Diabetes

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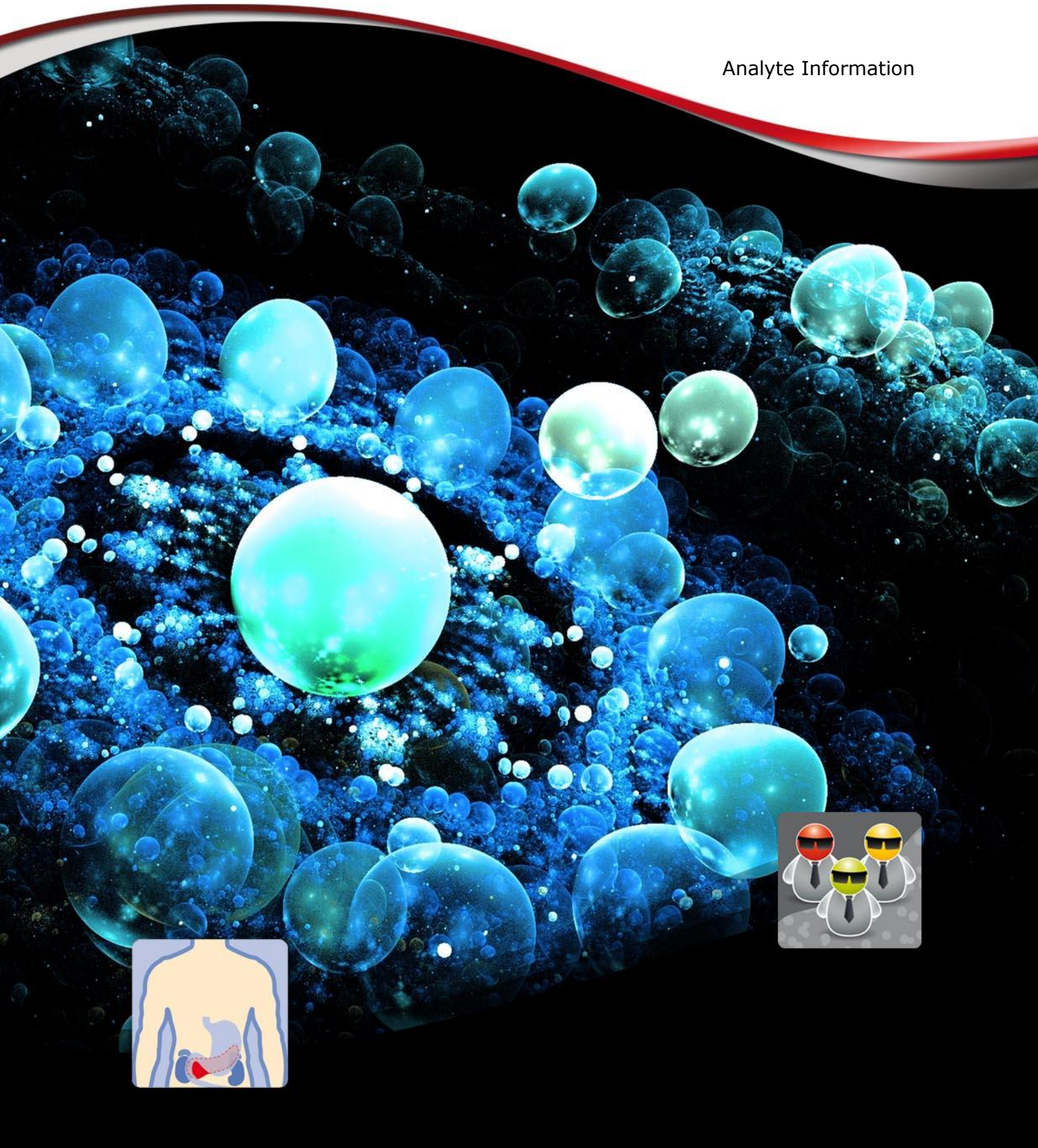


Diabetes Mellitus
and other disorders of endocrine pancreas

Introduction

The pancreas is an important glandular organ of digestive and endocrine systems. Two important functions of pancreas in human body comprise of:

- exocrine function, comprising in production of digestive juices
- endocrine function, comprising in production of hormones regulating utilization of glucose

Impaired function of endocrine pancreas leads to several serious clinical conditions characterised by either increased (hyperglycemia) or decreased (hypoglycemia) levels of glucose in blood.

Group of chronic disorders characterised by hyperglycaemia is called Diabetes mellitus (hereinafter DM). The word diabetes is derived from a Greek term meaning "going through" and mellitus is from the Latin word for "honey" or "sweet." This disease arises as a result of pancreatic hormone insulin insufficiency, and it represents significant risk factor for development of coronary heart disease and stroke. DM is also leading cause of end-stage renal disease or blindness. DM has become very serious health problem affecting more than 380 million people worldwide, i.e. 3.3% of the population. In 2011 it resulted in 1.4 million deaths worldwide making it the 8th leading cause of death.

DM occurs often in developed countries, but its prevalence is on the rise mainly in developing countries in Asia and Africa, especially due to changes in lifestyle and due to prolongation of life expectancy. Currently, the highest prevalence of diabetes is in Oceania, North Africa, the Middle East, and the Caribbean. The number of people with diabetes is expected to rise to 592 million by 2035.

