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Type 1 Diabetes – A Clinical Perspective

Lindy Kahanovitz, MSc[1,2], **Patrick M. Sluss, PhD**[3], and **Steven J. Russell, MD, PhD**[2,*]

[1]Department of Biotechnology Engineering, Ben Gurion University of the Negev, Beersheva, Israel

[2]Diabetes Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[3]Pathology Department, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 02114, USA

Abstract

Type 1 diabetes is a disease in which autoimmune destruction of pancreatic β-cells leads to insulin deficiency. Controlling blood glucose with an acceptable range is a major goal of therapy. Measurements of hemoglobin A1c and blood glucose levels are used for both the diagnosis and the long-term management of the disease. This chapter briefly describes the pathophysiology, diagnosis, and management of type 1 diabetes.

Keywords

Type 1 diabetes; hemoglobin A1c; C-peptide; point of care; self monitoring blood glucose; continuous glucose monitoring; insulin

Definition and Description

Type 1 diabetes (T1D) is a T-cell mediated autoimmune disease in which destruction of pancreatic β-cells causes insulin deficiency which leads to hyperglycemia and a tendency to ketoacidosis.[1] Excesses glucose levels must be managed by exogenous insulin injections several times a day.[2] Patients with T1D constitute 5-10% of all people with diabetes, the remainder having type 2 diabetes, monogenic forms of diabetes, or diabetes associated with other sources of islet cell injury. T1D commonly presents in childhood or adolescence; however the disease can appear at any age.[3]

Individuals at increased risk of developing type 1 diabetes can be identified by genetic markers and by the presence of characteristic autoantibodies.[1-3] Antibody markers of autoimmunity against β-cell include islet-cell autoantibodies, and autoantibodies against insulin, glutamic acid decarboxylase (GAD), or tyrosine phosphates IA-2 and IA-2β, and ZnT8.[3] At least one, and usually more than one, of these autoantibodies are present at the time fasting hyperglycemia is initially detected in the 85-90% of individuals who will

*Correspondence: Lindy Kahanovitz, Massachusetts General Hospital, Diabetes Research Center, 50 Staniford Street, Suite 340, Boston, MA, 02114, USA lkahanovitz@mgh.harvard.edu.

eventually develop type 1 diabetes.[1] Strong evidence links the human leukocyte antigen (HLA) genes DQA and DQB to susceptibility to the disease.[3] The rate of β-cell destruction is variable in T1D patients. Typically, more rapid rates of progression are seen in infants and children than in adults, although there is a great deal of variability within age groups.[3] Some patients, most typically children and adolescents, have ketoacidosis as the first symptom of the disease. Less commonly, and typically in older patients, T1D can present with mild fasting hyperglycemia or diminished glucose tolerance that can rapidly transition to severe hyperglycemia and/or ketoacidosis in the presence of infection or stress. During the later stage of the disease there is very little insulin secretion. Levels of C-peptide in plasma are low or undetectable with the most widely used assays,[1-3] although more sensitive assays have revealed the presence of very low levels of residual C-peptide secretion many years after diagnosis.[4-6]

The linear beta-cell decline hypothesis, postulated by Eisenbarth in 1986, remains the most widely referenced model for T1D.[7] However, some authors argue that disease progression in T1D is not a linear process, but rather proceeds at a variable pace in individual patients.[8,9,11] In this conception, T1D is a “relapsing-remitting” disease; fluctuations in beta cell mass occur over time as a result of waves of beta cell destruction that arise from a complex series of events that include regulatory elements and autoreactive cells.[8-11] The effect of complicating factors, such as aging, diet, immune cell metabolism, microbial pathogens, microbiomes, and epigenetic changes, which modulate the immune response that destroys β-cells, are still incompletely understood.

Signs and symptoms of severe insulin deficiency and hyperglycemia include: polydipsia (increased thirst), polyphagia (increased appetite), polyuria (increased urination), weight loss, and fatigue. These are due to defective transport of glucose from the bloodstream into tissues, resulting in increased glucose levels in the blood, elevated glucose in the urine, and concomitant calorie and fluid losses in the urine. When insulin levels fall to such low levels that lipolysis cannot be suppressed, products of fat metabolism called ketone bodies (primarily acetoacetate and β- hydroxybutyrate) accumulate in the blood, leading to metabolic acidosis and compensatory respiratory alkalosis due to hyperventilation. If untreated, compensatory mechanisms eventually fail and ketoacidosis results in cerebral edema, mental confusion, unconsciousness, coma, and death.

