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DIABETES MELLITUS: INSULIN SECRETION AND REGULATION

OBIDOV ABDULAHAD
IMPULS MEDICAL INSTITUTE

Abstract. This article examines the pathogenesis of diabetes mellitus, mechanisms of insulin hormone secretion, and its regulatory processes in the organism. The physiological foundations of insulin secretion, beta-cell function, glucose homeostasis regulation, and metabolic disorders occurring in various forms of diabetes are studied. The research demonstrates the importance of modern medical approaches and insulin therapy in diabetes management.

Keywords: diabetes mellitus, insulin, beta-cell, glucose metabolism, endocrine system, hormone regulation

INTRODUCTION

Diabetes mellitus is one of the most prevalent endocrine diseases of the 21st century, affecting approximately 10-12% of the world's population. Currently, 537 million people worldwide suffer from diabetes, and this number is projected to reach 783 million by 2045. Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels resulting from impaired insulin production or action.

Insulin is the body's primary anabolic hormone, playing a crucial role in regulating carbohydrate, protein, and lipid metabolism. Understanding the complex mechanisms of nutrient metabolism is essential for developing prevention and treatment strategies for diabetes.

Currently, extensive research is being conducted on the pathogenesis of diabetes mellitus, mechanisms of insulin secretion, and glucose homeostasis regulation systems. This knowledge enables the implementation of effective treatment methods in clinical practice.

The global burden of diabetes continues to increase, driven by factors such as sedentary lifestyles, obesity, aging populations, and urbanization. The economic impact is substantial, with healthcare costs for diabetes and its complications exceeding hundreds of billions of dollars annually. Therefore, comprehensive understanding of insulin biology and diabetes pathophysiology is imperative for addressing this growing health crisis.

PHYSIOLOGICAL SIGNIFICANCE OF INSULIN

Structure and Synthesis of Insulin

Insulin is a peptide hormone composed of 51 amino acids, produced by beta-cells in the pancreatic islets of Langerhans. The insulin molecule consists of two peptide chains (A-chain and B-chain) connected by disulfide bridges.

Insulin biosynthesis occurs in several stages:

1. Preproinsulin synthesis: Preproinsulin, consisting of 110 amino acids, is synthesized in the ribosomes as the initial form.

2. Proinsulin formation: The signal peptide is cleaved in the endoplasmic reticulum, forming proinsulin.

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3. Mature insulin production: In the Golgi apparatus, C-peptide is cleaved from proinsulin, producing the mature insulin molecule consisting of A and B chains.

4. Storage in granules: Insulin is stored in crystalline form within specialized secretory granules and released into the bloodstream when needed.

The gene encoding insulin is located on chromosome 11 in humans. The regulation of insulin gene expression is complex and influenced by various factors including glucose, hormones, and neural signals. Understanding this process is crucial for developing strategies to preserve or enhance beta-cell function in diabetes.

Primary Functions of Insulin

Insulin performs the following essential functions in the organism:

Carbohydrate metabolism:

- Enhances glucose uptake by peripheral tissues (muscle and adipose tissue)
- Stimulates glycogen synthesis in liver and muscles
- Inhibits gluconeogenesis (new glucose synthesis)
- Activates glycolysis

Protein metabolism:

- Increases transport of amino acids into cells
- Stimulates protein synthesis
- Inhibits protein degradation (proteolysis)
- Promotes cellular growth and differentiation

Lipid metabolism:

- Activates lipogenesis (fat synthesis) in adipose tissue
- Inhibits lipolysis (fat breakdown)
- Increases triglyceride synthesis
- Promotes very-low-density lipoprotein (VLDL) production

Additional functions:

- Promotes potassium uptake into cells
- Stimulates cellular growth and proliferation
- Has anti-inflammatory effects
- Influences cognitive function and appetite regulation

MECHANISMS OF INSULIN SECRETION

Glucose Sensing in Beta-Cells

Insulin secretion is regulated through complex molecular mechanisms. Elevated blood glucose concentration initiates the following processes in beta-cells:

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1. Glucose transport: Glucose enters beta-cells via the GLUT2 transporter protein. The high Km value of GLUT2 (approximately 15-20 mM) enables it to function as a glucose sensor.

2. Glucokinase reaction: The glucokinase enzyme phosphorylates glucose to glucose-6-phosphate. This enzyme functions as a "glucose sensor" because its activity is directly dependent on glucose concentration. Glucokinase is often referred to as the pancreatic glucose sensor due to its unique kinetic properties.