Role of pancreas in blood glucose regulation

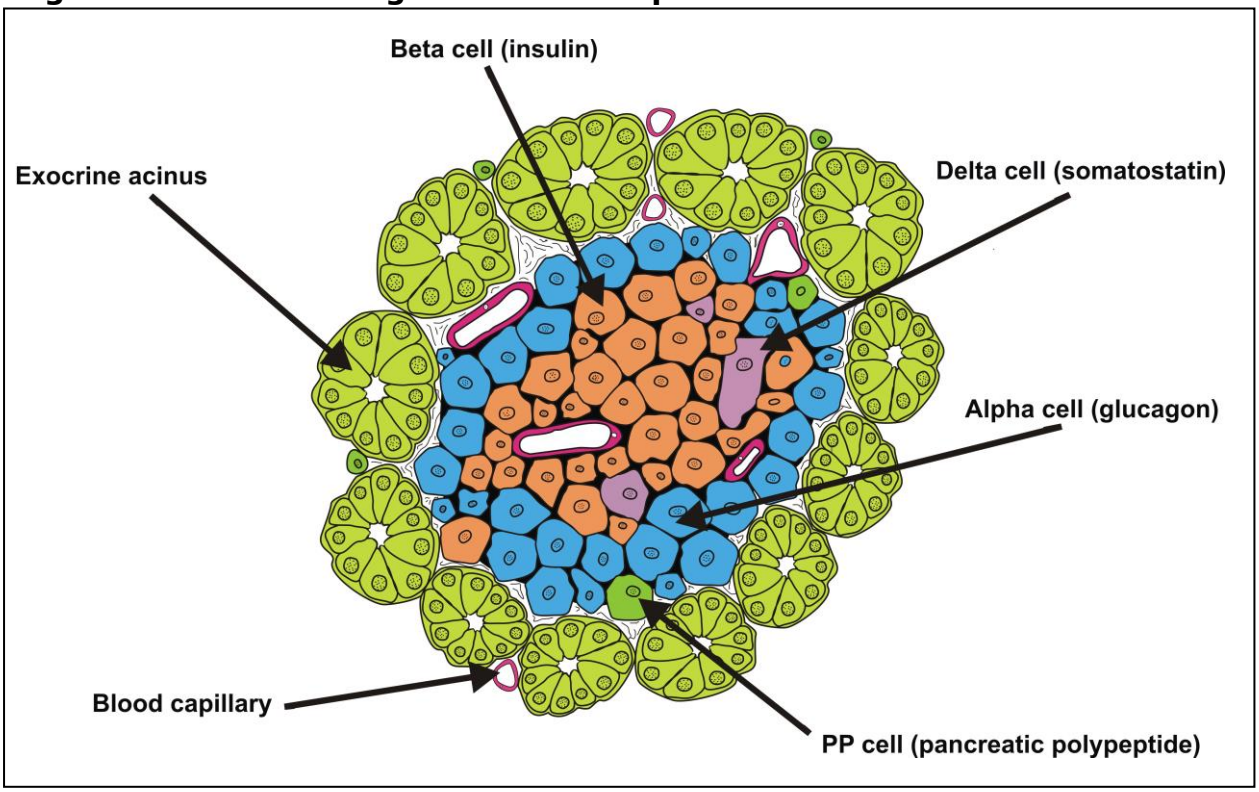
The pancreas is a dual-function gland, having both endocrine and exocrine features.

Exocrine pancreas consists of pancreatic acini, where digestive enzymes (trypsin, chymotrypsin, pancreatic lipase, and pancreatic amylase) and an alkaline fluid are produced before their secretion into small intestine.

Endocrine pancreas is made up of a million cell clusters called islets of Langerhans. There are four main cell types that differ according to substance they produce and secrete into blood:

- α cells secrete glucagon
- β cells secrete insulin and amylin
- δ cells secrete somatostatin and gastrin
- PP cells secrete pancreatic polypeptide

Fig.1: Structure of Langerhans islet of pancreas



Despite large fluctuations in the supply and demand of carbohydrates, the concentration of glucose in the blood is normally maintained within a narrow range by hormones that modulate the glucose movement in and out of the circulation.

The most important hormones regulating glucose are insulin and glucagon. Their effects on glucose, fat and protein metabolism are summarized in Tab.1. Insulin production rises in fed state and diminishes when fasting, glucagon behaves in opposite way. Insulin is the only hormone having a direct effect in lowering blood glucose levels, glucagon maintains blood glucose level between meals and during periods of fasting.

Other hormones that play role in increasing blood glucose include catecholamines, growth hormone, and glucocorticoids. Together with glucagon, they oppose the effects of insulin, being thus sometimes called counterregulatory hormones.

Tab.1: Effects of insulin and glucagon on glucose, fat and protein metabolism

		Insulin	Glucagon
Glucose	Glucose transport into muscles and adipose tissue	+	
	Glucose intake by liver, glycogen synthesis	+	-
	Gluconeogenesis	-	+
Fats	Triglyceride synthesis	+	
	Triglyceride transport into adipose tissue	+	
	Adipose cell lipase function, lipolysis in adipose tissue	-	+
Proteins	Transport of amino acids into cells	+	
	Transport of amino acids into hepatic cells		+
	Protein synthesis	+	
	Breakdown of proteins into amino acids	-	+
	Conversion of amino acids into glucose precursors		+

\+ stimulates
\- inhibits

Insulin

Insulin plays a key role in the regulation of glucose utilization. As it is the only hormone that directly lowers blood glucose concentration, a lack of insulin, or an inability to adequately respond to insulin, can each lead to the development of the symptoms of diabetes.

Insulin is secreted primarily in response to elevated blood glucose concentrations. The main actions of insulin are:

- to promote glucose uptake by target cells and stimulate glucose storage as glycogen
- to prevent fat and glycogen breakdown
- to inhibit gluconeogenesis and increase protein synthesis

The active form of the hormone is composed of two polypeptide chains—an A chain and a B chain, joined together by two disulfide bonds. It is formed in the β–cells from a larger molecule called proinsulin, by cleavage and excision of connecting peptide (called C-peptide). The cleaved C-peptide is co-secreted from β-cells with insulin, both are released into blood stream in equimolar quantity.

