The Vascular Complications of Type 1 Diabetes

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Abstract

Type 1 Diabetes is an autoimmune disease that affects millions of people worldwide. As the number of diabetic patients rises, research on the disease and its complications also increases. The main pathology of type 1 diabetes rests in how the ß-cells within the pancreas are attacked and ultimately destroyed by the immune system. Insulitis and autoantibodies lead to an attraction of various immune cells such as T-lymphocytes, B-lymphocytes, and macrophages that stimulate the immune response. Once the insulin-secreting ability of the ß-cells is defective, hyperglycemia develops and a patient is diagnosed as a type 1 diabetic. Over time, hyperglycemia promotes the development of vascular complications. Both microvascular and macrovascular complications result from hyperglycemia. Hyperglycemia depresses the erythrocytes' ability to function properly, and vascular problems then occur as body tissues are affected. Microvascular complications include diabetic retinopathy, neuropathy, and nephropathy. Macrovascular complications include atherosclerosis, cardiovascular disease, and coronary heart disease. Various laboratory tests are available to detect developing vascular complications. While the vascular complications are inevitable, there are several therapy options available to diabetics to lessen the effects of those complications.

Keywords: Hyperglycemia, microvascular, macrovascular

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According to the Juvenile Diabetes Research Foundation, around 1.25 million Americans deal with the reality of a non-functioning pancreas. Type 1 Diabetes—also known as T1D—is the serious disease that results when an individual's pancreas ceases insulin production and becomes non-functioning. This disease is autoimmune in nature and occurs in both children and adults. Hyperglycemia is the main symptom that develops from the lack of insulin secretion, and it is a major contributor to the many complications diabetics face (JDRF, 2016). Of the many complications T1D presents, the developing vascular complications are severe and threaten diabetics throughout a lifetime.

While the specific pathogenesis of type one diabetes is still under heavy debate, research has proved that the attack on insulin-producing ß-cells in the pancreas is the primary cause of diabetes. The autoimmune attack leads to the destruction of the ß-cells, which dramatically decreases the body's ability to secrete insulin. Atkinson (2012) mentions that several factors help promote the autoimmune attack on the pancreas such as the environment, seasonal changes, and genetics; he discusses that "genetic, autoantibody, and metabolic markers," found from Dr. George Eisenbarth's 1986 research, help track the pathogenesis of diabetes in recent studies. Because of these markers, scientists are able to find out how many ß-cells must deteriorate before hyperglycemia and clinical diabetes takes hold in a person—greater than 50%. Atkinson labels T1D as a "multifactorial disease" when referring to all the genes driving the autoimmune attack. The genes work together, but not all the genes may be necessary to cause T1D; some of the genes that increase susceptibility are the HLA loci, tandem repeats, CTLA-4, PTPN22, and CD25. Other reasons leading to T1D are insulitis and autoantibodies. Insulitis is the inflammation around islet cells in the pancreas. As insulitis occurs in the pancreas and attracts

immune cells, an immune response is stimulated by the incoming macrophages, T-lymphocytes, and B-lymphocytes. The B-lymphocytes sense the ß-cell antigens and begin producing autoantibodies. The autoantibodies are thought to drive the actual destruction of the ß-cells (Atkinson, 2012).

Once more than 50% of the ß-cells in the pancreas are rendered ineffective, hyperglycemia becomes more apparent and individuals must begin insulin therapy to control blood glucose levels (Atkinson, 2012). Development of T1D reduces the body's ability to control the glucose uptake into the cells found throughout the body. This lack of control allows glucose to accumulate in the blood and increase the overall blood glucose level, which is known as hyperglycemia. The major therapy for hyperglycemia is taking "exogenous insulin," insulin given through needle injection. Newly diagnosed patients will react well to the amount of insulin given, and their blood glucose levels will decrease quickly; however, as patients age and their diabetes ages, reducing hyperglycemia is challenged as the "exogenous insulin" leads to insulin insensitivity. Essentially, insulin insensitivity is the moment the cells decide they want to interact with more insulin before they accept the glucose into their cytoplasm. Patients with T1D become used to the amount of insulin given and slowly require more to decrease blood glucose levels. Because cells grow insensitive to insulin over time, the importance of regulating glucose levels and decreasing hyperglycemia is stressed (Bjornstad, Snell-Bergeon, Nadeau & Maahs, 2015).

Throughout a lifetime, hyperglycemia affects the body's ability to regulate proper metabolic processes involved in tissue oxygenation. When the red blood cell cannot properly take in glucose, the cell processes dealing with picking up and releasing oxygen are not efficient. A lack of proper circulation develops the moment oxygen is not delivered correctly to the various tissues. Thus, the vascular system begins impairing tissues around capillaries and major blood

compartments (Cade, 2008). Poor circulation develops and then affects the body in many ways because of how important blood flow through the body is. Concisely, T1D affects how much and where the blood can flow in both capillaries and the major blood compartments (Bjornstead, et al., 2015). Since diabetes has a "progressive nature," these complications involving the vascular system will continue to worsen as the patient ages. Vascular complications associated with T1D continue to threaten both newly diagnosed and veteran patients and appear as both microvascular and macrovascular complications (Cade, 2008).