Appropriate therapy will prevent severe ketoacidosis and severe hypoglycemia, but it is very difficult to control glucose levels to near-normal levels with exogenous insulin. Efforts to intensify therapy usually result in hypoglycemia, which can range from mild and uncomfortable to serious and life threatening.[12-15] Given these difficulties, at least mild-to-moderate hyperglycemia persists in the vast majority of people with T1D, and can cause damage over years of exposure. Long-term complications of poorly managed diabetes include damage to medium and large sized blood vessels leading to increased heart disease, stroke, and peripheral vascular disease, as well as problems resulting from damage to very small blood vessels (microvascular disease) including nephropathy that can lead to kidney failure, neuropathy that can lead to loss of sensory and autonomic function, and retinopathy that can lead to blindness. Hypertension and abnormalities of lipoprotein metabolism are often also present in people with diabetes. [1-3, 16]

Diagnosis criteria for DM

For many years the criteria for the diagnosis of diabetes mellitus required blood glucose measurements. In the presence of characteristic clinical symptoms, diabetes could be diagnosed based on a fasting plasma glucose (FPG) of ≥126 mg/dl or a random plasma glucose or 2-hour plasma glucose during a glucose tolerance test of ≥200mg/dl.[3] More recently, professional organizations, including the American Diabetes Association (ADA) have recommended the use of the hemoglobin A1c (HbA1c) for the diagnosis of diabetes. The HbA1c test should be performed using a method that is certified by the NGSP and standardized according to the DCCT.[3] Hemoglobin A1c (HbA1c) is a widely used marker for chronic glycemia that measures the non-enzymatic glycation of hemoglobin and reflects average blood glucose levels over a 2-3 month period of time. It can be used to diagnose diabetes with a threshold of ≥6.5% (consistent with an estimated average glucose of 140 mg/dl). The patient does not have to fast for an HbA1c test, making it much easier to screen individuals for diabetes. The HbA1c has several other advantages over fasting plasma glucose, including greater pre-analytical stability and less day-to-day variance during periods of illness and stress.[3] Limitations of the HbA1c tests include that it is more expensive than the BG measurements and that its availability can be limited in developing countries. In addition, HbA1c tests can be misleading in patients who have certain forms of anemia and hemoglobinopathies that shorten the lives of red blood cells. Therefore, for conditions with abnormal red cell turn over the diagnosis of diabetes must employ glucose criteria.[1-3] Laboratory HbA1c assays are highly standardized through the National Glycohemoglobin Standardization Program (NGSP).[17] Point-of-care A1C tests are not sufficiently accurate at this time to use for diagnostic purposes.[3]

Although both glucose and HbA1c criteria are available for the diagnosis of diabetes, one of these is usually sufficient to make the diagnosis in the setting of the characteristic clinical picture of polyuria, polydipsia, weight loss, and fatigue. Both an HbA1c test and glucose results consistent with diabetes may be required to make the diagnosis if the clinical picture is not clear.[1-3] Table 1 describes the current diagnostic criteria for diabetes, adapted from the ADA Classification and Diagnosis guidelines[3], and from Type 1 Diabetes Treatment and guideline.[16]

Medical Management of Diabetes

Once the diagnosis of diabetes is made, an important goal of therapy is to maintain the average glucose as near the normal range as possible without causing unacceptable amounts of hypoglycemia. The goal for most patients with diabetes is to maintain an HbA1c < 7.0% (estimated average glucose of < 154 mg/dL) if that can be achieved without hypoglycemia.[18] The HbA1c is typically checked at least twice a year to confirm that the goals of therapy are being met, or more frequently if the patient is not meeting goals of therapy and the management plan is being actively adjusted. Although the medical team of care providers can provide guidance on the insulin regimen, it is usually up to the patient (or in some cases a parent or caretaker) to administer the regimen, which can be complicated and time-consuming. Patients must use an array of point-of-care tests to get the information they need to make day-to-day decisions about their self-care.

Point-of-Care Medical Management

The objective of blood glucose (BG) point-of-care testing (POCT) is to provide diagnostic information needed for clinical decision making as quickly as possible. Self-monitoring of blood glucose (SMBG) is the use of POCT by patients to monitor and manage their own glucose. The availability of more immediate POCT for glucose measurements can improve glycemic control results.[19,20] To achieve ADA goals for therapy, self-monitoring of blood glucose (SMBG) should be performed at least 3-4 times daily for patients using multiple insulin injections or insulin pump therapy. In most cases, more daily tests are required to meet goals for care. SMBG enables patients to estimate their individual response to therapy and estimate whether their glycemic targets are being achieved.

