Molecular Signaling Mechanism of Insulin Action
Clinical utility of insulin and insulin analogs

Salih Sanlioglu VMD, PhD
Human Gene and Cell Therapy Center of Akdeniz University, Antalya, Türkiye, 07058
The pancreas is an elongated organ nestled next to the first part of the small intestine. The endocrine pancreas refers to those cells within the pancreas that synthesize and secrete hormones. The endocrine portion of the pancreas takes the form of many small clusters of cells called islets of Langerhans or, more simply, islets. Humans have roughly one million islets.

Pancreatic islets house three major cell types, each of which produces a different endocrine product: Alpha cells (A cells) secrete the hormone glucagon. Beta cells (B cells) produce insulin and are the most abundant of the islet cells. Delta cells (D cells) secrete the hormone somatostatin, which is also produced by a number of other endocrine cells in the body.

Islets are richly vascularized, allowing their secreted hormones ready access to the circulation. Although islets comprise only 1-2% of the mass of the pancreas, they receive about 10 to 15% of the pancreatic blood flow. Additionally, they are innervated by parasympathetic and sympathetic neurons, and nervous signals clearly modulate secretion of insulin and glucagon.
Glucagon

Glucagon, a peptide hormone (29-amino acid) secreted by the pancreas, raises blood glucose levels. Its effect is opposite that of insulin, which lowers blood glucose levels. The pancreas releases glucagon when blood sugar (glucose) levels fall too low. Glucagon causes the liver to convert stored glycogen into glucose, which is released into the bloodstream.

Glucagon is widely distributed and produced in the alpha-cells of pancreatic islets. It affects glucose metabolism in the liver by inhibiting glycogen synthesis, stimulating glycogenolysis and enhancing gluconeogenesis. It also increases mobilisation of glucose, free fatty acids and ketone bodies, which are metabolites produced in excess in diabetes mellitus.
Glucagon binds to the glucagon receptor, a G protein-coupled receptor located in the plasma membrane. The conformation change in the receptor activates G proteins, a heterotrimeric protein with α, β, and γ subunits. When the G protein interacts with the receptor, it undergoes a conformational change that results in the replacement of the GDP molecule that was bound to the α subunit with a GTP molecule. This substitution results in the releasing of the α subunit from the β and γ subunit. The alpha subunit specifically activates the next enzyme in the cascade, adenylate cyclase. Adenylate cyclase manufactures cAMP (cyclic AMP), which activates protein kinase A (cAMP-dependent protein kinase). This enzyme, in turn, activates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase, converting into the active form called phosphorylase A. Phosphorylase A is the enzyme responsible for the release of glucose-1-phosphate from glycogen polymers.
Insulin

Insulin is a peptide hormone composed of 51 amino acids. It is produced in the islets of Langerhans in the pancreas. Insulin is central to regulating carbohydrate and fat metabolism in the body.

Insulin causes cells in the liver, skeletal muscles, and fat tissue to take up glucose from the blood. In the liver and skeletal muscles, glucose is stored as glycogen, and in adipocytes it is stored as triglycerides.

Insulin stops the use of fat as an energy source by inhibiting the release of glucagon.

When insulin is absent, glucose is not taken up by body cells and the body begins to use fat as an energy source or gluconeogenesis; for example, by transfer of lipids from adipose tissue to the liver for mobilization as an energy source.

Insulin also influences other body functions, such as vascular compliance and cognition. Once insulin enters the human brain, it enhances learning and memory and in particular benefits verbal
In beta cells, insulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes, known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications of proinsulin remove the center portion of the molecule, from the C- and N- terminal ends of proinsulin. The remaining polypeptides (51 amino acids in total), the B- and A- chains, are bound together by disulfide bonds/disulphide bonds. Confusingly, the primary sequence of proinsulin goes in the order "B-C-A", since B (30 aa) and A chains (21 aa) were identified on the basis of mass, and the C-peptide (31 aa) was discovered after the others. Both C-peptide and mature insulin are biologically active.
C-Peptide