Some of the most notable microvascular complications seen in T1D patients are retinopathy, neuropathy, and nephropathy. Diabetic retinopathy is a condition where the capillaries in the eye either swell, burst, or grow abnormally and lead to change or loss of vision. Major areas of the eye that are affected include the peripheral retina and the macula; depending on the patient, it is possible to acquire retinal damage from only one of these areas (Cade, 2008). Retinal damage can be either background or proliferative. Background retinopathy happens as microaneurysms or leaking from the capillaries occurs from retinal edema. Proliferative retinal damage develops when new capillaries form; these new capillaries tend to hemorrhage and cause vision problems (Fowler, 2011). Diabetic proliferative retinopathy can vary from "nonproliferative, preprolifertive, and severely proliferative" depending on how long the patient has suffered from the disease and how much damage is done. Diagnosing diabetic retinopathy involves finding a lack in the total amount of pericytes—cells located in small vessels that regulate dilation and constriction. Other tests that may reveal an increased risk of diabetic retinopathy include high cholesterol, high triglyceride levels, and high homocysteine levels during pregnancy.

Diabetic neuropathy is another microvascular complication that decreases sensation in the arms and legs. Overall, neuropathy results from hyperglycemia, hypertension, ketoacidosis, and

other variable risk factors. The pericytes lose their ability to regulate the blood flow properly and cause demyelination, axonal loss, and membrane thickening. Patients with neuropathy experience pain in the areas where the pericytes lose blood-regulating ability (Cade, 2008). The signals arriving from the central nervous system are unable to conduct the electrical impulses all the way through the limbs because of damaged nerves. Corrupted microvasculature and nerve damage lead many uncontrolled diabetics to amputation of the extremities where the tissue dies. The goal is to catch symptoms like tingling and numbness before the nerves experience extensive damage and amputation is necessary.

Diabetic nephropathy is yet another microvascular complication that develops when a T1D patient experiences more hyperglycemia; the hyperglycemia mainly affects the glomerulus and the ability of the glomerulus to filter substances into the urine correctly. As the membranes in the glomerulus thicken and collect nodules, normal filtration ceases and proteins like albumin—or microalbumin—may filter out of the glomerulus and into the urine (Fowler, 2011). Changes in glomerular filtration, the glomerular matrix, and glomerular basement membrane contribute to the lack of proper filtration ability, which then allows excretion of albumin into the urine. Changes such as these will lead uncontrolled diabetics to renal disease and renal failure if left untreated. Protein appearing in the urine is a major indicator that the patient is having vascular problems in the kidney such as diabetic nephropathy (Cade, 2008). A strong laboratory finding of diabetic nephropathy is a proteinuria value of over 500 milligrams within twenty-four hours. However, microalbuminuria precedes extreme proteinuria and is found when patients excrete between 150 and 300 milligrams of albumin within twenty-four hours (Fowler, 2011). Microalbuminuria is monitored on most T1D patients in order to prevent renal disease progression. Normal amounts of albumin excretion are less than 150 milligrams per day (Butt,

Hall & Nurko, 2010). Procedures used to detect albumin in the urine include the immunoassay techniques. The immunoassay method works well, but may miss some albumin within diabetic patients' urine. A urine spot sample is collected in order to find out the albumin excretion rate or AER and the albumin/creatinine ratio. The sample can be tested through turbidimetry or with dye-binding processes. Common instruments include INTEGRA 700/800, Dimension Xpand, Roche Diagnostics Hitachi Cobas, and Siemens Healthcare Diagnostics machines (Martin, 2011).

Macrovascular complications in type 1 diabetic patients are atherosclerosis, coronary heart disease, and cardiovascular disease. Once T1D is diagnosed, the patient is placed at high risk for macrovascular complications. These complications revolve around the development of atherosclerosis in major blood chambers and vessels. Atherosclerosis is the "narrowing of arterial walls throughout the body" from a buildup of oxidized lipids and other cells in the major vessels. When the endothelium of major vessels experiences some form of trauma or inflammation, lipids accumulate and attract macrophages and T-lymphocytes. According to Fowler, these cells utilize the lipids, add collagen, and create a "lipid-rich atherosclerotic lesion with a fibrous cap." This lesion causes vessel narrowing and can lead to a heart attack, stroke, or obstruct blood flow to another organ if the cap ruptures. Coronary heart disease—also known as coronary artery disease, CAD—occurs when atherosclerosis develops in the coronary arteries and blood flow to the heart decreases. CAD is an extreme risk for type 1 diabetics because of hyperglycemia, blood glucose fluctuation, and a predisposition to atherosclerosis development. Hyperglycemia directly causes hypertension—an overall increase of heart rate. Hypertension within the coronary arteries initiates poor circulation to the heart muscles, as the blood does not

supply correct amounts of oxygen. When the heart muscles become ischemic from the lack of oxygen, a myocardial infarction or heart attack occurs (Fowler, 2011).