Despite ease of use and rapid reporting of point-of-care glucose monitoring devices (POCGMD) they have certain limitations. The accuracies of the available devices vary widely, and the accuracy of individual measurements depends on both the inherent accuracy of the instrument as well as many factors relating to the sample and patient characteristics, including variations in hematocrit levels, blood oxygen, pH, and the presence of interfering substances. In general, currently available POCGMDs exhibit the greatest accuracy within the physiological glucose range and lower accuracy in the lower and higher ranges.[21]

Minimally invasive continuous glucose monitoring (CGM) devices using subcutaneous sensors are approved for use as an adjunct to SMBG. These devices provide a new glucose measurement every 5-10 minutes, and therefore allow the user to track BG trends and set alarms for hyperglycemia and hypoglycemia. At the time of writing it appears that the first CGM will soon be approved as a replacement to POC glucometers for SMBG rather than solely as an adjunct to traditional POC SMBG using capillary blood.

Ketone bodies are produced by the liver through fatty acid metabolism when plasma insulin levels are very low. Ketone bodies are primarily acetoacetate and β-hydrobutyrate, but also include acetone. The measurement of ketone bodies is recommended for patients with T1D during acute illness, when blood glucose is elevated above 300 mg/dl, or when patients have signs of ketoacidosis. Patients with type 2 diabetes can also develop ketoacidosis, although this occurs less commonly and is often associated with significant illness and correspondingly severe insulin resistance. The preferred POCT for ketosis measures β-hydrobutyrate in the capillary blood, which is more sensitive and detects ketoacidosis earlier than using urine dipsticks to detect ketone bodies in the urine.[22, 23] Most commonly used methods for detection of ketone bodies in urine detect acetone and acetoacetate but not β-hydroxybutyrate.[23] Current blood ketone testing requires a small amount of blood and test results are obtained within 30 seconds. Ketone meters typically have a linear response range from ~0.0-6.0mmol/L of β-hydroxybutyrate. Blood β-hydroxybutyrate is negative within the range of 0.0-0.5mmol/L, mildly elevated within the range of 0.6-1.0 mmol/L, and moderately elevated, requiring treatment, above 1.0mmol/L.[23]

People with diabetes often have renal injury in the form of diabetic nephropathies. An early sign of diabetic nephropathy is an increase in urinary albumin secretion. Annual diabetic kidney disease screening should be performed by measuring the urine albumin to creatinine

ratio on a spot urine sample. Two out of three urine albumin to creatinine ratios collected over 3 to 6 months should be abnormal (> 30 mg albumin/g creatinine) before a patient is considered to have microalbuminuria.[16] Once there is evidence of diabetic kidney damage, measures are taken to slow the progression of kidney damage, which may include redoubling efforts to tightly control the BG levels, as well as treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Renal function should be monitored annually by measuring the serum creatinine, from which the estimated glomerlular filtration rate may be calculated.

The Future of Diabetes Management

Maintaining blood glucose concentrations near the normal range is critical for successful long term health of patients with diabetes.[19,20, 24,25] Current therapies required to achieve good glucose control in insulin-dependent diabetes are extremely demanding, requiring frequent blood control checks and calculations of insulin requirements to treat meals and glucose excursions above the target range. Once the dose is calculated, patients must manually administer the insulin by injection or using an insulin pump. The rate of insulin absorption after subcutaneous injection is slower than the absorption of carbohydrates from food, adding to the difficulty of maintaining glucose levels within the target range. Rapid-acting insulin analogs which became available in the 1990s have improved pharmacokinetic properties, but are still far from ideal, and insulin absorbance rates are highly variable from patient to patient, and even for the same patient on different occasions. This contributes to the difficulty of knowing the correct dosage of insulin for a given situation. [13, 14, 26] Insulin's more rapid absorption kinetics are being developed and nearing approval.

