Type I Diabetes

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What Is Diabetes

- A chronic, often debilitating and sometimes fatal disease, in which the body either cannot produce insulin or cannot properly use the insulin it produces.[1]
- 230 BCE – Greece: The word "diabetes" is coined. 'Dia' - through, 'betes' - to go.[2,3]
  - The literal translation, "to go through" or siphon, reflects an understanding of a disease that drains people of more fluids than they consume.

Diabetes

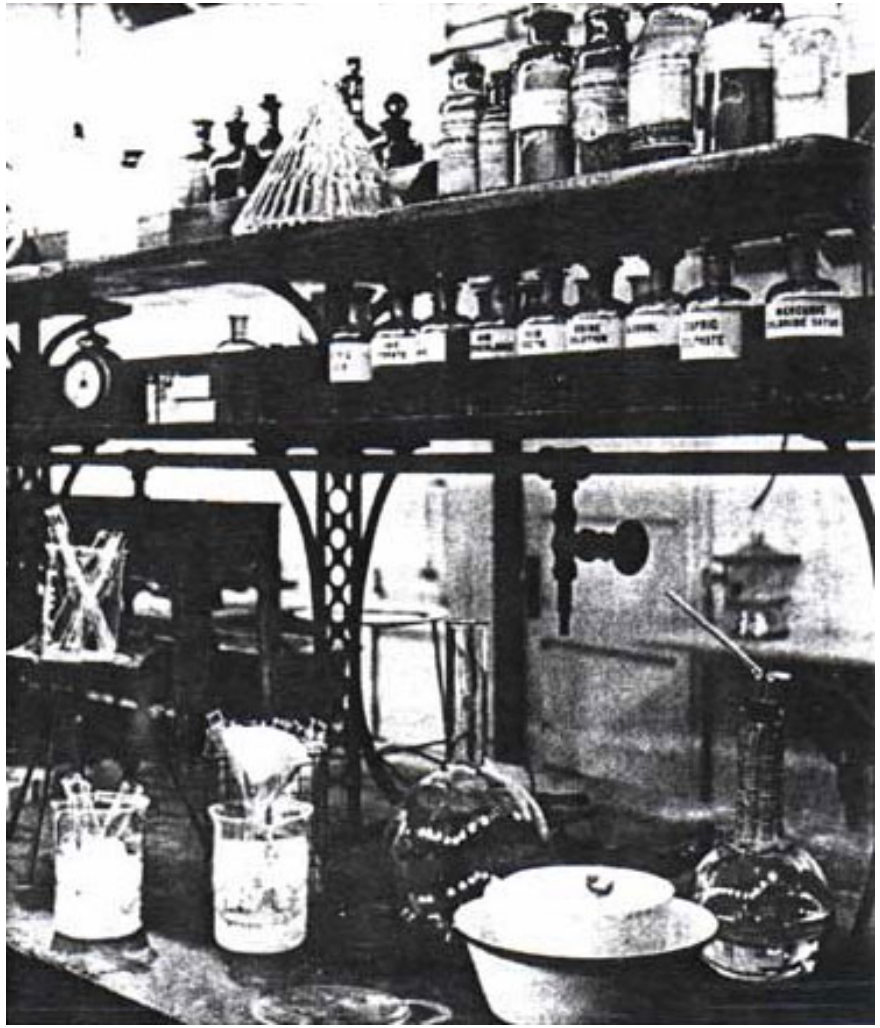
- **Population Statistics**
  - About 11 million cases of diabetes in Canada [1]
  - Up to 1,100,000 Canadians with T1D
- **Diagnostic criteria -** One of the following criteria must be met: [4]
  - **A1C** ≥6.5%
    - May not be elevated in rapid onset T1D
  - **Fasting Plasma Glucose** ≥126 mg/dL (7.0 mmol/L)
  - **Oral Glucose Tolerance Test** ≥200 mg/dL (11.1 mmol/L)
  - In patients with classic symptoms of hyperglycemia: Random plasma glucose ≥200 mg/dL (11.1 mmol/L)