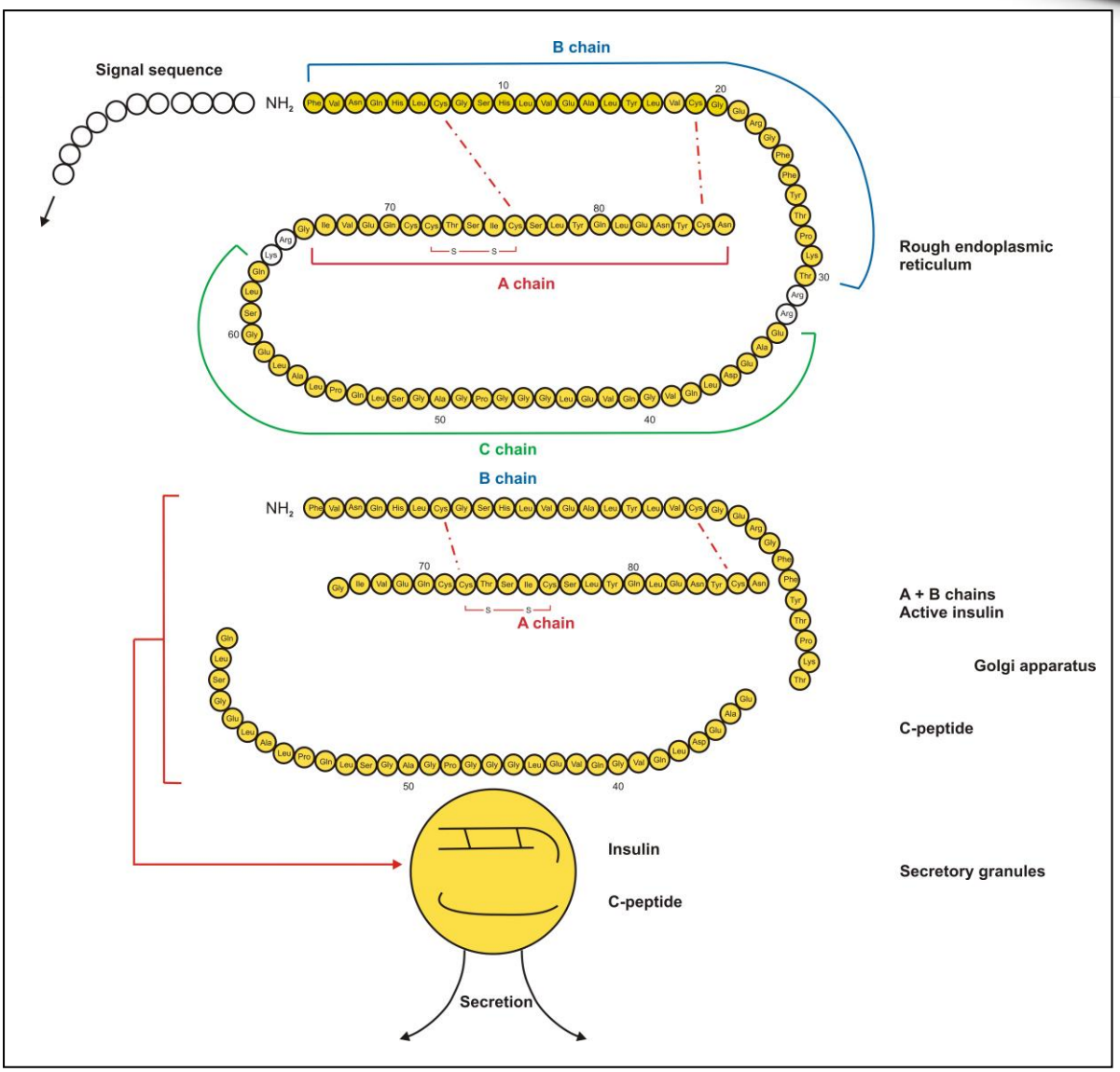
Insulin secretion is stimulated by food intake and consequent increase of blood glucose level. Blood glucose enters the β–cell via glucose transporter, causes depolarization of the cells and, finally, the release of insulin.

The secretion consists of two phases:

– the **early phase** appear quicly and lasts about 10 minutes (the peak being between 3 – 6 minutes) after secretory impulse. Insulin released in the early phase represents endogenous stock of ready insulin stored in β-cells secretory granules.

- the **late phase** comes slowly after 10 minutes, and endures for at least 60 minutes or for the period of secretory stimulus duration. This secretory phase is a manifestation of a new insulin formation.

Fig.2: Insulin and C-peptide synthesis

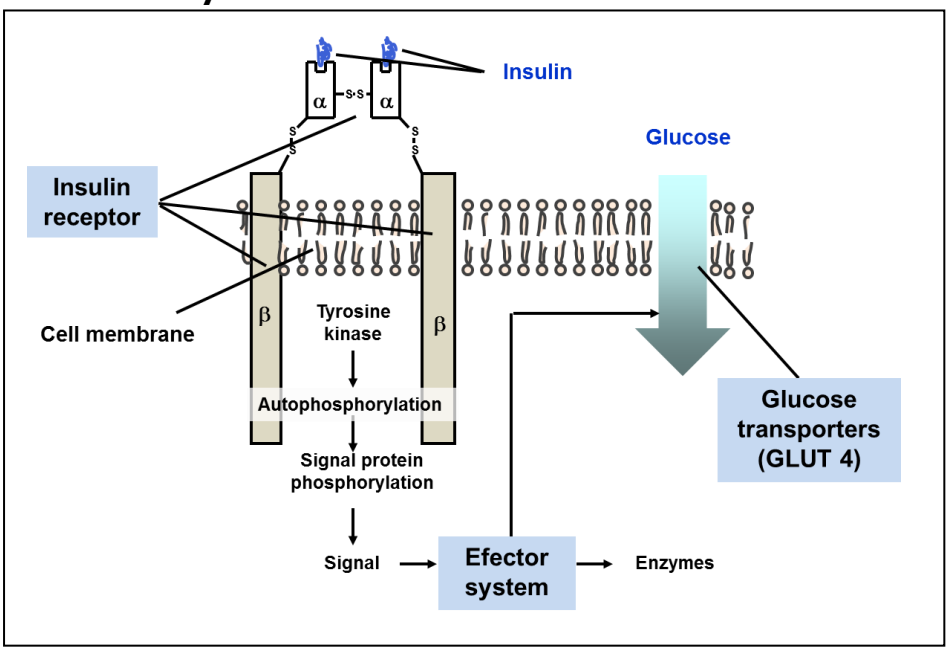


Insulin is transported from Langerhans islets to liver via v. portae. In liver, insulin is being taken in to variable extent - to 60 % in the average – depending on metabolic situation.