The connecting peptide, or C-peptide, is a short 31-amino-acid protein that connects insulin's A-chain to its B-chain in the proinsulin molecule. In the insulin synthesis pathway, first preproinsulin (110 aa) is synthesized within the beta cells of the pancreas with an A-chain, a C-peptide, a B-chain, and a signal sequence. The signal sequence (24 aa) is cleaved from the N-terminus of the peptide by a signal peptidase, leaving proinsulin (86 aa). Then the C-peptide is removed (31 aa), leaving the A-chain (21 aa) and B-chain (30 aa) that constitute the insulin (51 aa).

Newly diagnosed diabetes patients often get their C-peptide levels measured as a means of distinguishing type 1 diabetes and type 2 diabetes. The pancreas of patients with type 1 diabetes is unable to produce insulin, and, therefore, they will usually have a decreased level of C-peptide, whereas C-peptide levels in type 2 patients are normal or higher than normal.

In vivo studies in animal models of type 1 diabetes have established that C-peptide administration results in significant improvements in nerve and kidney function. C-peptide also has been reported to have anti-inflammatory effects as well as aid repair of smooth muscle cells.
Simplistic View of Glucose Induced Insulin Secretion

Glucose is transported into the beta cell by a specific glucose-transporter protein (GLUT-2) on the cell surface. Glycolytic enzyme glucokinase catalyzes the transfer of phosphate from ATP to glucose to form glucose-6-phosphate. By means of this reaction, glucokinase functions as the glucose sensor of the beta cell. The generation of ATP by glycolysis and the Krebs cycle leads to inhibition and closure of the ATP-sensitive potassium channels (the target of sulfonylurea drugs), depolarization of the plasma membrane, opening of the voltage-dependent calcium channels, and influx of extracellular calcium and mobilization of calcium from intracellular stores, leading to the fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin into the circulation.
Molecular Mechanism of Glucose Induced Insulin Secretion

Mechanism of Glucose-Stimulated Insulin Secretion

Glucose is the most potent stimulator of insulin secretion, but the amount of insulin released from pancreatic beta cells is determined by both extracellular and intracellular signaling including nutritional, neuronal, and hormonal factors. Glucose breakdown in beta cells increases ATP/ADP ratio, then closes KATP channels. Membrane depolarization followed by Ca2+ influx into the cell results in insulin secretion (Henquin 2009). In addition to glucose, gastrointestinal hormones, amino acids, fatty acids, and neurotransmitters can modulate glucose-induced insulin secretion via cAMP-mediated pathways (Henquin 2000).

Insulin secretion is naturally increased following meals, a physiological phenomenon known as postprandial insulin secretion. This process involves the combined action of glucose, gastrointestinal hormones, and neurotransmitters released from autonomic nerves.

Acetylcholine released as a result of vagal nerve activation triggers insulin secretion during the early phase of meal ingestion (Ahren 2000). Thus, there is a sudden increase in plasma insulin levels right before digestion of the meal even before blood glucose excursion (Ahren & Holst 2001).

Apart from acetylcholine, there are other neurotransmitters (PACAP & VIP) that stimulate insulin secretion via vagal nerve activation.
In muscle and adipose tissue, activation of the insulin receptor by insulin results in tyrosine phosphorylation of several substrates, including the insulin receptor substrate 1 (IRS-1), IRS-2 and IRS-3 (in the adipose tissue). Following tyrosine phosphorylation, IRSs bind and activate the PI3-K enzyme. Once activated, PI3-K mediates the increase in serine phosphorylation of protein kinase B (Akt), which, in turn, stimulates glucose transport and lipogenesis.
Insulin signal transduction pathway in skeletal muscle. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of "docking" proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p65, p110, and phosphatidylinositol-3' kinase (PI-3-kinase)]. Insulin increases glucose transport through PI-3-kinase and the Cbl pathway, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane.
The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals — one of the effects of a sugar-rich vs a starch-rich meal is highlighted.
Pathways stimulated by insulin:

- Storage of glucose in the liver as glycogen
- Storage in adipose tissue as triglycerides
- Storage of amino acids in muscle as protein
- Utilization of glucose in muscle for energy

Pathways inhibited by insulin:

- Breakdown of triglycerides, glycogen, and protein
- Conversion of amino acids to glucose (gluconeogenesis)
Defects in Insulin Synthesis and Secretion

Diabetes

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles.

