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Progression to Type 2 Diabetes: Beta-Cell Failure
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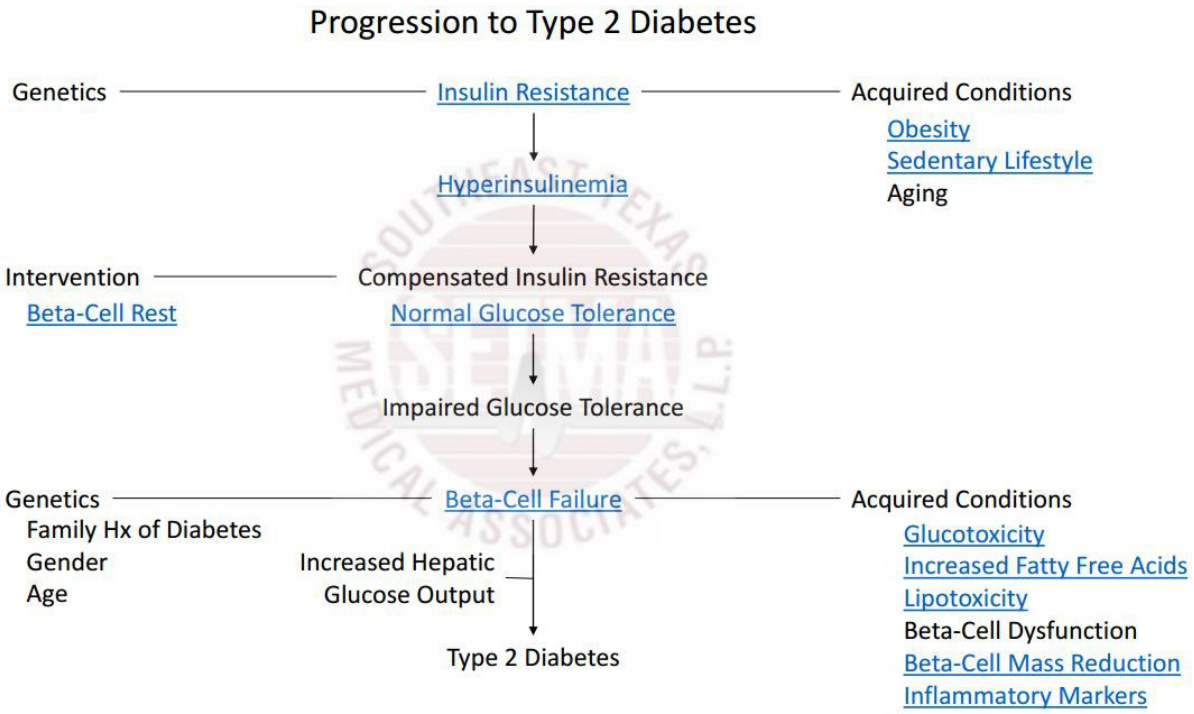
In the past three weeks, we have addressed the development of insulin resistance, where the body does not respond to insulin as it should, and hyperinsulinism, where the pancreas and its beta cells produce more and more insulin in an attempt for the body to compensate for insulin resistance. At the stage of "compensated insulin resistance," it is possible for the progression to type 2 diabetes to be reversed. Often, it is possible to prevent the development of diabetes and it is always possible to delay the onset of diabetes.

Once the progression to Type 2 Diabetes goes beyond "impaired glucose tolerance," beta cell failure sets in. After this starts, it is very difficult to stop the procession to diabetes. After the process result in the loss of beta cell mass, it is impossible to reverse it.



Chronic elevations of blood sugar produces a condition referred to as “glucotoxicity,” which simple refers to the fact that chronic elevations of sugar in the blood causes damage to a number of organs , including those summarized below. Remember, diabetes does not cause complications in the body; uncontrolled diabetes causes complications. Uncontrolled diabetes is characterized by chronic elevation of sugar (glucose) in the blood.

The term “glucose toxicity” was originally coined to describe the adverse effects of chronic exposure of pancreatic β-cells to high concentrations of glucose. First suggested in β-cells by the observations of Haist in 1940, the notion that high glucose exerts multiple pathological effects on many cells and tissues has been established by abundant evidence for its causative role in the chronic microvascular complications of diabetes, its effects on insulin action in metabolic target tissues, and in several other adverse outcomes noted in people with diabetes, such as frequent fungal infections and an increased frequency of congenital birth defects

“Glucose toxicity” describes the role of high glucose in causing damage to multiple organ systems as outlined below. The following organs are damaged by chronic elevations of blood sugar.