Insulin acts on target tissues via its binding to a membrane receptor. The receptor is composed of four subunits - a pair of larger α subunits that extend outside the cell membrane and are involved in insulin binding, and a smaller pair of β subunits that are predominantly inside the cell membrane and contain a

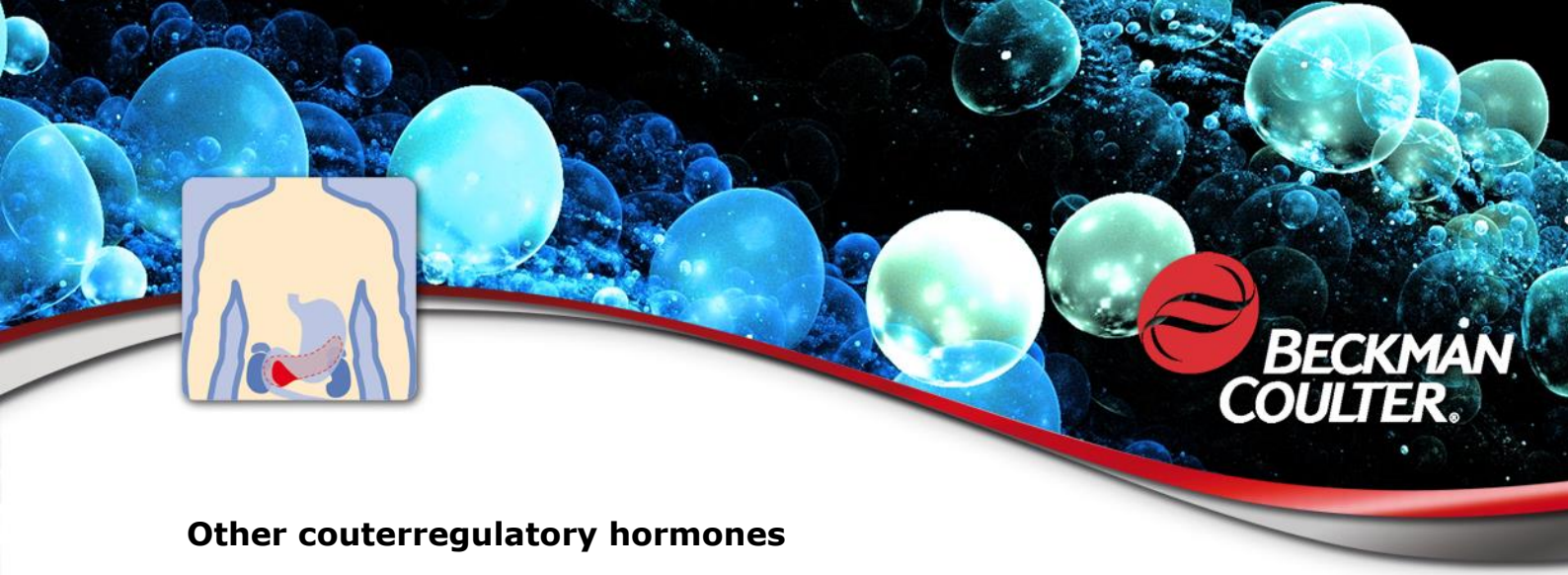
kinase enzyme that becomes activated during insulin binding (fig.3). Cell membranes are not permeable for glucose, its transport is mediated via special glucose transporters that moves glucose from the blood into the cell. There is a family of glucose transporters (GLUT-1, GLUT-2, and others), and the presence of particular transporter depends on the tissue. GLUT-4 is the insulin dependent glucose transporter for skeletal muscle and adipose tissue. GLUT-2 is the major transporter of glucose into β–cells and liver cells. It has a low affinity for glucose and acts as a transporter only when plasma glucose levels are relatively high, such as after a meal. GLUT-1 is present in all tissues. It does not require the actions of insulin and is important in transport of glucose into the nervous system.

Fig.3: Scheme of glucose transport into muscle and adipose tissue cell, mediated by insulin



Glucagon

Glucagon, a polypeptide molecule produced by the α-cells of the islets of Langerhans, maintains blood glucose between meals and during periods of fasting. Like insulin, glucagon travels through the portal vein to the liver, where it exerts its main action by initiation of liver glycogen breakdown, usually within several minutes. Glucagon also increases the transport of amino acids into the liver and stimulates their conversion into glucose - gluconeogenesis.



Other couterregulatory hormones

Catecholamins epinephrine and norepinephrine help to maintain blood glucose levels during periods of stress. Epinephrine inhibits insulin release and promotes glycogenolysis by stimulating the conversion of muscle and liver glycogen to glucose. They also increase lipase activity and thereby increase mobilization of fatty acids.

Growth hormone increases protein synthesis in all cells of the body, mobilizes fatty acids from adipose tissue, and antagonizes the effects of insulin. Growth hormone decreases cellular uptake and use of glucose, thereby increasing the level of blood glucose. The secretion of growth hormone normally is inhibited by insulin and increased levels of blood glucose. On the contrary, growth hormone levels increase during fasting, exercise or stress. Chronic hypersecretion of growth hormone, as occurs in acromegaly, can result in the development of diabetes mellitus.