History of Diabetes

- **1500 BCE – Egypt**: The physician Hesy-Ra describes an illness of frequent urination.[2,3]
  - Treatment: liquid extract of bones, grain, grit, wheat, green lead and earth
  - Prosthetic toes have been discovered in tombs
- **400 BCE – India**: physician Sushruta observed that flies and ants were attracted to the sweet tasting urine of those afflicted with certain diseases. [2,3]
- **4 CE – India**: surgeon Charaka built on Sushruta's work [2,3]
  - First recoded distinction between type 1 and 2 diabetes
  - Noticed some develop the disease at a young age and other heavier people who develop diabetes at an older age. The young tended to die very quickly.
- **1700 CE** – Britain: Physician Thomas Willis treated the condition with a high carbohydrate diet [2,3]

History of Diabetes – 1900's

- **1921** – Banting and Best working with dogs discovered insulin at the University of Toronto with the permission of J.J.R. Macleod
- **1922** – Banting and Best tried a refined serum on Leonard Thompson, 14.
  - First and second attempt did not go well. Didn't work as well as expected and Leo developed an abscess at the injection site
  - Third attempt with a better serum worked! Blood glucose and ketone levels fell.
  - Glucose fell from 520 to 120 mg/dL in about 24 hour (28.86 to 6.66 mmol/L)



Lab of Banting and Best

("Diabetes India - Diabetes," 2017)

History of Diabetes – 1900's

- **1922** - Eli Lilly & Co enter a deal for mass production of insulin
- **1923** - Banting and Macleod are awarded the Nobel Prize in Physiology or Medicine.
- **1936** – Sir H.P. Himsworth began to explain the physiologic difference in insulin sensitivity between patients.
- This later helps lead to the diabetes classifications of 1 and 2 in 1959 by Yalow and Berson who used pioneering immunoassays techniques to clearly demonstrated that type 1 diabetes was an insulin-deficient state[5]
- Confirmed in later autopsies insulin was almost undetectable in the pancreata of diabetic patients who died before the age of 20 years, whereas pancreata from individuals over that age contained on average 40-50% as much insulin[6]

Then: 1950's – Management and Prognosis[7]

- Prior to the discovery of insulin, T1D was essentially a death sentence.
- 33% died within 25 years of T1D diagnosis.
- 25% developed kidney failure within 25 years of T1D diagnosis.
  - Doctors could not detect early kidney disease and had no tools for slowing its progression to kidney failure.
  - Survival after kidney failure was poor, with 1 of 10 patients dying each year.
- 90% of people with T1D developed diabetic retinopathy within 25 years of diagnosis
- Major birth defects in the offspring of mothers with type 1 diabetes were 3x higher than in the general population

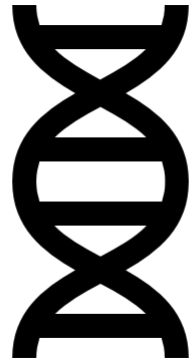
- Patients relied on injections of animal-derived insulin
- Studies had not yet shown the need for intensive glucose control to delay or prevent the debilitating eye, nerve, kidney, heart, and blood vessel complications of diabetes
- Patients monitored their glucose levels with urine tests, which recognized high but not dangerously low glucose levels and reflected past, not current, glucose levels.

What We Know Now

- Type 1 diabetes is characterized by an "**immune-mediated depletion of β-cells that results in lifelong dependence on exogenous insulin**". [8]
- How did we come to know which factors take us from a healthy, functioning pancreas to β-cell death?
  - Environmental
  - Genetic
  - Immune

Genetics

- **Early Geneticists**
  - Studied inheritance, not genetic marks.
  - Early studies looked at family heritability saw greater inheritance among families with a history of the disease
- **Genetic susceptibility:**[9-14]
  - No family history – 0.4%
  - Child of T1D mother – 1 to 4%
  - Child of T1D father – 3 to 8%
  - Child of T1D mother and father – up to 30%
  - Sibling of T1D patient (non-twin) – 3 to 6%
  - Fraternal twin – 8%
  - Identical twin – 65% by age 60