The spectrum of glucose toxicity	
Eyes	Retinopathy (microaneurysms, hemorrhages, exudates, neovascularization)
Kidneys	Nephropathy (albuminuria, nephrotic syndrome, hyporeninemic hypoaldosteronism, end stage renal disease)
Nerves	Neuropathy (distal sensory ± motor neuropathy, mononeuritis multiplex, autonomic neuropathy, amyotrophy, chronic demyelinating immune polyneuropathy)
Skin/Mucous Membranes	Microvascular lesions, necrobiosis lipoidica diabeticorum, staphylococcus/streptococcus infection/cellulitis, fungal infections
Fetus	Macrosomia, congenital anomalies (neural tube defects), shoulder dystocia
Pancreas	Endocrine - decreased insulin secretion, β-cell failure Exocrine - decreased digestive enzyme synthesis and secretion
Insulin target tissues	Insulin resistance in fat, muscle and liver
Vascular system	Atherosclerosis, endothelial cell dysfunction (decreased vasodilatation), restenosis

Lipotoxicity

There are other complications caused by diabetes some of which are referred to as "lipotoxicity." There is increasing evidence that the damaging effects of elevated glucose in the blood and of elevate lipids (fatty acids) are interrelated rather than separate damaging effects on beta cells. Because type 2 diabetes in humans is frequently associated with obesity and hyperlipidemia (elevated cholesterol and triglycerides) as well as hyperglycemia, many investigators have examined whether high levels of free fatty acids or other lipids might be harmful to islet cell function.

Indeed, there is ample evidence that fatty acids, which under normal circumstances are physiological fuels for the β-cell, become toxic when present at elevated concentrations for prolonged periods of time. Adverse effects of chronic exposure of the β-cell to elevated fatty acid concentrations include decreased glucose-induced insulin secretion, impaired insulin gene expression, and increased cell death.

The mechanisms by which fatty acids impair β-cell function are largely unknown. Overall findings support the hypothesis that lipotoxicity only occurs in the context of chronic hyperglycemia, consistent with the observation that most individuals with increased circulating lipid levels have normal β-cell function

Key Concepts and new terminology

Dysfunctional Fat Cells – fat cells which do not respond to insulin. These cells become very active metabolically producing adipocytokine which are harmful to the body with one exception. Insulin decreases lipolysis in the fat cell and therefore decreases free fatty acids circulating in the blood. It is the visceral fat cells which do this. Visceral fat increase is associated with the "apple" body shape. This is the fat around the waist body shape.

Ectopic Fat – Fat outside of adipocytes (fat cells), in muscle and liver which causes insulin resistance. Decreasing visceral fat will restore insulin sensitivity in the muscle and liver. This is commonly called "weight reduction."

Lipotoxicity --- the damaging effect of chronic FFA elevation on insulin secretion by the pancreatic beta cells. Lipotoxicity accelerates beta cell apoptosis (cell death) and decreases beta cell mass by more than 50%. Once this happens, the reversal of diabetes is impossible.

Fat Cell as an Endocrine Organ – Adipocyte (fat cell) is a metabolic factory, producing a wide variety of adipocytokines. All of these are bad for the body except for one.

Adipocyte, inflammation and insulin resistance – link between chronic inflammation, insulin resistance, type 2 diabetes mellitus and atherosclerosis is the dysfunctional fat cell.

Overflow Hypothesis – inability to store fat in adipose tissue leads to ectopic accumulation of triglycerides in muscle and liver causing hepatic and muscle insulin resistance, glucose intolerance and overt diabetes.

Can dysfunctional fat cells be converted to healthy adipocytes? – Yes. Triazolidinediones decrease intra-abdominal fat and increase subcutaneous fat increasing insulin sensitivity and decreasing bad adipocytokines. In the case of Triazoidinediones, total body fat actually may increase but visceral fat decreases which is good and subcutaneous fat increases which is not bad.

In addition, voluntary fat loss via caloric restriction and exercise will convert dysfunctional fat cells into healthy adipocyte.

Dysfunctional Fat Cell Syndrome – insulin resistance, hypertension, accelerated atherosclerosis in type 2 diabetes and obesity, which are all the result of ectopic (visceral) fat accumulation with the production of adipocytokines.

Summary

The progression to diabetes type 2 in the human body is finalized by chronic increases of sugar in the blood (glucose, glucotoxicity) and chronic elevations of fats in the blood (lipids, cholesterol, triglycerides and free fatty acids, lipotoxicity).

The most important means of improving your health, if you have diabetes, is to make sure your blood pressure is controlled. In addition controlling your blood sugar and your blood lipids are critical.

Next week, we will discuss ways in which do accomplish these goals.