The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria).

This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss.

Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).
Diabetes is a huge and growing problem, and the costs to society are high and escalating.
Global health expenditure due to diabetes (20-79 years)

548 billion USD in 2013

627 billion USD in 2035

Diabetes caused 5.1 million deaths in 2013. Every six seconds a person dies from diabetes.
Diabetes

Currently, 382 million people have been reported to have diabetes in the world, and 90% of them has type 2 diabetes mellitus (T2DM).

Increase in obesity rates has been correlated with an increase in the prevalence of diabetes. Diabetes is now considered to be the world’s biggest pandemic disease with a prevalence of 8%.

Five million people have died in 2013 because of the secondary complications of diabetes including coronary heart disease and peripheral vascular diseases.

Furthermore, diabetes has been reported to be the most important cause of blindness and renal failure in developed countries.

Although diabetes is primarily managed by lifestyle changes and dietary modifications, administration of a pharmacological agent is required especially when treatment goals are not achieved.
Diabetes

Diabetes is a group of metabolic diseases due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

• Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.

• Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.

• Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood-sugar level.
Insulin Production and Type 1 Diabetes
Diabetes mellitus type 1 (type 1 diabetes, T1DM, formerly insulin dependent or juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose.

Type 1 diabetes causes an estimated 5–10% of all diabetes cases. Diabetes type 1 is induced by one or more of the following: genetic susceptibility, a diabetogenic trigger and/or exposure to a driving antigen. Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its onset.
Although the association of specific HLA alleles and haplo-types with type 1 diabetes is very strong, this genetic locus is estimated to account for 50% of genetic contributions to disease susceptibility. Diabetogenic alleles are not fully penetrant, implying that not every individual who inherits the gene develops the disease.

Type 1 diabetes is a T-cell–mediated autoimmune disease in which autoreactive cytotoxic T-cells recognize a number of antigenic determinants expressed in pancreatic beta-cells.

Similarly to other autoimmune disorders, in type 1 diabetes many components of the inflammatory responses, including CD4 and CD8 T-cells, macrophages, dendritic cells, natural killer (NK) cells, cytokines, free oxygen, nitric oxide radicals, etc., contribute to beta-cell destruction.
An islet inflammation (insulitis) generally precedes the development of type 1 diabetes. This process requires the involvement of local professional antigen presenting cells (APC), such as dendritic cells, macrophages and B cells, in addition to CD4+ T cells and CD8+ T cells (Panel A).

A prolonged period of insulitis may lead to the preferential amplification of autoreactive CD8+ T cells bearing high affinity T cell receptors (TCR). The differentiation of high affinity CD8+ pre-CTLs into CTLs is accomplished via TCR recognition of target peptide-MHC I complexes on local APC in CD4+ T helper (Th) independent manner (Panel B).

Co-stimulatory pathways involving CD28-B7 are believed to be essential for this process.
**Effector Phase of T1D:** Unknown environmental factors cause MHC class I restricted presentation of the beta cell antigen on the beta-cell surface. CD8+ T cells recognizing this antigen generates MHC class I restricted beta cell damage through the secretion of INF gamma or TNF/TRAIL or the perforin/granzyme system.

Liberated beta-cell components, such as insulin are taken up by the dendritic cells in islets and transported to the regional pancreatic lymph nodes, where the antigens are processed and presented to CD4+ T cells.

After the clonal expansion, CD4+ T cells will move to the islets to perform CD4+ T cell-mediated killing using FasL/Fas system.