Genes related to T1D susceptibility

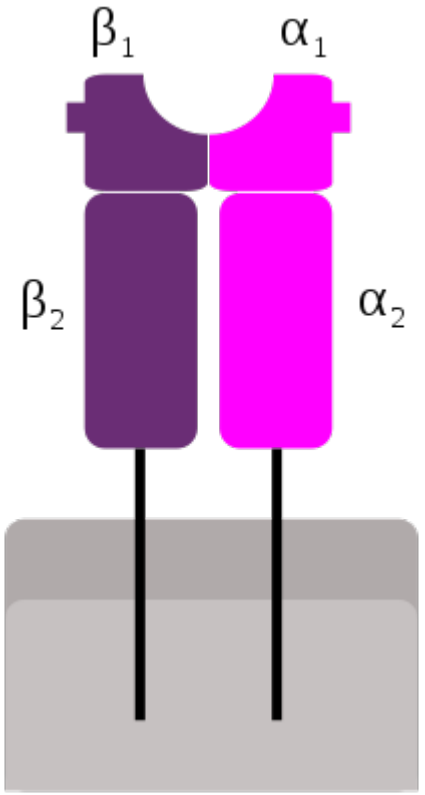
- The major histocompatibility complex (MHC) and the Human leukocyte antigen (HLA) genes were identified by immunologists working toward human transplantation in the 1970's.[15]
- Mouse models had also identified them as playing a role in immune function as researchers were able to identify different immune responses to virus-induced leukemia based on variations in the MHC region.[15]
- This research spawned a search for MCH/HLA disease links in humans. By 1974, associations had been reported between T1D and the HLA genes.[15]

Genes related to T1D susceptibility

- **Polygenic disease**: small handful of genes that have large effects and a great many number of genes that may play a smaller role.
  - Genes that confer the greatest susceptibility for type 1 diabetes are in the HLA region.[16]
- Human leukocyte antigen (HLA) genes
  - Risk is conferred by HLA DR/DQ alleles (HLA DR3 or DR4)
  - 90% of patients with T1D carry DR4 and/or DR3 alleles [16]

Genes related to T1D susceptibility

- MHC class II molecules are expressed on the surface of antigen-presenting cells (macrophages, dendritic cells).
- These MHC molecules has an alpha and beta chain that form the peptide-binding site where antigens are bound.
- MHC presents these antigens to antigen receptors on T cells, which play a primary role in catalyzing the process that ends up destroying the β-cells.
- Their antigen presenting ability is influenced by the amino acid composition of the alpha and beta chains.
- **The DR3/DR4 variants can alter the composition of these chain – causing amino acid substitutions that may increase binding of autoantigens involved in T1D pathogenesis and therefore confer greater susceptibility.** [17,18]

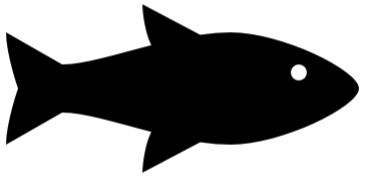


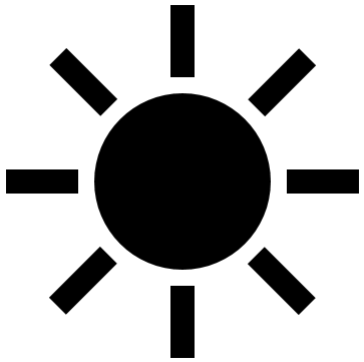
MHC class II molecules

("MHC class II - Uptodate," 2017)

Potential Environmental Triggers

- **Viruses**
  - Coxsackie B4
- **Dietary Factors**
  - Cow's milk
  - Vitamin D
  - Omega-3's





Environmental Triggers

- Mumps had been proposed as a cause of diabetes back in 1864.[15] Further studies in the 1920 seemed to confirm the link that diagnosis of diabetes peaked in the months following an mumps outbreak.
- Coxsackie virus B4 also emerged as a virus of interest, as it was correlated with increased diagnoses of T1D and it was known to cause pancreatitis in animal models.[19]
- Of the viruses examined, evidence for C-B4s involvement in T1D has been the most compelling.
- **Animal Data**: In susceptible mice, infection with Coxsackie virus B4 saw 90% producing islet autoantigen within 4-6 weeks' post-infection. Eventually led to near complete β-cell death in all exposed mice. [20]
- **Human Data**: Coxsackie virus B4 has been isolated from natural killer cells and islet cells in T1D patients at far higher rates than non-T1D counterparts. Islets from C-B4 positive samples showed reduced insulin secretion in response to glucose. [21]

Environmental Triggers

- 39% of children with newly diagnosed T1D have C-B4 virus-specific IgM response compared to only 6% of non-T1D children. [22]
- Autopsies showed inconsistent data:
  - No evidence of persisting infection from the above could be seen. [23]
  - Could be due to C-B4 only having acute effects as a potential inciting event.
  - Evidence remains conflicting and no conclusive pathogenic connection has been found between viral infection and human islet autoimmunity.