Glucocorticoid hormones are critical for survival during periods of fasting and starvation. They stimulate gluconeogenesis by the liver, sometimes leading to a 6- to 10-fold increase in hepatic glucose production. These hormones also moderately decrease tissue use of glucose. Most important glucocorticoid is cortisol, which accounts for approximately 95% of all glucocorticoid activity and appears in stress.

Diabetes mellitus
and other disorders that alter glucose metabolism

Diabetes mellitus - classification

Diabetes mellitus is the most frequent endocrine disorder. It is characterised by hyperglycaemia and it is caused by imbalance between insulin availability and insulin need, with significant impact on carbohydrate, protein, and fat metabolism. DM may occur due to an absolute insulin deficiency, impaired release of insulin by the pancreatic β–cells, inadequate or defective insulin receptors, or the production of inactive insulin or insulin that is destroyed before it can carry out its action. A person with uncontrolled diabetes is unable to transport glucose into fat and muscle cells; as a result, the body cells are starved, and the breakdown of fat and protein is increased. Classification of different types of diabetes is shown in Tab.2.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG) reflect intermediate metabolic stages between normal glucose homeostasis and diabetes, and these conditions are therefore considered as prediabetes. Approximately 5% of people with IGT and/or IFG progress to diabetic stage each year.

Tab.2: Classification of etiological types of DM

Type 1	β–cell destruction, usually leading to absolute insulin deficiency A. Immune mediated B. Idiopathic
Type 2	Predominantly insulin resistance with relative insulin deficiency or predominantly secretory defect with/without insulin resistance
Other specific types	A. Genetic defects in β–cell function e.g., glucokinase
	B. Genetic defects in insulin action, e.g., leprechaunism, Rabson-Mendenhall syndrome
	C. Diseases of exocrine pancreas, e.g., pancreatitis, neoplasms, cystic fibrosis
	D. Endocrine disorders, e.g., acromegaly, Cushing's syndrome
	E. Drug or chemical induced, e.g., Vacor, glucocorticosteroids, thiazide diuretics, interferon-alfa
	F. Infections, e.g., congenital rubella, cytomegalovirus
	G. Uncommon forms of immune-mediated diabetes, e.g., "Stiff-man syndrome"
	H. Other genetic syndromes sometimes associated with diabetes, e.g., Down's, Klinefelter's or Turner's syndrome
Gestational diabetes mellitus (GDM)	Any degree of glucose intolerance with onset or first recognition during pregnancy

Tab.3: Clinical staging of DM and other categories of glucose tolerance

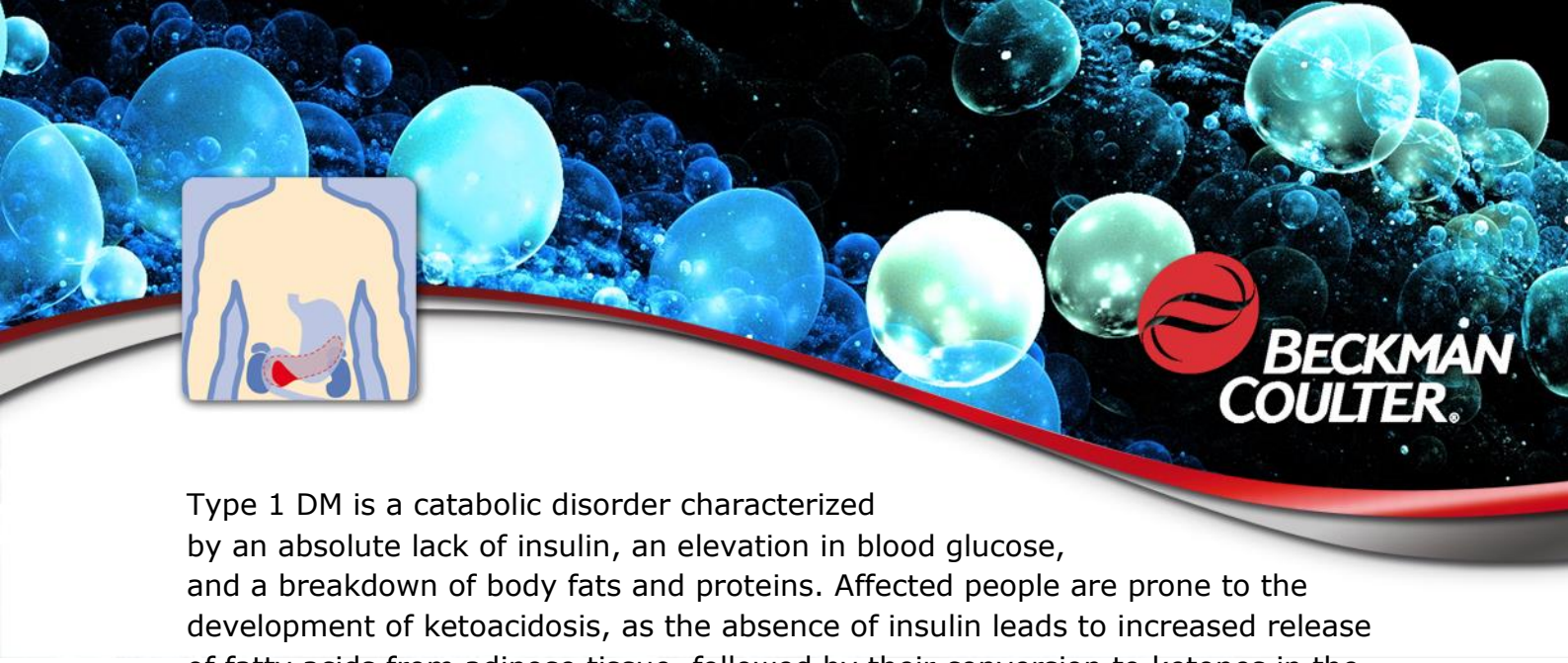
	Glucose concentration, mmol/L		
	Whole blood Venous	Whole blood Capillary	Plasma Venous
Diabetes Mellitus:			
Fasting *and/or*	≥6.1	≥6.1	≥7.0
2-h post glucose load	≥10.0	≥11.1	≥11.1
Impaired Glucose Tolerance (IGT):			
Fasting (if measured) *and*	<6.1	<6.1	<7.0
2-h post glucose load	6.7 - 10.0	7.8 - 11.1	7.8 - 11.1
Impaired Fasting Glycaemia (IFG):			
Fasting *and*	5.6 - 6.1	5.6 - 6.1	6.1 - 7.0
2-h post glucose load (if measured)	<6.7	<7.8	<7.8