In addition, the interaction between the APC and T cells initiates an inflammatory response resulting in the production of high concentrations of proinflammatory cytokines locally in the islets. These cytokines then facilitate the induction of apoptotic signaling cascades in the pancreatic beta cells. Both CD8+ and CD4+ T cells can secrete TNF and INF-gamma upon antigen recognition. TNF enhances autoantigen presentation and IL-1 secretion by local APC. By binding to specific receptors on beta cells, these proinflammatory cytokines induce either apoptosis through caspase cleavage (TNF) or necrosis through NO production (INF-gamma and IL-1). These three cytokines can also upregulate Fas and MHC I expression on beta cells in order to facilitate cell recognition and cell death.

Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin; insulin pumps and inhaled insulin have been available at various times. Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dl (4.4–7.8 mmol/L). The ultimate goal of normalizing BG is to avoid long-term complications that affect the nervous system (e.g. peripheral neuropathy leading to pain and/or loss of feeling in the extremities), and the cardiovascular system (e.g. heart attacks, vision loss). People with type 1 diabetes always need to use insulin, but treatment can lead to low BG (hypoglycemia), i.e. BG less than 70 mg/dl (3.9 mmol/l).
Association of insulin monomers in the presence and absence of zinc and phenolic excipients. Insulin readily associates into dimers, aggregates and (in the presence of divalent cations such as zinc), into hexameric forms. The presence of phenolic excipients causes these hexamers to undergo conformational changes that increase their stability. Key: \( R_6 \) = hexamer with insulin molecules whose B1–B8 residues are in an \( \alpha \)-helical (R) conformation; \( T_6 \) = hexamer with insulin molecules whose B1–B8 residues are in an extended (T) conformation. Adapted from Beals et al. Informa Healthcare: New York, 2008;265–80

Hydrogen bonding between the C-termini of B chains facilitates insulin monomers to form dimers in solution, while the presence of Zn2+ forces insulin dimers into hexamers. The fact that monomers and dimers can easily disperse in the blood, but hexamers cannot, has an important clinical implication in the treatment of diabetes.
Molecular structure of fast and long-acting insulin analogs. P(B28) and K(B29) residues at the COO- terminus of B chain are reversed in Insulin Lispro. Insulin Aspart has D residue in place of P at B28. K(B29) residue is changed to E and N(B3) is substituted with K in Insulin Glulisin. Glargine has an addition of two dibasic aa (RR) at the COO- end of B chain (B31 and B32) in addition to a substitution of N to G at position A21. B29K residue is attached to a fatty acid (myristic acid) in Insulin Detemir which lacks T(B30) (LysB29 (N-tetradecanoyl)des(B30)). In Insulin Degludec, however, T(B30) is deleted and K(B29) has been coupled to a fatty acid (hexadecanedionic acid) via E (Glu) bridge.

Fast Acting Insulin Analogues

The first of the marketed “fast-acting” insulin analogues called insulin lispro is bioengineered such that the penultimate lysine and proline residues on the C-terminal end of the B-chain are reversed. This change does not modify receptor binding, but effectively prevents the formation of insulin dimers and hexamers allowing larger amounts of active monomeric insulin to be immediately available for postprandial injections.

Another fast-acting insulin analogue is insulin aspart (marketed by Novo Nordisk as "NovoLog/NovoRapid"). In insulin aspart the amino acid B28 that is normally a proline has been replaced with an aspartic acid residue permitting increased charge repulsion to further prevent hexamer formation.

The newest addition to the class of rapid acting recombinant insulin analogs is the insulin glulisine (Apidra® sold by Sanofi-Aventis). Insulin glulisine (3BLys29BGlu-human insulin) differs from human insulin such that the asparagine at position B3 has been replaced by a lysine and the lysine in position B29 is now glutamic acid. While zinc is required for stabilization in hexameric forms to achieve a practical shelf life for aspart and lispro, the oligomeric molecules of glulisine are stable without the addition of zinc apparently due to the unaltered proline at position B28 leading to molecular dimerization.