Dietary Triggers – Cow's Milk

- **The protein beta-casein has been implicated in the pathogenesis of T1D.**
  - Bovine caseins produce a bioactive peptide called beta-casomorphin-7 after in digestion with the help of intestinal enzymes. Beta-casomorphin-7 is thought to have opioid-like properties that can cause immunosuppression.
- A case control study found that, when exposed to bovine beta-casein, 24 of the 47 subjects with recent-onset T1D saw specific proliferation of T lymphocytes.
  - Only 1 of the 36 controls saw a positive response. [25]
- An epidemiological study of children ages 0-14 in 10 countries saw a strong correlation between beta-casein consumption and T1D ($r = +0.982$). [26]
- However, initial RCT's have yielded mixed data.
  - A large 10-year prospective trial of 2,159 infants is currently underway with results finalized in 2017 (the TRIGR trial). It compares hydrolyzed to conventional formula. Results at the 6-year mark reported no difference in the appearance of autoantibodies between the two study groups. [28]

Dietary Triggers – Vitamin D

- It is thought vitamin D may decrease risk of T1D through its immunosuppressive or immunomodulating effects.
- A case control study across seven countries (820 patients and 2335 control subject) showed supplementation with vitamin D reduced the incidence of T1D. [29]
- A birth-cohort study of over 10,000 children found that those who took vitamin D regularly (~2,000 IU/day) had reduced risk of T1D development. [30]

Dietary Triggers – Omega-3's

- Preliminary animal data shows that omega-3's can suppress the inflammatory response associated with autoimmune islet cell destruction. [31,32]
- A longitudinal observational study of 1,770 children at increased risk for T1D (either possessing the HLA genotype or having a first-degree relative with T1D) saw a moderate inverse relationship between omega-3 intake and development of islet autoimmunity. [33]
- A primary prevention trial of the effect of docosahexaenoic acid on incidence of T1D is currently underway. [34]

