Diabetes & Obesity Protein Biomarkers

The Centers for Disease Control and Prevention reports that diabetes impacts more than 34 million people in the United States alone, and that an additional 88 million people have prediabetes. Ninety percent of prediabetics are unaware of their condition. Left unchecked, prediabetes and diabetes lead to severe health issues that gravely impact quality of life. The good news is that diagnosis and lifestyle changes can cut the risk of developing type 2 diabetes in half. To understand the underlying mechanisms of these conditions and explore possible therapeutic pathways, researchers measure and study the impacts of a variety of protein biomarkers.

Proinsulin

Proinsulin is a precursor molecule produced by pancreatic ß-cells, primarily in response to glucose, that is cleaved equally into insulin and c-peptide. Elevated levels of proinsulin are associated with insulinomas and insulin resistance while proinsulin to insulin ratios help elucidate ß-cell function.[1,2] Proinsulin levels are also an independent marker of cardiovascular risk. Some studies suggest that intact proinsulin has potential as an early indicator of insulin resistance, where levels of intact proinsulin and intermediates (des-31,32) become disproportionately high in subjects with glucose intolerance. Further, they suggest measurement of fasting intact proinsulin may aid in therapy selection and monitoring in type 2 diabetes progression.[1,3]

Insulin

Insulin is a hormone produced in the pancreas by ß-cells inside the Islets of Langerhans when proinsulin splits. Insulin signals the body to store glucose, the main type of sugar in the blood and the body's major source of energy, thereby lowering blood sugar levels. Insulin binds to specific receptors on the cell wall, initiating a series of complex processes that permit cells to take in and use just enough glucose to complete necessary functions.[4] Levels of insulin correlate to many conditions including insulin resistance, diabetes, hypertension, and metabolic syndrome. Measuring insulin allows researchers to distinguish between type 1 and type 2 diabetes, to predict diabetic risk and engage patients in prevention programs, and to monitor the progress of prediabetes and insulin resistance.

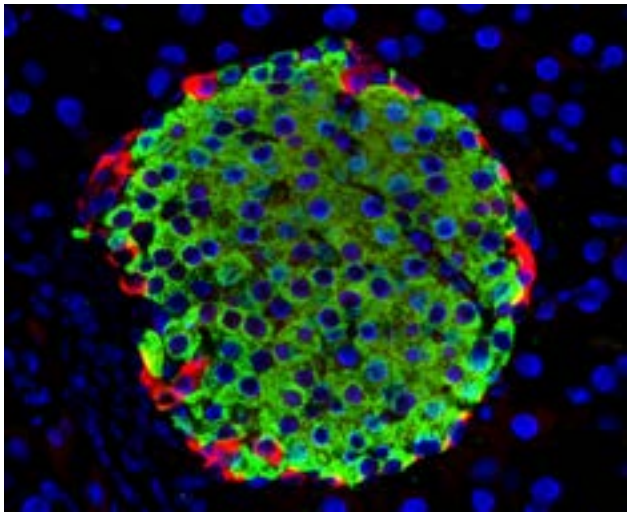

Figure 1: Staining of pancreatic islet cell network.

C-peptide

C-peptide is produced in the pancreas when proinsulin splits. C-peptide is often measured in lieu of insulin as it is made 1:1 and does not break down as quickly. C-peptide's half-life is ~30 minutes compared to about three minutes for insulin, making c-peptide an attractive biomarker for indirectly estimating glucose-stimulated insulin secretion, understanding ß-cell function, and identifying ß-cell functional mass. Measuring c-peptide level is analogous to measuring insulin level and allows investigators to distinguish between type 1 or type 2 diabetes. Recently, c-peptide has shown therapeutic potential for the treatment of diabetes-associated microvascular complications.[5,6] Further, in studies of animal models of type 1 diabetes, c-peptide administration significantly improved nerve and kidney function.[6]

Glucagon

Glucagon is a peptide hormone made by α-cells inside pancreatic islets when blood sugar levels are lower than normal, typically in response to fasting or exercise.[7] Glucagon works with the liver to convert sugar into glucose which is released into the blood to support increased energy expenditure and help maintain energy homeostasis. In addition, glucagon reduces food intake and may have a role in appetite regulation.[8] Glucagon is essential for the maintenance of normal blood glucose in diabetes, and its measurement helps doctors monitor patient glucose control.[9] Elevated glucagon levels also indicate the presence of a glucagonoma, which is a rare pancreatic tumor that secretes glucagon: Type 2 diabetes is present in ~80% of glucaganoma cases.[10]

Adiponectin

Adiponectin (ADP) is a fat-derived protein that increases glucose use and plays an important role in protecting against insulin resistance, diabetes, and atherosclerosis. Low ADP levels are an indicator in the development of type 2 diabetes, obesity, and cardiovascular disease.[11] While there are several isoforms of ADP in circulation, High Molecular Weight (HMW), Total ADP, and the ratio of HMW to Total ADP are commonly measured. Studies show that HMW value is the most accurate predictor of insulin resistance and metabolic syndrome.[12] In addition, adiponectin yields many therapeutic benefits including increasing insulin sensitivity, reducing inflammation and atherosclerosis, and in certain circumstances decreasing body weight.[11]