Despite these advantages, fast acting insulin analogs have several side effects like hypoglycemia and allergic reactions (particularly at the site of injection). The purpose of amino acid substitutions of fast-acting insulin analogs is to endorse monomer stability with rapid dissociation and absorption after subcutaneous injection. Nevertheless, fast-acting insulin analogs are prescribed in combination with longer-acting insulin to maintain proper glycemic control.
Long Acting Insulin Analogues

Despite the emphasis on developing recombinant forms of insulin that resist hexamer formation, hexamers are desirable when the duration of insulin action is to be prolonged. For example, insulin glargine (LANTUS®) is a long-acting form of insulin injected once a day for T1D or T2D patients. A glycine substitution for asparagine at A21 and the addition of two arginine residues at the carboxyl terminal of B chain allow glargine to form a precipitate (hexamer-micro crystals) upon injection. Intriguingly, it is the only 24-hour insulin approved exclusively for once-a-day use.

The other long-acting human insulin analog currently available is insulin detemir (Levemir, Novo Nordisk) has the last amino acid in the B chain (threonine) deleted and a fatty acid (myristic acid) covalently linked to the B29 allowing it to bind to albumin in circulation. Although detemir is quickly absorbed after injection, dissociation from albumin in blood is relatively slow thus prolonging its efficacy.

Since hexamer formation slows down the absorption of insulin while it increases its duration of efficacy, soluble multihexamers were formulated to generate ultralong-acting insulin analogs – one of which is insulin degludec developed by Novo Nordisk. Insulin degludec is basal insulin that forms soluble multihexamers after subcutaneous injection, resulting in an ultralong action. Insulin degludec was intended to provide optimal basal insulin coverage for patients. Because its effect may last as long as 40 hours unlike 18-26 hours achieved with insulin glargine and insulin detemir, three subcutaneous injections are sufficient to control blood glucose levels of diabetic patients up to a week.
Although insulin analogues are either absorbed quickly to mimic insulin action (as in the case of lispro, aspart and glulisine), or gradually (as with insulin detemir, glargine and degludec), these agents lower serum glucose levels by enhancing glucose uptake into skeletal muscle and fat tissue and simultaneously preventing gluconeogenesis, glycogenolysis and lipolysis.

Despite these advantages, currently available insulin analogs fail to mimic the endogenous insulin secretion profile especially when used at high doses. When these agents are used at low doses, diabetic patients would not have 24 h insulin coverage.

In addition, metabolic variability among individuals further complicates management of diabetes based on insulin analogs. In these patients, insulin-induced recurrent hypoglycemia seems to be a major limiting factor preventing the achievement of an ideal glycemic control.

Insulin glargine has a greater affinity for the insulin-like growth factor receptor (IGF-1R) than native insulin. Activation of the IGF-1R by high levels of insulin results in mitogenic signaling and has been associated with increased tumor cell proliferation. Since circulating IGF-1 is linked to the development of solid tumors and leukemia, patients using some of the new insulin analogs might be posed to an increased risk for cancer. Intriguingly, European Medicines Agency (EMEA) neither confirm nor exclude the potential risk associated with the use of insulin analogs and cancer.

One of the main problems associated with insulin replacement therapy is that it is almost impossible to deliver insulin from outside in such a way that could mimic beta cell function. Obviously, manifestation of physiological actions of insulin and at least its dynamics are different based on the route of delivery.
Frequent insulin dosage titration is required to maintain glycemic control in diabetic patients. To circumvent the need for dosage titration, Hygieia Inc. has developed the Diabetes Insulin Guidance System (DIGS), which measures patient’s blood glucose, analyzes patterns in these measurements and then automates insulin dosage titration based on these values. on December 1st of 2011, the U.S. FDA released new guidelines to speed up the development of an artificial pancreas system and soon after approved the first outpatient clinical trial for an artificial pancreas (March of 2012) that could potentially automate insulin care for millions of T1D patients living in the U.S.