Environmental Triggers

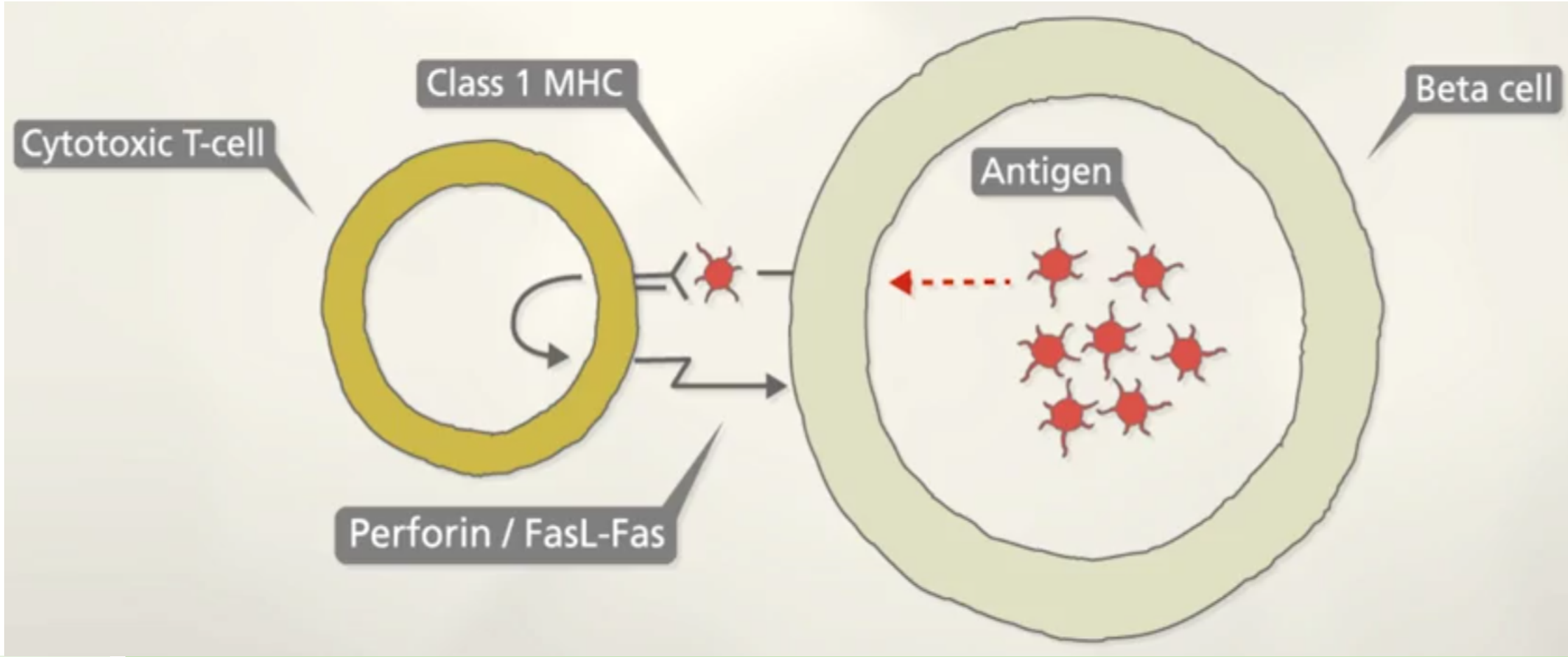
- Many additional risk factors have been associated with increased or decreased risk of T1D.
- A recent review found that the following were linked to increase risk [24]:
  - enteroviral infections in pregnant women
  - older maternal age (39-42 years)
  - preeclampsia
  - cesarean section delivery
  - increased birthweight
  - early introduction of **cow's milk proteins**
  - increased rate of postnatal growth (weight and height).
- Decreased risk was seen in optimal **vitamin D supplementation**. [24]

Immunity

- Autoantibodies were commonly detected in the 1960s and many attempts had been made to identify autoantibodies to insulin or pancreatic tissues by 1974, the year when autoantibodies to β-cell were discovered.[35]
- In retrospect, part of the problem was due to "poor illumination provided by earlier generations of microscopes"[35]

β-cell Death

A cytotoxic T cell recognizes a "self" antigen presented by the MCH class I complex on the surface of the β-cell. This triggers cytotoxic t-cell effector mechanisms



("Diabetes, Type 1," 2013)

Your Beta Cells Are Dead – Now What?

- **There is no cure or preventative treatment for T1D**
- **Only option - intensive glucose management**
  - Injections of long and short acting insulins
  - Matching insulin dosage to carbohydrate intake
  - Monitoring of blood glucose levels periodically throughout the day and night via finger pricks/blood samples

Long-Term Complications

- **Microvascular disease**
  - Retinopathy
  - Nephropathy
  - Neuropathy
- **Macrovascular disease**
  - Cardiovascular disease

Long-Term Complications

- **Microvascular disease**
  - Retinopathy[36]
    - Primarily caused by the metabolic effects of chronic hyperglycemia and results in retinal injury.
    - It is the most common microvascular complication.
    - Can be mitigated through regular eye exams and laser eye surgery, if needed

Long-Term Complications

- **Microvascular disease**
  - Nephropathy[37]
    - The most common cause of renal failure in T1D's although the number who progress to end stage renal disease has been declining. [38]
    - Drug therapies are available to help slow kidney disease.

Long-Term Complications

- **Microvascular disease**
  - Neuropathy
    - Damage of the blood vessels brought about by chronically elevated blood glucose levels can lead to the eventual damage of nerves.
    - Can result in poor wound healing or amputation in severe cases.
    - Intensive glucose management can slow or prevent its progression.[40]

Long-Term Complications

- Those at greatest risk of developing microvascular complications (retinopathy, nephropathy, and neuropathy) are those with A1C values above 12%. [41]
  - Risk still exists at values below this.
- A meta-analysis of 12 trials looking at glycemic targets for T1D patients found that, compared with standard care:
  - Intensive glucose management significantly reduced risk of developing retinopathy, nephropathy, and neuropathy. [42]
  - Median A1C values were 2% lower for the intensive group compared to the conventional treatment group.