Leptin

Leptin is a hormone produced by fat cells that signals the body to stop eating. Leptin reduces hunger and helps regulate energy balance. Leptin tells the brain how much fat is stored in body cells. Generally, increased leptin levels correlate to an increase in fat, and decreased leptin levels correlate to lower body fat. However, about 5% of obese people have very high levels of leptin indicating a lack of sensitivity to the hormone, a condition known as leptin resistance.[13] As a therapeutic target, leptin shows value in reducing caloric intake, increasing weight loss, and improving insulin function.[14]

Ghrelin

Ghrelin is a hormone produced and released primarily by the stomach when it's empty, and by the small intestines, pancreas, and brain. Ghrelin enters the blood and signals the brain to feel hungry, thereby stimulating appetite, increasing consumption, and promoting fat storage: it is the only circulating hormone with this effect. Ghrelin plays a key role in regulating calorie intake and body fat levels, and its levels indicate nutritional status and body fat stores.[13] Higher levels correlate to feeling hungry while lower levels correlate to feeling full. Ghrelin has broad therapeutic potential for conditions including eating disorders, neurogenerative disorders, GI disorders, and metabolic syndrome.[15]

Obestatin

Obestatin is a hormone secreted from the stomach and present in the spleen, mammary glands, breast milk, and plasma. Obestatin signals fullness, suppressing appetite, decreasing food intake, and reducing weight gain. Circulating obestatin levels generally have an inverse association with obesity and diabetes.[16] Obestatin levels have also shown a negative correlation with c-peptide and anti-insulin antibodies in type 1 diabetes onset, potentially indicating islet dysfunction.[17]

PYY

PYY is a hormone secreted by the small intestines into the bloodstream in response to food consumption. PYY signals the brain that it is full, slows down digestion, and decreases appetite for about 12 hours. The amount of PYY released depends on the type and amount of food eaten.[18] High PYY levels are associated with conditions that lead to weight loss like eating disorders, IBD, and some cancers. Low PYY levels are associated with increased appetite and weight gain, and correlate to obesity, making PYY a potential therapeutic target to treat the condition.[19]

Myostatin

Myostatin is a small protein produced and released by skeletal muscle cells when muscles contract. Skeletal muscle is the largest insulin-sensitive organ. Myostatin restrains skeletal muscle growth. Elevated myostatin levels are associated with obesity and with development of insulin resistance and type 2 diabetes.[20] Investigators study how myostatin inhibits muscle growth and the resulting effect on glucose uptake. Myostatin is also a therapeutic target since inhibiting it may improve muscle strength and insulin sensitivity.[21]

Incretin Hormones

The incretins are hormones made in the intestines that, among other functions, increase insulin production in the pancreas. The phrase "incretin effect" refers to the fact that the body does a much better job of stimulating insulin production when food is consumed orally rather than when glucose is administered via injection. In other words, the direct islet cell response to glucose combines with the islet cell response to incretins to maximize overall insulin output. Incretins such as GIP, GLP-1, and GLP-2 are responsible for this effect.

Glucose-dependent insulinotropic polypeptide (GIP)

GIP is an incretin, a signaling hormone primarily produced in the small intestine in response to glucose, protein, or fat ingestion.[22,23] GIP stimulates insulin release from pancreatic ß-cells following food consumption, encouraging energy storage in adipose tissue. GIP receptors are also present in α-cells, where GIP stimulates glucagon release and contributes to insulin secretion through paracrine signaling. GIP is an indicator for high-fat diet (HFD)-induced obesity and insulin resistance.

Glucagon-like peptide-1 (GLP-1)

GLP-1 is an incretin hormone, produced in intestinal L cells, that stimulates insulin release from pancreatic ß-cells following food consumption. Studies show that GLP-1 has regulatory effects on glucagon secretion, however those effects are debated. Previously, it was accepted that GLP-1 inhibits glucagon secretion but the underlying mechanisms were not well-described. More recently, studies demonstrate that GLP-1 can either stimulate or inhibit glucagon secretion depending on glucose levels or physiological need.[24] Low levels of GLP-1 are an indicator for type 2 diabetes. GLP-1 reduces body weight and food intake and slows gastric emptying.[25] GLP-1 also promotes weight loss and is therefore a therapeutic target for diabetes and obesity. In humans, the majority of GLP-1 in circulation is the active GLP-1 (7-36) form.[26]

Further Reading:

Research Review: Explore Root Causes, Detection, and Prevention of Insulin Resistance
Research Review: The Role of Incretins GIP and GLP-1 in Diabetes and Obesity
Research Review: Biomarkers of Energy Homeostasis
eBook: The Generation and Function of Active GLP-1
Data Package: Active GLP-1

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