3. ATP synthesis: Glucose metabolism results in ATP production through oxidative phosphorylation in mitochondria, increasing the ATP/ADP ratio.

4. K-ATP channel closure: Increased ATP causes closure of ATP-sensitive potassium (K-ATP) channels, leading to membrane depolarization.

5. Calcium channel opening: Membrane depolarization opens voltage-dependent calcium channels, allowing Ca^{2+} ions to enter the cell.

6. Exocytosis: Increased cytoplasmic calcium concentration stimulates fusion of insulin granules with the cell membrane and insulin release through exocytosis.

This elegant coupling mechanism between glucose metabolism and insulin secretion ensures that insulin release is precisely matched to metabolic needs. Defects at any step in this pathway can contribute to diabetes pathogenesis.

Biphasic Nature of Insulin Secretion

Insulin secretion in response to glucose occurs in two distinct phases:

First phase (rapid phase): Begins immediately after glucose stimulation and lasts 5-10 minutes. This phase involves release of pre-formed insulin granules. First-phase secretion is crucial for preventing acute spikes in blood glucose levels and priming peripheral tissues for glucose uptake.

Second phase (slow phase): Occurs during sustained glucose exposure and can last several hours. This phase involves newly synthesized insulin. Second-phase secretion provides long-term glucose homeostasis and is essential for maintaining euglycemia during prolonged feeding.

Loss of first-phase insulin secretion is an early marker of beta-cell dysfunction in type 2 diabetes and can precede overt hyperglycemia by years. Preservation or restoration of this biphasic pattern is an important goal in diabetes treatment.

Factors Regulating Insulin Secretion

Insulin secretion is regulated not only by glucose but also by numerous other factors:

Stimulatory factors:

- Glucose (primary stimulator)
- Amino acids (especially arginine and leucine)
- Fatty acids
- GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide)
- Parasympathetic nerves (acetylcholine)

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- Sulfonylurea drugs
- Neural inputs during cephalic phase of feeding

Inhibitory factors:

- Somatostatin
- Epinephrine and norepinephrine (sympathetic activation)
- Leptin
- Glucagon (at high concentrations)
- Galanin
- Certain medications (diazoxide, phenytoin)

Potentiating factors:

- Incretin hormones (GLP-1, GIP) – enhance glucose-stimulated insulin secretion
- Neural signals during food ingestion
- Gastrointestinal hormones

Understanding these regulatory mechanisms has led to development of therapeutic agents that modulate insulin secretion, such as GLP-1 receptor agonists and DPP-4 inhibitors.

TYPES AND PATHOGENESIS OF DIABETES MELLITUS

Type 1 Diabetes (Insulin-Dependent)

Type 1 diabetes is a disease resulting from autoimmune destruction of pancreatic beta-cells, leading to insufficient insulin production.

Pathogenesis:

- Autoimmune attack on beta-cells by T-lymphocytes
- Destruction of 85-90% of beta-cells
- Absolute insulin deficiency develops
- Usually manifests in youth or childhood
- Combination of genetic predisposition and environmental factors
- Presence of autoantibodies (GAD, IA-2, insulin autoantibodies)

Genetic factors:

- Strong HLA association (DR3, DR4, DQ)
- Multiple susceptibility genes identified
- Family history increases risk but most cases are sporadic

Environmental triggers:

- Viral infections (enteroviruses, coxsackievirus)
- Early dietary exposures
- Vitamin D deficiency
- Hygiene hypothesis

Clinical manifestations:

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- Polyuria (excessive urination)
- Polydipsia (excessive thirst)
- Polyphagia (excessive eating)
- Rapid weight loss
- Weakness and fatigue
- Risk of ketoacidosis
- Acute onset of symptoms

Type 2 Diabetes (Non-Insulin Dependent)

Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency, widely prevalent among adults.