Because regular human insulin and insulin analogues do not contain C-peptide, there is a great debate on whether C-peptide should be included in insulin preparations since it provided some beneficial effects to diabetic patients in recent studies. Skepticism arose because early stage T2D patients unexpectedly displayed high levels of C-peptide in their blood. It is now clear that C-peptide is not simply an insulin marker, but it also has some beneficial effects for diabetics in terms of improving kidney function, nerve function and blood flow to vital organs. One proposed mechanism of C-peptide function involves the activation of GLUT1 transporter leading to glucose clearance by way of adenosine triphosphate (ATP) release from red blood cells, a known stimulus for the blood vessel dilator nitric oxide.

In addition, insulin therapy does not include amylin replacement. Amylin is a peptide also known as Islet Amyloid Polypeptide (IAPP), which is needed for optimum glycemic control since it slows down gastric emptying and blocks glucagon production. Pramlintide, a synthetic analog of human amylin, was approved for adult use in conjunction with insulin in patients with both T1D and T2D before a meal to better manage postprandial glucose excursion.

Finally, there is also a strong argument favoring leptin use as an adjunctive therapy to insulin injection in patients with T1D.
Type 2 diabetes is another heterogeneous disease, and it is the most common form of diabetes, accounting for 90% of cases and in many industrialized countries affecting 10–20% of individuals over the age of 45 years.

In type 2 diabetes, both relative loss of beta-cell mass and intrinsic beta-cell secretory defects, including selective loss of sensitivity to glucose, may explain the failure of pancreatic beta-cells to meet the increased secretory demand caused by insulin resistance.

There is a wealth of data indicating that systemic inflammation plays a role in the chain of events leading to type 2 diabetes, athero-sclerosis, obesity, and fatty liver disease.
Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy. This is partly due to a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations. In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure. Other complications include: sexual dysfunction, and frequent infections.
Islet autoimmunity and systemic inflammation in adult patients with diabetes

There is a wide spectrum of associations between inflammatory reactions and the various diabetic syndromes. At one end of the spectrum there is type 1 diabetes, for which there is convincing evidence that a chronic inflammation of the islets is an important feature of disease pathogenesis. At the opposite end is type 2 diabetes, which is clearly associated with systemic inflammation that could be either the cause or the consequence of some of the main features of the disease. Finally, somewhere between these two extremes, one finds LADA, which seems to share some features of both extremes, thereby raising the question of its pathogenesis.

Pietropaolo M et al, 2007 Diabetes
Relationship between islet autoimmunity and systemic inflammation in adult patients with diabetes

Insulin resistance may precede the clinical onset of both type 1 and type 2 diabetes. In the initial stages of the natural history of these two diseases, nondiabetic subjects adapt to insulin resistance by increasing beta-cell mass (beta-cell hypertrophy) and function in an effort to maintain glycemic and metabolic homeostasis.

Islet autoimmunity and systemic inflammation follow two separate avenues, and their pathogenic mechanisms leading to disease are diverse. In autoimmune diabetes, there is convincing evidence that chronic inflammation of pancreatic islets leads the chain of events culminating in beta-cell death.

Conversely, the activation of the acute-phase response and systemic inflammation play fundamental roles for the pathoetiology of type 2 diabetes and metabolic syndrome. Systemic inflammatory responses are associated with variations of a wide array of plasma proteins and proinflammatory cytokines (i.e., CRP, TNF-alpha, IL-6, etc.), whereas chronic islet inflammation is caused by an altered balance between pathogenic T-cells (that mediate disease) and regulatory T-cells (Tregs) that control autoimmunity.
At least three lines of evidence firmly indicate that systemic inflammation plays a role in the pathogenesis of insulin resistance and type 2 diabetes. Findings from numerous major epidemiologic studies indicate that the presence of different combinations of inflammatory markers, namely C-reactive protein, fibrinogen, IL-6, IL-1, and plasminogen activator inhibitor (PAI)-1, are significant predictors of type 2 diabetes.