Integrating continuous (CGM) technology with insulin pumps and a control algorithm to create a system for automated insulin delivery (so-called “artificial pancreas” or “bionic pancreas” systems) has the potential to significantly improve glycemic control, reduce hypoglycemia, and reduce the burden of care in TID.[27-32] One of the main challenges in optimizing automated insulin delivery stems from the large differences in inter-individual and intra-individual insulin absorption rates. There is a significant risk of giving excess insulin if the pending effect of previously administered insulin is underestimated, and this will lead to hypoglycemia, a life threatening condition.[32-34] Plasma insulin levels aren't routinely measured in insulin-treated patients; rather some basic assumptions are currently used to estimate the insulin levels on-board. There is interest in continuously measuring the levels of insulin in real-time, in a way that is analogous to the measurement of glucose levels in real-time with CGM devices, and first steps have been made towards developing this technology.[35]

References

1. American Diabetes Association. Diagnostics and Classification of Diabetes Mellitus. Diabetes Care. 2014; 37:S81–90. [PubMed: 24357215]
2. American Diabetes Association. Standards in Medical care in Diabetes. Diabetes Care. 2010; 33:S11–61. [PubMed: 20042772]
3. American Diabetes Association. Classification and diagnosis of diabetes. Standard of Medical Care in Diabetes. Diabetes Care. 2016; 39:S13–22. [PubMed: 26696675]

4. Wang L, et al. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. Diabetes Care. 2012; 35:465–470. [PubMed: 22355018]
5. Oram RA, et al. The majority of patients with long duration type 1 diabetes are insulin microsecretors and have functioning beta cells. Diabetologia. 2014; 57:187–191. [PubMed: 24121625]
6. Kuhtreiber WM, et al. Low levels of C-peptide have clinical significance for established type 1 diabetics. Diabetic Medicine. 2015; 32:1346–1353. [PubMed: 26172028]
7. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med. 1986; 314:1360–1368. [PubMed: 3517648]
8. Christoffersson G, Rodriguez-Calvo T, Von Herrath M. Recent advances in understanding Type 1 Diabetes. F1000Faculty Rev. 2016; 5:1–8.
9. Van Belle TL, Coppieters KT, Von Herrath M. Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies. Physiol Rev. 2011; 91:79–118. [PubMed: 21248163]
10. Bonifacio E, Scirpoli M, Kredel K, Fuchtenbusch M, Ziegler AG. Early autoantibody responses in prediabetes are IgG1 dominated and suggest antigen-specific regulation. J Immunol. 1999; 163:525–532. [PubMed: 10384157]
11. Atkinson MA, Von Herrath M, Powers AC, Clare-Salzler M. Current Concepts on the Pathogenesis of Type 1 Diabetes-consideration for Attempts to Prevent and Reverse the Disease. Diabetes Care. 2015; 38:979–988. [PubMed: 25998290]
12. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med. 1991; 90:450–459. [PubMed: 2012085]
13. Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. Diabetes. 1997; 46:271–286. [PubMed: 9000705]
14. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD. DARTS/MEMO Collaboration: Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 Diabetes: A population-based study of health service resource use. Diabetes Care. 2003; 26:1176–1180. [PubMed: 12663593]
15. Weinstock RS, Xing D, Maahs DM, et al. for the T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013; 98:3411–3419. [PubMed: 23760624]
16. Group Health Cooperative. Type 1 Diabetes Treatment Guideline. 1996-2015:1–12.
17. Hanas R, John G. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care. 2010; 33:1903–1904. [PubMed: 20519665]
18. American Diabetes Association. Glycemic Targets. Standards of Medical Care in Diabetes—2016. Diabetes Care. 2016; 39(Supplement 1):S39–S46. [PubMed: 26696679]
19. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med. 1993; 329:977–986. [PubMed: 8366922]
20. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005; 353:2643–2653. [PubMed: 16371630]
21. Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. J Diabetes Sci Technol. 2012; 6:396–411. [PubMed: 22538154]
22. Pluddemann A, Heneghan C, Price Christopher P, Wolstenholme J, Thompson M. Point-of-care blood test for ketones in patients with diabetes. Diabetes Spectrum. 2004; 17:244–248.
23. Laffel L. Improving Outcomes with POCT for HbA1c and Blood Ketone Testing. J Diabetes Sci Technol. 2007; 1:133–136. [PubMed: 19888393]
24. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Effect of intensive therapy on the micro-vascular complications of type 1 diabetes mellitus. JAMMA. 2002; 287:2563–2569.
25. American Diabetes Associations: Standards of Medical Care in Diabetes. Diabetes Care. 2009; 32:S13–S61. [PubMed: 19118286]

26. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G, Marcovina S, Pihoker C, Standiford D, Waitzfelder B, Mayer-Davis E. SEARCH for Diabetes in Youth Study Group: Glycemic control in youth with diabetes: The SEARCH for diabetes in Youth Study. J Pediatr. 2009; 155:668–672. [PubMed: 19643434]

27. Doyle FJ, Huyett LM, Lee JB, Zisser HC, Dassau E. Closed-Loop Artificial Pancreas Systems: Engineering the Algorithms. Diabetes Care. 2014; 37:1191–1197. [PubMed: 24757226]

28. Peyser T, Dassau E, Breton M, Skyler JS. The artificial pancreas: current status and future prospects in the management of diabetes. Ann NY Acad Sci. 2014; 1311:102–123. [PubMed: 24725149]

29. Leelarathna L, Dellweg S, Mader JK, Allen JM, Benesch C, Doll W, Ellmerer M, Hartnell S, Heinemann L, Kojzar H, Michalewski L, Nodale M, Thabit H, Wilinska ME, Pieber TR, Arnolds S, Evans ML, Hovorka R. Day and Night Home Closed-Loop Insulin Delivery in Adults With Type 1 Diabetes: Three-Center Randomized Crossover Study. Diabetes Care. 2014; 37:1931–1937. [PubMed: 24963110]

30. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, Mckeon K, Goergen LG, Balliro C, Hillard MA, Nathan DM, Damiano ER. Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes. New Engl J Med. 2014; 371:313–325. [PubMed: 24931572]

31. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes. 2006; 55:3344–3350. [PubMed: 17130478]

32. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type one diabetes. Sci Transl Med. 2010; 2:1–12.

33. Russell SJ, El-Khatib FH, Nathan DM, Damiano ER. Efficacy determinants of subcutaneous microdose glucagon during closed-loop control. Journal of Diabetes Science and Technology. 2010; 4:1288–1296. [PubMed: 21129323]

34. El-Khatib FH, Russell SJ, Magar KL, Sinha M, McKeon K, Nathan DM, Damiano ER. Autonomous and Continuous Adaptation of a Bihormonal Bionic Pancreas in Adults and Adolescents with Type 1 Diabetes. Journal of Endocrinology Metabolism. 2014; 99:1701–1711.

35. Kahanovitz L, Seker E, Marks RS, Yarmush ML, Konry T, Russell SJ. J Diabetes Sci Technol. 2016; 10:689–696. [PubMed: 26721524]

Abbreviations

T1D	Type 1 Diabetes
DM	Diabetes Mellitus
GAD	Glutamic Acid Decarboxylase
HLA	Human Leukocyte Antigen
HbA1c	Hemoglobin A1c
NGSP	National Glycohemoglobin Standardization Program
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
OGTT	Oral Glucose Tolerance Test
DCCT	Diabetes Control and Complication Trial
WHO	World Health Organization
POCT	Point of Care Testing

SMBG	Self-Monitoring of Blood Glucose
ADA	American Diabetes Association
POCGMD	Point of Care Glucose Monitoring Devices
CGM	Continuous Glucose Monitoring
BG	Blood Glucose

Table 1

Diagnosing Diabetes

Test	Results	Interpretation
HbA1c[1]	≥ 6.5%	Diabetes
	5.7-6.4%	Impaired glucose tolerance[2]
	≤ 5.7%	Normal
Fasting Plasma Glucose[3]	≥ 126 mg/dL (7.0 mmol/L)	Diabetes
	100–125 mg/dL	Impaired glucose tolerance[2]
	≤100 mg/dL	Normal
Two-hour plasma glucose during an OGTT[4]	≥ 200 mg/dL (11.1 mmol/L)	Diabetes
Random plasma glucose or patients with classic symptoms of hyperglycemia or hyperglycemic crisis	≥ 200 mg/dL (11.1 mmol/L)	Diabetes
	140–199 mg/dL	Impaired glucose tolerance[1]
	≤ 140 mg/dL	Normal

[1]The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

[2]Impaired glucose tolerance (IGT) is similar to impaired fasting glucose (IFG) but is diagnosed with a confirmed oral glucose tolerance test (OGTT). Both IGT and IFG are risk factors for future diabetes and for cardiovascular disease. They are sometimes jointly referred to as pre-diabetes. Group Health recommends avoiding the term pre-diabetes because not all patients with IGT and/or IFG will develop diabetes.

[3]Fasting is defined as no calorie intake for at least 8 hours.

[4]The test should be performed as described by the WHO using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.