Pathogenesis:

- Insulin resistance: decreased tissue sensitivity to insulin
- Beta-cells compensate by producing more insulin
- Over time, beta-cells become "exhausted" and function deteriorates
- Relative insulin deficiency develops
- Usually occurs in people over 40 years old
- Progressive disease with multiple pathophysiological defects

Mechanisms of insulin resistance:

- Decreased insulin receptor expression
- Impaired insulin signaling pathways
- Ectopic fat deposition in liver and muscle
- Chronic inflammation
- Mitochondrial dysfunction
- Altered adipokine secretion

Risk factors:

- Obesity (especially abdominal type)
- Physical inactivity
- Genetic predisposition
- Age (over 40 years)
- Arterial hypertension
- Dyslipidemia
- History of gestational diabetes
- Ethnicity (higher risk in certain populations)
- Metabolic syndrome
- Low birth weight

Clinical features:

- Gradual development
- Often asymptomatic
- Detected during routine examinations
- Higher prevalence of chronic complications
- May present with complications at diagnosis

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Gestational Diabetes

Glucose metabolism disorder first detected during pregnancy. Pregnancy hormones (progesterone, cortisol, placental lactogen) increase insulin resistance.

Pathophysiology:

- Placental hormones induce insulin resistance
- Beta-cells unable to compensate adequately
- Usually develops in second or third trimester
- Resolves after delivery but indicates future diabetes risk

Complications:

- Maternal: preeclampsia, cesarean delivery
- Fetal: macrosomia, birth trauma, neonatal hypoglycemia
- Long-term: increased risk of type 2 diabetes in mother and offspring

Management:

- Dietary modifications
- Blood glucose monitoring
- Insulin therapy if needed
- Regular obstetric surveillance

Other Specific Types

Monogenic diabetes:

- MODY (Maturity-Onset Diabetes of the Young)
- Neonatal diabetes
- Single gene mutations affecting beta-cell function

Secondary diabetes:

- Pancreatic diseases (pancreatitis, cystic fibrosis)
- Endocrinopathies (Cushing's syndrome, acromegaly)
- Drug-induced (glucocorticoids, thiazides)
- Post-transplantation

REGULATION OF GLUCOSE HOMEOSTASIS

Metabolism of Orally Ingested Glucose

After eating, glucose is absorbed through the intestinal wall and distributed throughout the body via blood:

1. Postprandial period (after eating):

- Blood glucose level rises (to 7-10 mM)
- Insulin secretion sharply increases

- Liver takes up glucose and stores it as glycogen
- Muscle and adipose tissues actively absorb glucose
- Gluconeogenesis and glycogenolysis are inhibited
- Peripheral glucose uptake increases 3-4 fold
- Hepatic glucose output is suppressed

2. Postabsorptive period (between meals):

- Blood glucose level decreases (3.5-5.5 mM)
- Insulin secretion decreases
- Glucagon secretion increases
- Liver produces glucose through glycogenolysis and gluconeogenesis
- Adipose tissue releases fatty acids
- Muscle utilizes fatty acids for energy
- Brain continues glucose utilization

3. Fasting state:

- Glucagon and cortisol play leading roles
- Gluconeogenesis actively continues
- Ketogenesis (ketone body synthesis) intensifies
- Brain metabolism partially shifts to ketone bodies
- Protein catabolism increases
- Adipose tissue lipolysis increases significantly

Counter-Regulatory Hormones

Hormones that counteract insulin action:

Glucagon:

- Produced in alpha-cells
- Activates glycogenolysis and gluconeogenesis
- Insulin antagonist
- Stimulates hepatic glucose output
- Promotes ketogenesis during fasting

Epinephrine:

- Released during stress situations
- Enhances glycogenolysis
- Inhibits insulin secretion
- Increases hepatic glucose production
- Stimulates lipolysis

Cortisol:

- Stimulates gluconeogenesis
- Decreases peripheral tissue sensitivity to insulin
- Increases protein catabolism
- Permissive for other counter-regulatory hormones

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Growth hormone:

- Enhances lipolysis
- Increases insulin resistance
- Promotes protein synthesis
- Stimulates gluconeogenesis

Thyroid hormones:

- Increase metabolic rate
- Enhance glucose absorption from intestine
- Increase insulin degradation

These counter-regulatory hormones work in concert to prevent hypoglycemia and maintain adequate glucose supply to the brain and other vital organs during fasting or stress.

