland P. (). Why high blood sugar is bad. [2011 March; cited 2015 January 11]. Available from: http://www.mayoclinic.org/diseases-conditions/diabetes/expert-blog/high-blood-sugar/bgp-20056519.
8. Mayo Clinic [Internet]. Davidson NK, Moreland P. Diseases and Conditions: Diabetes. [2009 December; cited 2014 September 24]. Available from: http://www.mayoclinic.org/diseases-conditions/diabetes/expert-blog/diabetes-blog/bgp-20056550.
9. World Health Organization [Internet] Use of Glycated Hemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. [2011. cited 2015 January 11]. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf.
10. Bailey C, Day C. Metformin: its botanical background. Practical Diabetes International, 2004;21(3),115-7. http://dx.doi.org/10.1002/pdi.606.
11. Rotenstein LS, Ran N, Shivers JP, et al. Opportunities and challenges for biosimilars: What's on the horizon in the global insulin market? Clinical Diabetes 2012:30(4),138-50. http://dx.doi.org/10.2337/diaclin.30.4.138.
12. American Diabetes Association [Internet]. Diabetes basics: Type 1. (n.d.). [cited 2013 February 8]. http://www. diabetes.org/diabetes-basics/type-1/.
13. Juvenile Diabetes Research Foundation [Internet]. Type 1 Diabetes Facts. (n.d.). [cited 2015 April 27] from website: http://jdrf.org/about-jdrf/fact-sheets/type-1-diabetes-facts/.

14. Yoon, JW, Jun, HS. Autoimmune Destruction of Pancreatic β Cells. American Journal of Therapeutics 2005:12(6),580-91.
15. Dotta F, Censini S, van Halteren A, et.al. Coxsackie B4 virus infection of β cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proceedings of the National Academy of Sciences of the United States of America, 2007;104(12),5115. http://dx.doi.org/10.1073/pnas.0700442 104.
16. Bishop ML, Fody, EP, & Schoeff, LE. Clinical Chemistry, 7th Ed, , Baltimore, MD: Lippincott Williams & Wilkins; 2013
17. American Diabetes Association [Internet]. Ketoacidosis (DKA) - American Diabetes Association®. (n.d.). [cited 2013 August 29] Available from http://www.diabetes.org/living-with-diabetes/complications/ke toacidosis-dka.html.
18. Winter WE, Pittman D. The clinical application of islet autoantibody testing for the diagnosis of autoimmune diabetes. MLO Med Lab Obs 2013:45(10).
19. Mayo Clinic [Internet]. (). Diseases and Conditions: Diabetic Ketoacidosis. [2012, October 23. cited 2014 September 24] Available from: http://www.mayoclinic.org/ diseases-conditions/diabetic-ketoacidosis/basics/symptoms/con-20026470.
20. Mayo Clinic [Internet]. Diabetic Ketoacidosis- Treatment & drugs. [2012, October. cited 2013 August 28] Available from: http://www.mayoclinic.org/diseases-conditions/diabetic-ketoacidosis/basics/treatment/con-20026470.
21. Mayo Clinic [Internet]. Type 1 diabetes. [2013, January. cited 2013 February 22] Available from website: http://www.mayoclinic.org/diseases-conditions/type-1-diabetes/basics/complications/con-20019573.
22. American Diabetes Association [Internet]. Diabetes Basics-Type 2. (n.d.). [cited 2013 March 2] Available from: http://www.diabetes. org/diabetes-basics/type-2/.
23. PubMed Health [Internet]. Type 2 diabetes. [2011, June. cited 2013 March 2] Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001356/.
24. American Diabetes Association [Internet]. Statistics about Diabetes. [2014, June. cited February 5, 2015]. Available from: http://www.diabetes.org/diabetes-basics/statistics/.
25. National Kidney Foundation [Internet]. Diabetes- A Major Risk Factor for Kidney Disease. (n.d.).[cited 2015 February 6]. Available from: https://www.kidney.org/atoz/content/diabetes.
26. U.S. Department of Health & Human Services- National Diabetics Information Clearinghouse [Internet]. Diabetic Neuropathies: The Nerve Damage of Diabetes. [2009, February. cited 2015 February 6] Available from website: http://diabetes.niddk.nih. gov/dm/pubs/neuropathies/.
27. National Eye Institute [Internet]. Information for Healthy Vision-What You Should Know. (n.d.). [cited 2015 February 6] Available from:https://www.nei.nih.gov/diabetes/content/english/know.
28. Centers for Disease Control and Prevention [Internet]. Diabetes- Successes and Opportunities for Population-Based Prevention and Control At A Glance 2011. [2011, August. cited 2015 February 5] Available from website: http://www.cdc.gov/chronicdisease/resources/publications/AAG/ddt.htm.
29. Mayo Clinic [Internet]. Diseases and Conditions- Diabetes-Lifestyle and Home Remedies. [2014, July 31. cited 2015 February 6,] Available from: http://www.mayoclinic.org/diseases-conditions/diabetes/basics/lifestyle-home-remedies/con-20033 091.
30. D'Adamo E, Caprio S. Type 2 diabetes in youth: epidemiology and pathophysiology. Diabetes Care 2011;34(2),s161-5. http://dx.doi.org/10.2337/dc11-s212.
31. American Diabetes Association [Internet]. Preventing Type 2 in Children. (n.d.). [cited 2013 September 15] Available from: http://www.diabetes.org/living-with-diabetes/parents-and-kids/children-and-type-2/preventing-type-2-in-children.html.
32. American Diabetes Association [Internet]. What is Gestational Diabetes? (n.d.). [cited March 16, 2013] Available from: http://www.diabetes.org/diabetes-basics/gestational/what-is-gestational-diabetes.html.
33. Coustan DR: Gestational diabetes. In Diabetes in America, 2nd Ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995, 703-17.
34. DeSisto CL, Kim, SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, pregnancy risk assessment monitoring system (PRAMS), 2007–2010. Preventing Chronic Disease2014;11. http://dx.doi.org/10.5888/pcd11.130415.
35. Mayo Clinic [Internet]. Gestational diabetes. [2011, March 24. cited 2013 March 16] Available from: http://www.mayoclinic.org/diseases-conditions/gestational-diabetes/basics/causes/con-20014854.
36. Centers for disease control and prevention [Internet] 2011 National Diabetes Factsheet. [2011, May. cited 2013 September 4,] Available from: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf .
37. Suissa S, Kezouh A, Ernst P. Inhaled Corticosteroids and the Risks of Diabetes Onset and Progression. The American Journal of Medicine 2010:123(11),1001-6. http://dx.doi.org/ 10.1016/j.amjmed.2010.06.019.
38. Cleveland Clinic [Internet]. Drugs & Supplements-Corticosteroids. (n.d.). [cited 2015February 25] Available from: http://my.clevelandclinic.org/health/drugs devices supplements /hic Corticosteroids.
39. University of Michigan Health System [Internet]. Roisen D. (n.d.). Steroid induced diabetes. [cited 2015 January 11] Available from website: http://www.cancer.med.umich.edu/files/steroid-induced-diabe tes.pdf.
40. Diabetes Genes [Internet]. Maturity-Onset Diabetes of the Young (MODY). (n.d.). [cited 2014 September 24] Available from: http://www.diabetesgenes.org.
41. National Diabetes Information Clearinghouse [Internet]. Monogenic Forms of Diabetes: Neonatal Diabetes Mellitus and Maturity-onset Diabetes of the Young. [2014, August. Retrieved 2015 May 14] Available from: http://www.diabetes.niddk.nih.gov/dm/pubs/mody/.