Long-Term Complications

- **Macrovascular disease**
  - Cardiovascular disease is the most well documented in those with T1D.
    - When stratified among those with T1D, those in the highest quartile of mean A1C levels had increased all-cause and cardiovascular mortality compared to those in the lowest quartile. [44]
    - A study comparing 33,915 T1D subjects and 169,249 non-diabetic controls, those who had T1D showed greater risk of all-cause and cardiovascular mortality. [45]
    - Even T1D subjects with an A1C consistently ≤6.9% showed an elevated risk for all-cause and cardiovascular mortality. [45]

Now: 2010's – Management and Prognosis[7]

- 7 percent die within 25 years of diagnosis (down from 33%)
  - Still significantly increased compared to general population
- Improved control of glucose and blood pressure and the use of specific antihypertensive drugs prevent or delay the progression of kidney disease to kidney failure.
- People with advanced diabetic retinopathy can reduce their risk of blindness by 90 percent, with appropriate early intervention
- Major birth defects in the offspring of mothers with T1D is close to that of general population
- Patients use genetically engineered human insulin in a variety of formulations (Rapid, long-lasting)
- Intensive glucose control dramatically delays or prevents the eye, nerve, and kidney complications of type 1 diabetes

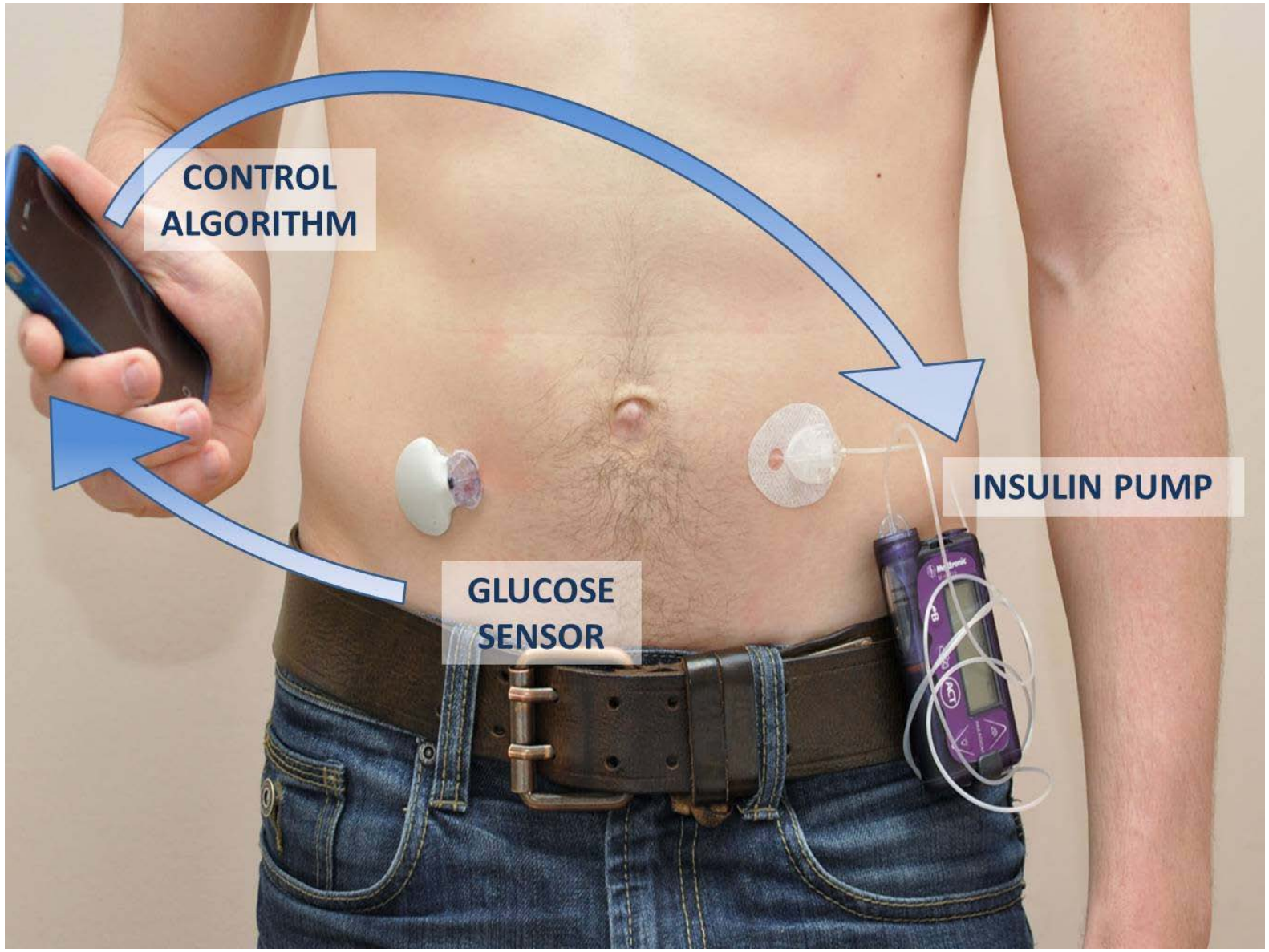
Now and Then

2017 – t:slim

1971 - Ames Reflectance Meter

("History of Blood Glucose Meters," 2017) (DiabetesCare.net, 2017)

Future Care: Artificial Pancreas



("The Artificial Pancreas - Diabetes & Control," 2017)