The second line of evidence relates to the paradigm that chronic inflammation is involved in the pathogenesis of atherosclerosis, a common complication of type 2 diabetes and insulin resistance. A large number of investigations have convincingly shown that low-grade elevation of circulating markers of inflammation, such as CRP, sialic acid, and proinflammatory cytokines, is associated with cardiovascular mortality, coronary heart disease, peripheral vascular disease, and stroke.

The third line of evidence derives from the association of gestational diabetes, a risk factor for type 2 diabetes, and activated innate immunity with increased acute-phase proteins. Elevated CRP levels during the first trimester of pregnancy are more pronounced in women who develop gestational diabetes later in their pregnancy.
In humans, it has been reported that TNF-alpha levels positively correlate with levels of insulin and BMI, suggesting that production or regulation of TNF-alpha may be involved in the pathogenesis of type 2 diabetes and insulin resistance observed in obesity. TNF-alpha is involved in the development of insulin resistance by inhibiting the tyrosine kinase activity of the insulin receptor.

TNF-alpha may also impair insulin secretion in pancreatic islet cells and may stimulate IL-6 production, which leads to beta-cell destruction. IL-1 beta induces nitric oxide (NO) production in pancreatic beta-cells, and it may also promote an impairment of insulin secretion in beta-cells.

In addition, several studies have suggested that pro-inflammatory cytokines, such as IL-1 beta, gamma-interferon (IFN-gamma), and free radicals, are mediators of pancreatic beta-cell death in both human and rodent islet cells.
Insulin resistance (IR) is a pathological condition of insulin signaling pathway in which cells fail to respond to the normal actions of the hormone insulin leading to high blood sugar. Beta cells in the pancreas subsequently increase their production of insulin, further contributing to a high blood insulin level. It is well known that insulin resistance commonly coexists with sedentary life style and obesity. Dietary fat has long been implicated as a driver of insulin resistance. Elevated levels of free fatty acids and triglycerides in the blood stream and tissues have been found in many studies to contribute to diminished insulin sensitivity.
Hepatic insulin resistance is important in type 2 diabetes as it exacerbates fasting glucose concentrations and diminishes postprandial glucose tolerance. The insulin-resistant liver produces excess triglyceride and cholesterol that progresses to systemic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and obesity. How insulin resistance leads to both hyperglycemia and hyperlipidemia is a complex question of immense clinical importance.

Treatments for fatty liver disease are poorly established, but drugs that improve hepatic insulin sensitivity and glucose tolerance—including metformin (N,N-di-methylimidodicarbonimidic diamide) can be beneficial.

Metformin (Glucophage) is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. Metformin improves hyperglycemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one third.
Insulin, Metformin Hepatic Insulin Resistance
Insulin and Metformin Signaling to aPKC in Liver. Elements of the IRS2 branch of the insulin signaling cascade are shaded gray, whereas elements of the IRS1 branch of the cascade are not shaded. IRS1 and IRS2 play a common role in the activation of the PI3 kinase/[PDK1/AKT]/FOXO cascade. The IRS2/PI3 kinase/[PDK1/aPKC\_lambda]/CBP cascade inactivates the CREB:CBP:CRTC2 transcription complex. Metformin also activates aPKC\_lambda through a different mechanism, which circumvents hepatic insulin resistance to phosphorylate CBP and inactivate the CREB:CBP:CRTC2 transcription complex, especially during hepatic insulin resistance associated with obesity and type 2 diabetes. Phosphorylation sites (pS or pY) highlighted in green indicate activation steps, whereas sites highlighted in red indicate inhibitory steps.
Impaired glucose tolerance (IGT) is a pre-diabetic state of dysglycemia, that is associated with insulin resistance and increased risk of cardiovascular pathology. Prediabetes is the medical stage in which not all of the symptoms required to label a person as diabetic are present, but blood sugar is abnormally high. IGT may precede type 2 diabetes mellitus by many years. IGT is also a risk factor for mortality.