INSULIN THERAPY AND MANAGEMENT

Types of Insulin Preparations

Modern medicine employs various insulin preparations:

1. Ultra-rapid-acting insulins:

- Onset of action: 5-15 minutes
- Peak effect: 1-2 hours
- Duration: 3-5 hours
- Examples: insulin lispro, aspart, glulisine
- Ideal for mealtime coverage

2. Short-acting (regular) insulins:

- Onset of action: 30 minutes
- Peak effect: 2-4 hours
- Duration: 6-8 hours
- Can be administered intravenously
- Used in hospital settings

3. Intermediate-acting insulins:

- Onset of action: 1-2 hours
- Peak effect: 4-8 hours
- Duration: 12-18 hours
- Examples: NPH insulin
- Often combined with rapid-acting insulins

4. Long-acting insulins:

- Onset of action: 1-2 hours
- No peak effect (steady action)
- Duration: 20-24 hours

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- Examples: insulin glargine, detemir, degludec
- Provide basal insulin coverage
- Reduced hypoglycemia risk compared to NPH

5. Ultra-long-acting insulins:

- Duration: beyond 24 hours (up to 42 hours for degludec)
- Most stable basal coverage
- Allows flexible dosing timing

Insulin Therapy Regimens

Basal-bolus regimen:

- Long-acting insulin (basal) 1-2 times daily
- Rapid-acting insulin (bolus) before each meal
- Mimics physiological insulin secretion
- Most flexible and physiological approach
- Requires carbohydrate counting

Premixed insulin regimen:

- Mixture of intermediate and rapid-acting insulins
- 2-3 times daily
- Simple but less flexible
- Fixed ratio limits dose adjustment
- Suitable for patients with regular meal patterns

Insulin pump therapy:

- Continuous subcutaneous insulin infusion
- Most precise glucose control
- High-tech solution
- Reduces hypoglycemia risk
- Allows for very small dose adjustments
- Improves quality of life

Conventional therapy:

- Fixed doses of intermediate-acting insulin
- 1-2 daily injections
- Less physiological
- Higher risk of hypoglycemia and hyperglycemia
- Rarely used today

Hypoglycemia and Prevention

Causes of hypoglycemia:

- Excessive insulin dosage
- Missed meals or delayed eating

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- Excessive physical activity
- Alcohol consumption
- Impaired awareness of hypoglycemia
- Renal or hepatic insufficiency
- Drug interactions

Symptoms:

- Trembling, sweating
- Tachycardia, palpitations
- Dizziness, confusion
- Decreased mental function
- Hunger, nausea
- Loss of consciousness (in severe cases)
- Seizures (if prolonged)

Classification:

- Level 1: glucose <70 mg/dL but ≥ 54 mg/dL
- Level 2: glucose <54 mg/dL (clinically significant)
- Level 3: severe hypoglycemia requiring assistance

Treatment:

- 15-20 g of fast-acting carbohydrates
- Recheck glucose after 15 minutes
- Repeat carbohydrates if needed
- Glucagon injection for severe hypoglycemia
- Intravenous dextrose in hospital settings

Prevention strategies:

- Patient education on recognition and treatment
- Glucose monitoring before driving and exercise
- Carbohydrate counting skills
- Insulin dose adjustment for activity
- CGM with low glucose alerts
- Regular meal timing

MODERN APPROACHES AND PERSPECTIVES

Novel Pharmacological Treatment Methods

GLP-1 receptor agonists:

- Increase insulin secretion in glucose-dependent manner
- Decrease glucagon secretion
- Slow gastric emptying
- Promote weight loss
- Cardiovascular benefits demonstrated
- Examples: liraglutide, semaglutide, dulaglutide

- Weekly formulations available

DPP-4 inhibitors:

- Prevent degradation of GLP-1
- Improve insulin secretion
- Low risk of hypoglycemia
- Weight neutral
- Examples: sitagliptin, saxagliptin, linagliptin
- Oral administration

SGLT-2 inhibitors:

- Inhibit glucose reabsorption in kidneys
- Increase urinary glucose excretion
- Reduce cardiovascular risk
- Decrease heart failure hospitalizations
- Weight loss benefit
- Examples: empagliflozin, dapagliflozin, canagliflozin
- Renal protective effects

Combination therapies:

- GLP-1 RA + basal insulin
- Multiple oral agents with complementary mechanisms
- Personalized treatment approach based on patient characteristics

Artificial Pancreas Systems

Closed-loop systems created using modern technologies:

Components:

- Continuous glucose monitoring sensor (CGM)
- Insulin pump
- Control algorithms (artificial intelligence)
- Communication between devices

Advantages:

- Automatic insulin dose adjustment
- Prevention of hypoglycemia and hyperglycemia
- Improved quality of life for patients
- Reduced glycemic variability
- Decreased diabetes distress
- Better overnight glucose control

Current systems:

- Hybrid closed-loop (requires meal announcements)
- Fully automated systems in development

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- Dual-hormone systems (insulin + glucagon)

Challenges:

- Cost and accessibility
- Technical malfunctions
- Patient training requirements
- Insurance coverage issues

Regenerative Medicine

Beta-cell transplantation:

- Transplantation of donor pancreatic islets
- Limited donor source problem
- Edmonton protocol demonstrated feasibility
- Immunosuppression requirements
- Success in select patients achieving insulin independence

Stem cell therapy:

- Generation of beta-cells from stem cells
- Promising future direction
- Challenges in maturation and function
- Encapsulation strategies to avoid immunosuppression
- Clinical trials underway

Gene therapy:

- Genetic modification to restore insulin production
- Enhancement of beta-cell survival
- Modulation of immune response
- Experimental stage

Immunotherapy:

- Stopping autoimmune process in type 1 diabetes
- Preserving beta-cells in early stages
- Monoclonal antibodies (teplizumab approved for delay of T1D)
- Antigen-specific immunotherapies
- Combination approaches

Precision Medicine in Diabetes

Genetic profiling:

- Identification of diabetes subtypes
- Personalized treatment selection
- Monogenic diabetes recognition
- Pharmacogenomics for drug response

Biomarkers:

- C-peptide for residual beta-cell function
- Autoantibodies for type 1 diabetes risk
- Novel markers of complications
- Metabolomics and proteomics approaches

Digital health technologies:

- Mobile applications for self-management
- Telemedicine for remote monitoring
- AI-based decision support systems
- Data integration and analytics

COMPLICATIONS OF DIABETES

Acute Complications

Diabetic ketoacidosis (DKA):

- Absolute insulin deficiency
- Hyperglycemia, ketosis, metabolic acidosis
- Life-threatening if untreated
- More common in type 1 diabetes
- Precipitants: infection, insulin omission, new-onset diabetes

Hyperosmolar hyperglycemic state (HHS):

- Severe hyperglycemia without significant ketosis
- Marked dehydration
- More common in type 2 diabetes
- Higher mortality than DKA
- Requires aggressive fluid resuscitation

Chronic Complications

Microvascular complications:

- Diabetic retinopathy (leading cause of blindness)
- Diabetic nephropathy (leading cause of ESRD)
- Diabetic neuropathy (peripheral and autonomic)

Macrovascular complications:

- Coronary artery disease
- Cerebrovascular disease
- Peripheral arterial disease

Other complications:

- Diabetic foot disease

- Cognitive impairment
- Depression
- Sexual dysfunction
- Infections

Prevention strategies:

- Glycemic control (HbA1c targets)
- Blood pressure management
- Lipid optimization
- Smoking cessation
- Regular screening
- Multifactorial risk reduction

CONCLUSION. Diabetes mellitus is a complex metabolic disease associated with impaired insulin secretion or action. Insulin hormone plays a crucial role in regulating carbohydrate, protein, and lipid metabolism in the organism. Insulin biosynthesis and secretion in beta-cells are controlled through complex molecular mechanisms, and disruption of these processes leads to various diabetic pathologies.

Modern medicine has achieved significant advances in treating diabetes mellitus. Various insulin preparations, oral hypoglycemic drugs, continuous glucose monitoring systems, and artificial pancreas technologies significantly improve patients' quality of life. The development of incretin-based therapies and SGLT-2 inhibitors has expanded treatment options and provided additional benefits beyond glucose lowering.

In the future, regenerative medicine, stem cell therapy, and immunotherapy are expected to offer new treatment possibilities. Deeper understanding of the molecular mechanisms of diabetes and personalized medicine approaches are crucial in developing effective prevention and treatment strategies.

Comprehensive management of diabetes requires a multifaceted approach: pharmacological treatment, rational nutrition, physical activity, and regular medical supervision. Patient education and development of self-management skills are also essential in preventing complications. The integration of technology, including continuous glucose monitors, insulin pumps, and digital health tools, has revolutionized diabetes care.

Early detection through screening programs, intensive lifestyle interventions for high-risk individuals, and efforts to address social determinants of health are critical for reducing the global burden of diabetes. As our understanding of diabetes pathophysiology continues to evolve, so too will our ability to prevent, treat, and ultimately cure this challenging disease.

The future of diabetes care lies in precision medicine approaches that tailor treatment to individual patient characteristics, integration of advanced technologies for seamless disease management, and development of disease-modifying therapies that address the underlying causes rather than just managing symptoms. With continued research and innovation, the goal of a world without diabetes comes closer to reality.

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