References

1.Types of Diabetes. 2016; http://www.diabetes.ca/about-diabetes/types-of-diabetes, 2016.
2.Lakhtakia R. The history of diabetes mellitus. Sultan Qaboos Univ Med J. 2013;13(3):368-370.
3.Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23(4):373-378.
4.American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90.
5.Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest. 1960;39:1157-1175.
6.Wrenshall GA, Bogoch A, Ritchie RC. Extractable insulin of pancreas; correlation with pathological and clinical findings in diabetic and nondiabetic cases. Diabetes. 1952;1(2):87-107.
7.Diabetes, Type 1. 2013; https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=120.
8.Chiang JL, Kirkman MS, Laffel LM, Peters AL, Type 1 Diabetes Sourcebook A. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014;37(7):2034-2054.
9.Steck AK, Barriga KJ, Emery LM, Fiallo-Scharer RV, Gottlieb PA, Rewers MJ. Secondary attack rate of type 1 diabetes in Colorado families. Diabetes Care. 2005;28(2):296-300.
10 Tillil H, Kobberling J. Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. Diabetes. 1987;36(1):93-99.
11 Guo SW, Tuomilehto J. Preferential transmission of type 1 diabetes from parents to offspring: fact or artifact? Genet Epidemiol. 2002;23(4):323-334.
12 Olmos P, A'Hern R, Heaton DA, et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. Diabetologia. 1988;31(10):747-750.
13 Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. N Engl J Med. 2008;359(26):2849-2850.
14.Tuomilehto J, Podar T, Tuomilehto-Wolf E, Virtala E. Evidence for importance of gender and birth cohort for risk of IDDM in offspring of IDDM parents. Diabetologia. 1995;38(8):975-982.
15.Gale EA. The discovery of type 1 diabetes. Diabetes. 2001;50(2):217-226.
16.Thomson G, Robinson WP, Kuhner MK, et al. Genetic heterogeneity, modes of inheritance, and risk estimates for a joint study of Caucasians with insulin-dependent diabetes mellitus. Am J Hum Genet. 1988;43(6):799-816.
17.Khalil I, d'Auriol L, Gobet M, et al. A combination of HLA-DQ beta Asp57-negative and HLA DQ alpha Arg52 confers susceptibility to insulin-dependent diabetes mellitus. J Clin Invest. 1990;85(4):1315-1319.
18.Rowe RE, Leech NJ, Nepom GT, McCulloch DK. High genetic risk for IDDM in the Pacific Northwest. First report from the Washington State Diabetes Prediction Study. Diabetes. 1994;43(1):87-94.
19.Gamble DR, Kinsley ML, FitzGerald MG, Bolton R, Taylor KW. Viral antibodies in diabetes mellitus. Br Med J. 1969;3(5671):627-630.
20.Gerling I, Chatterjee NK, Nejman C. Coxsackievirus B4-induced development of antibodies to 64,000-Mr islet autoantigen and hyperglycemia in mice. Autoimmunity. 1991;10(1):49-56.
21.Dotta F, Censini S, van Halteren AG, et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proc Natl Acad Sci U S A. 2007;104(12):5115-5120.
22.King ML, Shaikh A, Bidwell D, Voller A, Banatvala JE. Coxsackie-B-virus-specific IgM responses in children with insulin-dependent (juvenile-onset; type I) diabetes mellitus. Lancet. 1983;1(8339):1397-1399.