Diabetes mellitus type 1

Prevalence of DM type 1 is approximately 0.3%, and it corresponds to approximately 10% of all people with diabetes.

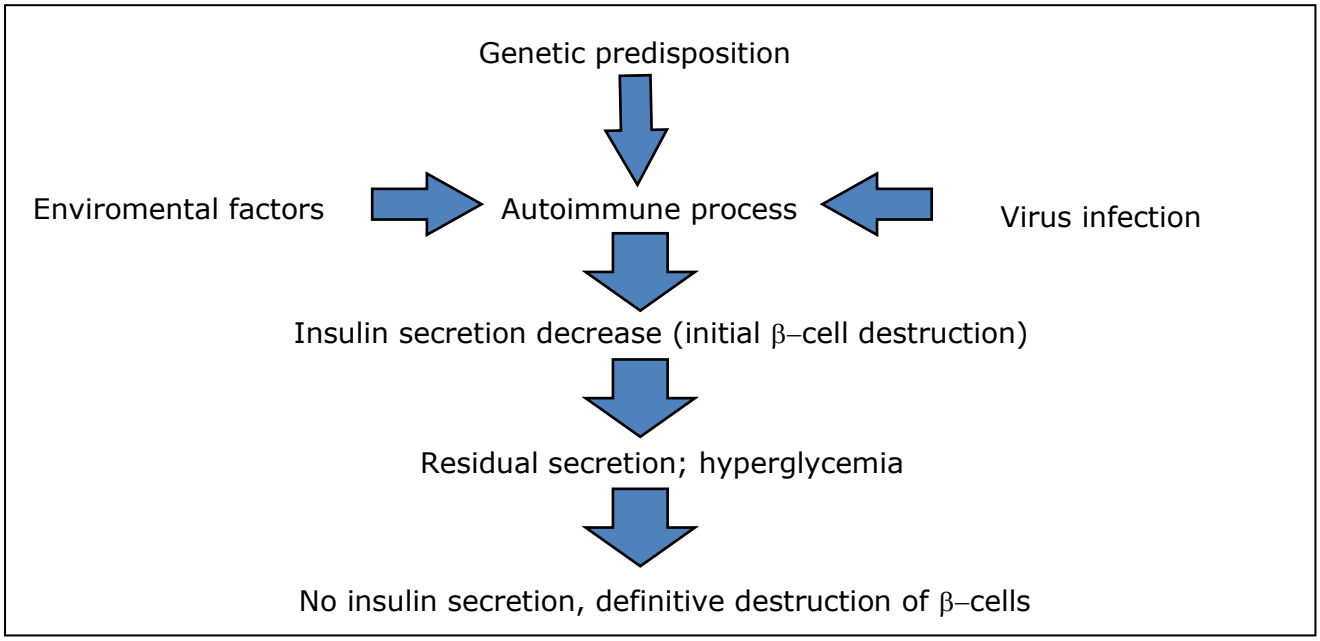
Type 1 DM is associated with remarkably decreased insulin secretion, even down to zero level, as a result of destruction of pancreatic Langerhans islet β–cells. This disorder was earlier termed IDDM (Insulin Dependent Diabetes Mellitus), as the diabetic patients with this form of disease are dependent on endogenic insulin application.

Type 1 diabetes mellitus is characterized by destruction of the pancreatic β–cells, mostly (approx. in 95%) by autoimmune mechanism. It typically occurs in young persons, but it may also develop later during the life. The form with slow progression is sometimes referred to as Latent autoimmune diabetes in adults (LADA). It is considered that this form may represent up to 10% of people who are currently wrongly classified as having DM type 2.