The highest-risk macrovascular complication for type 1 diabetics is cardiovascular disease or CVD. Several studies have shown that diabetes and cardiovascular disease link to each other, and according to Cade (2008), "people with diabetes have a 4-fold-greater risk for having a CVD event." CVD includes any condition that affects the heart or heart vessels' ability to function from lack of blood flow, blockage, inflammation or cardiac tissue damage. For example, coronary artery disease is a subcategory of CVD dealing with a blockage in the coronary arteries (Cade, 2008). Congestive heart failure is another form of CVD that occurs when many cardiac tissues cease appropriate function. Hyperglycemia is the main culprit that places diabetics at high-risk for CVD because it leads to the development of atherosclerosis and reduces blood flow throughout various heart vessels. Any area of the heart such as blood chambers, arteries, coronary arteries, may be affected. Risk factors for heart disease in T1D include the following: insulin resistance, hypertension, low HDL and high LDL cholesterol, high triglycerides and several other factors. These risk factors are monitored at least every three months in diabetic patients in order to help catch early CVD cases and prevent heart disease as much as possible (Fowler, 2011).

The laboratory detects CVD when there is an abnormal presence of LDL cholesterol or an absence of HDL cholesterol. An increased cardiovascular disease risk is noted with increased LDL and decreased HDL cholesterol levels. One method used to measure and analyze cholesterol is ß-quantification. This technique utilizes ultracentrifugation to isolate the lipoproteins and perform a "cholesterol reference." Another method is the DCM or designated comparison method that is similar to ß-quantification; however, a smaller sample is used to

improve results and the throughput. Samples are prepared by making a NaBr and 2-mercaptoethanol solution and combining that solution with designated serum from the patient. During centrifugation, the LDL and HDL groups are separated by 2-mercaptoethanol, known as the "Lp[a]-dissociating agent." The spinning process allows the HDL and LDL to settle into specific bottom fractions in the tube. The bottom fractions of cholesterol are then analyzed by the High Performance Liquid Chromatography or HPLC method. This method utilizes the previous dilution in conjunction with ethanol, incubation, shaking, and oxidation from chromic acid (Dong et al., 2011).

While the vascular complications associated with T1D are aggressive, therapies are available to reduce the risk of microvascular and macrovascular complications. The main treatment against vascular complications is by gaining strict control over blood glucose levels and decreasing hyperglycemic blood glucose levels. As hyperglycemia decreases, the risk of pericyte loss, vessel endothelium damage, or developing atherosclerosis also decreases. A tight range of the blood glucose will allow patients with T1D to function as normal as possible. Blood glucose levels are mainly managed with artificial insulin injections (JDRF, 2016). The best ways to prevent any vascular disease with T1D outside of insulin therapy is to embrace regular exercise, eating a diet filled with fruits and vegetables, eating few fats, and striving for a low HbA1c (Bjornstad et al., 2015). When diet and exercise are not as effective as they need to be, doctors prescribe patients to take ACE inhibitor medications (JDRF, 2016).

Overall, T1D leads to the development of both microvascular and macrovascular complications. The factors that contribute to vascular problems are insulin insensitivity and hyperglycemia; both are key factors that affect how the red blood cell transports oxygen and nourishes various body tissues. Disease progression and prognosis rely on many factors but can

improve through insulin therapy, diet maintenance, and exercise. Hopefully, researchers will discover the cure to T1D sometime in the near future and the threat of vascular problems will decrease rapidly. Until then diabetics will make daily sacrifices to prevent vascular complications.

References

Atkinson, M. A. (2012). The pathogenesis and natural history of type 1 diabetes. *Cold Spring Harbor Perspectives in Medicine*, *2*(11), a007641.

Bjornstad, P., Snell-Bergeon, J. K., Nadeau, K. J., & Maahs, D. M. (2015). Insulin sensitivity and complications in type 1 diabetes: New insights. *World Journal of Diabetes*, *6*(1), 8–16. http://doi.org/10.4239/wjd.v6.i1.8

Butt, S., Hall, P., & Nurko, S. (2010). Diabetic nephropathy. Retrieved from http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/

Cade, W. T. (2008). Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical Therapy,* 88(11), 1322-1335. Accessed October 05, 2016.

Dong, J., Guo, H., Yang, R., Li, H., Wang, S., Zhang, J., & Chen, W. (2011). Serum LDL- and HDL-cholesterol determined by ultracentrifugation and HPLC. *Journal of Lipid Research*, *52*(2), 383–388.

Fowler, M. J. (2011). Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*, *29* (3), 116-122. (Source 4)

JDRF (2016). *Type 1 diabetes facts*. Retrieved from: http://www.jdrf.org/about/fact-sheets/type-1-diabetes-facts/

Martin, H. (2011). Laboratory measurement of urine albumin and urine total protein in screening for proteinuria in chronic kidney disease. *The Clinical Biochemist Reviews*, *32*(2), 97–102.