In people with impaired glucose tolerance, blood glucose levels are higher than normal but less than the level required for a diagnosis of diabetes. Blood glucose levels normally rise after eating a meal then gradually fall as the meal is digested. However in people with impaired glucose tolerance, these levels remain elevated.

Impaired glucose tolerance is detected through the same test used to detect diabetes - the oral glucose tolerance test. Improvements in glucose tolerance can be achieved through participation in regular physical activity and weight reduction.
Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by the GLUT2 glucose transporter; subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for drugs that act as insulin secretagogues (sulfonylurea class of antidiabetic drugs). Mutations in the events or proteins involved in glucose induced insulin secretion cause diabetes. SUR, sulfonylurea receptor; ATP, adenosine triphosphate; ADP, adenosine diphosphate, cAMP, cyclic adenosine monophosphate.
Beta Cell Loss

An increase in beta-cell apoptosis, but not a decrease in beta-cell replication or new islet formation, has been blamed for the loss of beta-cell mass observed in T2D patients (Butler et al. 2003). In this scenario, antigens from apoptotic beta cells stimulate autoreactive T cells leading to the autoimmune destruction of pancreatic beta cells both in T2D and in T1D.

Medical intervention may be useful in recovering beta-cell function or restoring beta-cell mass, but only during early stages of T2D. Because the decrease in beta-cell mass is considered to be one of the most important defects in T2D patients, antiapoptotic strategies are very crucial in protecting pancreatic islets from destruction. While the potential need for an anti-inflammatory medication is appreciated, both targeted and efficacious anti-inflammatory drugs are yet to be developed for the treatment of T2D.

As impaired insulin secretion is the primary defect in diabetics, agents that stimulate glucose-induced insulin secretion (insulinotropic agents) while protecting cells from apoptosis represent a novel class of medications for the treatment of diabetes. An ideal beta-cell-preserving agent is expected to protect beta cells from apoptosis and stimulate postprandial insulin secretion along with increasing beta-cell replication and/or islet neogenesis.
Maturity onset diabetes of the young: Diabetes mellitus that has early onset (usually before the age of 25), is non-insulin-dependent, rare, and is inherited in an autosomal dominant manner. MODY is used to be considered a subtype of type 2 diabetes but it is unlike the usual type 2 diabetes in that insulin production, not the action of insulin, is impaired. There is no problem with insulin sensitivity.

MODY is often referred to as "monogenic diabetes" to distinguish it from the more common types of diabetes (especially type 1 and type 2), which involve more complex combinations of causes involving multiple genes (i.e., "polygenic") and environmental factors. MODY should not be confused with latent autoimmune diabetes of adults (LADA) — a form of type 1 DM, with slower progression to insulin dependence in later life.

MODY accounts for 2-5% of all non-insulin-dependent diabetes. The severity of the different types varies considerably, but most commonly MODY acts like a very mild version of type 1 diabetes, with continued partial insulin production and normal insulin sensitivity. MODY is not type 2 diabetes in a young person, as might erroneously be inferred from the name.
Latent autoimmune diabetes of the adult (LADA)

The definition of LADA pertains to adults who have a slowly progressive form of autoimmune or type 1 diabetes that can be treated initially without insulin injections.

This definition was intended to distinguish LADA from adult-onset type 1 diabetes, whereby insulin is necessary at disease onset, and from type 2 diabetes, whereby insulin therapy may or may not be required for a number of years after diagnosis.

The term “LADA ” was coined because without testing for islet-related autoantibodies, it would not be possible to diagnose autoimmune diabetes.

Thus far, there is no evidence that markers of systemic inflammation are linked with LADA, as the natural history of this condition is unknown.
References


• Tip 1 diyabetli hastalarda insulin tedavisinde ve insulin gen terapisinde güncel gelişmeler. Klinik Tıp Bilimleri Dergisi, Clinical Medical Sciences, Diyabet özel sayısı. Nisan 2012 1-5