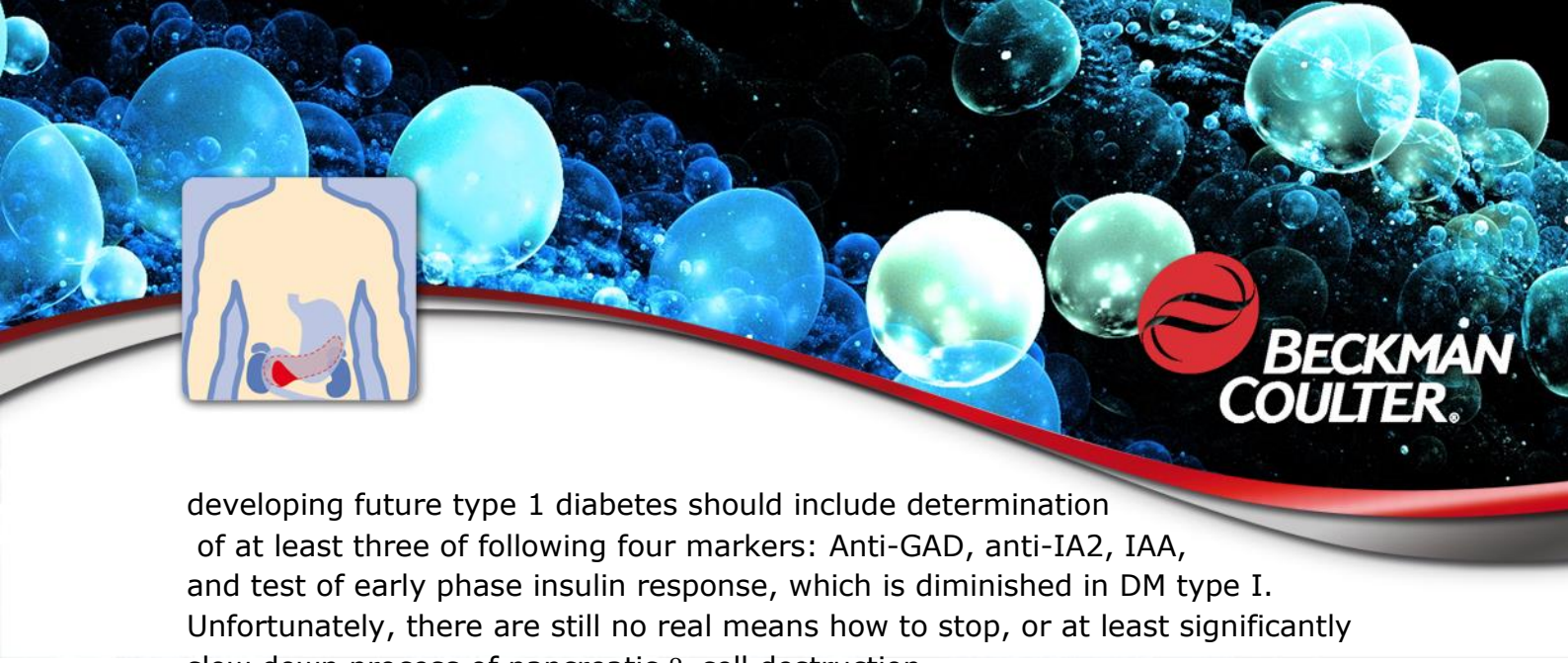
Type 1 DM is a catabolic disorder characterized by an absolute lack of insulin, an elevation in blood glucose, and a breakdown of body fats and proteins. Affected people are prone to the development of ketoacidosis, as the absence of insulin leads to increased release of fatty acids from adipose tissue, followed by their conversion to ketones in the liver.

Fig.4: Development of DM type 1



More than 90% of insulin cells are destroyed at the time of manifestation of the disease. Even after diagnosis, symptoms of diabetes may disappear for certain time and insulin may be withdrawn. This short period of β–cell regeneration is called honeymoon.

Diabetes-associated antibodies may exist during the autoimmune process, and they occur already many years before clinical manifestation of the disease. These comprise autoantibodies against glutamic acid decarboxylase (anti-GAD), antibodies against tyrosine phosphatase (anti-IA2) and insulin (IAA). Whilst antibodies against GAD are the most common, antibodies against insulin frequently precede anti-GAD and anti-IA2 and may be the only antibodies detected in young children. Strategies for full evaluation of the risk for



developing future type 1 diabetes should include determination of at least three of following four markers: Anti-GAD, anti-IA2, IAA, and test of early phase insulin response, which is diminished in DM type I. Unfortunately, there are still no real means how to stop, or at least significantly slow down process of pancreatic β–cell destruction.

Laboratory findings in DM type 1 are:

- High levels of blood glucose
- Low levels of basal insulin and C-peptide
- Glucose tolerance test giving non-standard, flat shape of the C-peptide and insulin curve
- Diabetes-associated antibodies appearance

Diabetes mellitus type 2

Prevalence of DM type 2 is approximately 3%, and it corresponds to approximately 90% of all people with diabetes.

Type 2 diabetes mellitus is a heterogeneous disease characterized by the presence of hyperglycemia in association with relative insulin deficiency. It was earlier termed NIDDM (Non-Insulin Dependent Diabetes Mellitus), neglecting the fact that some patients in advanced disease may become insulin-dependent, too. Insulin levels may be low, normal, or even high, with hyperglycemia caused by decreased sensitivity to insulin – insulin resistance. Type 2 diabetes is therefore a disorder of both insulin levels (β–cell dysfunction) and insulin function (insulin resistance). The three metabolic abnormalities that result in hyperglycemia in DM type 2 are:

- impaired β–cell function with defect of insulin secretion
- increased glucose production in liver
- insulin resistance

Most people with type 2 diabetes are older and overweight, but it becomes more frequent also among obese adolescents.

Insulin resistance initially produces an increase in β–cell secretion of insulin (resulting in hyperinsulinemia) as the body attempts to maintain a normoglycemic state. Later on, the insulin response declines because of

increasing β–cell dysfunction. This initially leads to elevation of blood glucose levels postprandially and then also to rise of fasting glucose level and development of real type 2 DM.

Like in type 1, patient may also develop absolute insulin deficiency because of progressive β–cell failure.