23.Foulis AK, McGill M, Farquharson MA, Hilton DA. A search for evidence of viral infection in pancreases of newly diagnosed patients with IDDM. Diabetologia. 1997;40(1):53-61.
24.Soltesz G, Patterson CC, Dahlquist G, Group ES. Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? Pediatr Diabetes. 2007;8 Suppl 6:6-14.
25.Cavallo MG, Fava D, Monetini L, Barone F, Pozzilli P. Cell-mediated immune response to beta casein in recent-onset insulin-dependent diabetes: implications for disease pathogenesis. Lancet. 1996;348(9032):926-928.
26.Elliott RB, Harris DP, Hill JP, Bibby NJ, Wasmuth HE. Type I (insulin-dependent) diabetes mellitus and cow milk: casein variant consumption. Diabetologia. 1999;42(3):292-296.
27.Knip M, Virtanen SM, Seppa K, et al. Dietary intervention in infancy and later signs of beta-cell autoimmunity. N Engl J Med. 2010;363(20):1900-1908.
28.Knip M, Akerblom HK, Becker D, et al. Hydrolyzed infant formula and early beta-cell autoimmunity: a randomized clinical trial. JAMA. 2014;311(22):2279-2287.
29.Group ESS. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. The EURODIAB Substudy 2 Study Group. Diabetologia. 1999;42(1):51-54.
30.Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358(9292):1500-1503.
31.Kleemann R, Scott FW, Worz-Pagenstert U, Nimal Ratnayake WM, Kolb H. Impact of dietary fat on Th1/Th2 cytokine gene expression in the pancreas and gut of diabetes-prone BB rats. J Autoimmun. 1998;11(1):97-103.
32.Krishna Mohan I, Das UN. Prevention of chemically induced diabetes mellitus in experimental animals by polyunsaturated fatty acids. Nutrition. 2001;17(2):126-151.
33.Norris JM, Yin X, Lamb MM, et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA. 2007;298(12):1420-1428.
34.Skyler J. Nutritional Intervention to Prevent Diabetes. clinicaltrials.gov: U.S. National Institutes of Health; 2016.
35.Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet. 1974;2(7892):1279-1283.
36.Diabetic Retinopathy - National Library of Medicine - PubMed Health. 2016; https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0027944/.
37.Kidney Disease (Nephropathy). 2017; http://www.diabetes.org/living-with-diabetes/complications/kidney-disease-nephropathy.html.
38.Daneman D. Type 1 diabetes. Lancet. 2006;367(9513):847-858.
39.Neuropathy (Nerve Damage). 2017; http://www.diabetes.org/living-with-diabetes/complications/neuropathy/.
40.Group DR. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. Ann Intern Med. 1995;122(8):561-568.
41.Barzilay J, Warram JH, Bak M, Laffel LM, Canessa M, Krolewski AS. Predisposition to hypertension: risk factor for nephropathy and hypertension in IDDM. Kidney Int. 1992;41(4):723-730.
42.Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014(2):CD009122.
43.Cardiovascular disease - Diabetes UK. 2017; https://www.diabetes.org.uk/Guide-to-diabetes/Complications/Cardiovascular_disease/.
44.Shankar A, Klein R, Klein BE, Moss SE. Association between glycosylated hemoglobin level and cardiovascular and all-cause mortality in type 1 diabetes. Am J Epidemiol. 2007;166(4):393-402.
45.Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371(21):1972-1982.