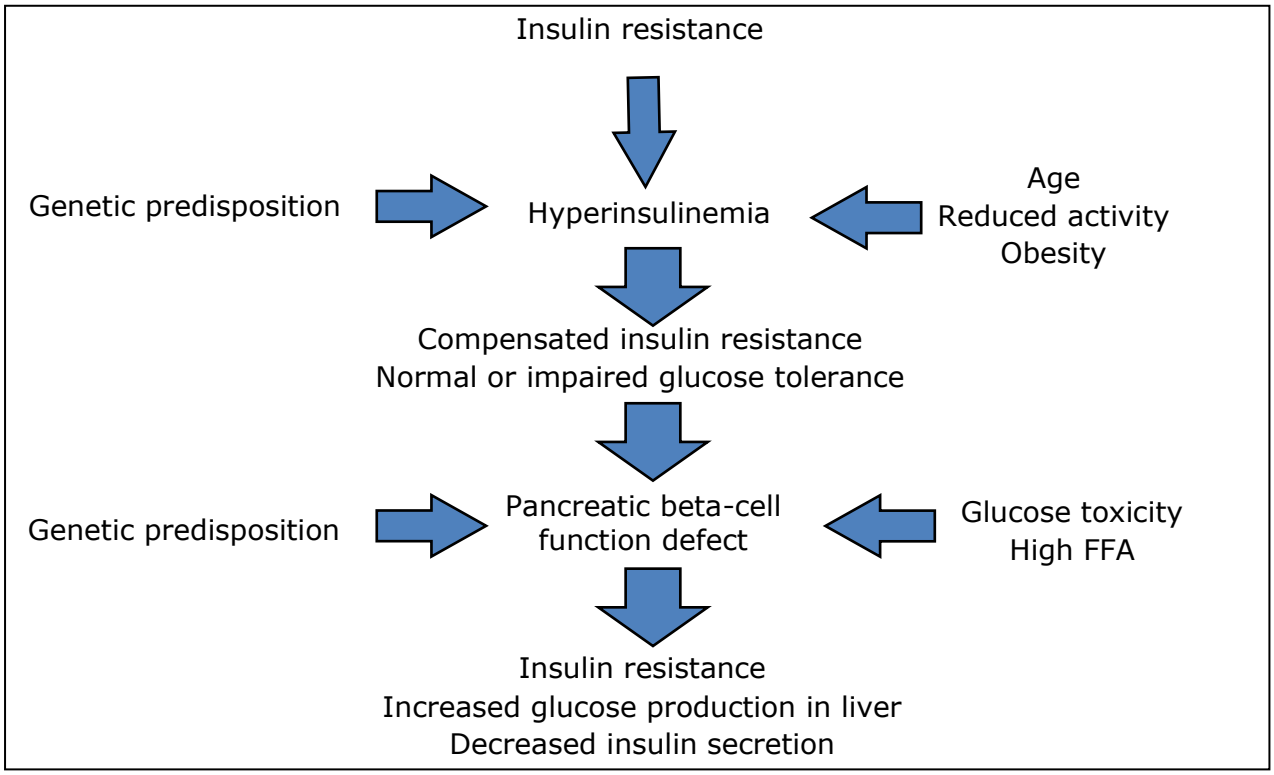
The cause of type 2 DM and hyperinsulinemia is not easy to ascertain. Abnormal insulin receptor may be found in some case, defect of one or more aspects of insulin signaling in other cases, and sometimes no defect may be identified at all.

Disease is controlled through dietary therapy and hypoglycemic agents, insulin administration may be required in advanced disease.

Laboratory findings in DM type 2 are:

- High levels of blood glucose
- Basal levels of insulin and C-peptide normal or even slightly elevated (or lower in advanced form)
- No evidence of autoimmune destruction of islets' cells

Fig.5: Development of DM type 2



Insulin resistance and metabolic syndrome

Insulin resistance, as a disorder of energy utilization and storage, is not only direct cause of DM type 2, but also of some other abnormalities. Insulin resistance is associated with increase in triglyceride and total cholesterol levels, with parallel decrease of HDL (high density lipoproteins). Other abnormalities comprise hypertension, systemic inflammations, abnormal fibrinolysis, abnormal function of the vascular endothelium, macrovascular disease, polycystic ovary syndrome in women. Combination of some of these conditions, together with hyperglycemia, hyperinsulinism and central obesity, is referred to as metabolic syndrome (also insulin resistance syndrome, syndrome X, or Raven syndrome). It is not surprising that metabolic syndrome increases significantly the risk of developing diabetes, but it represents also significant risk factor for development of cardiovascular disease, particularly heart failure.

Tab.4: Criteria for a diagnosis of metabolic syndrome

At least three of the following conditions confirm metabolic syndrome diagnosis:	
Abdominal obesity - waist circumference	>90 cm in women or >100 cm in men
Triglycerides	≥1.7 nmol/L
High-density lipoproteins (HDL)	<1.3 nmol/L in women or <1.04 nmol/L in men
Blood pressure	>130/85 mm Hg
Fasting plasma glucose	>6.1 mmol/L

Other specific types of DM

Formerly known as secondary diabetes, these are the types of diabetes associated with certain other conditions and syndromes. They are much less frequent than DM type 1 and 2. They can occur together with other endocrine diseases, such as acromegaly, Cushing's syndrome, or pheochromocytoma, as well as due to pancreatic disease or the removal of pancreatic tissue.

Other specific types of diabetes are associated with monogenetic defects in β–cell function, caused by mutations in gene responsible for the disruption of insulin production. These specific types resemble DM type 2 but occur at an earlier age (usually before 25 years of age), and they are known as maturity-onset diabetes of the young (MODY). 1 - 2% of diabetics have this type of diabetes.

Diabetes is also induced by environmental agents like viruses (e.g. mumps) or chemical agents (e.g. certain drugs or toxins).

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance that is detected during pregnancy first. The precise mechanisms underlying gestational diabetes remain unknown. Pregnancy hormones and other factors are thought to interfere with the action of insulin by binding to the insulin receptor, and causing thus insulin resistance.

Risk factors for gestational diabetes are a family history of diabetes, glycosuria, a history of stillbirth or spontaneous abortion, fetal anomalies in a previous pregnancy, previous large or heavy baby, obesity, advanced maternal age, or personal history of five or more pregnancies.

Diagnosis and careful medical management are very important as women with GDM are at higher risk for complications of pregnancy, mortality, and fetal abnormalities. Fetal abnormalities include macrosomia (i.e., large body size), hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

All pregnant women in risk should undergo plasma glucose testing. If the initial result is negative, they should be retested between 24 and 28 weeks of gestation. Several tests are used, including fasting glucose determination, random glucose determination, 2 hour postprandial glucose test. The most reliable is oral glucose tolerance test (see page 20).

GDM is treated by diabetic diet and, if the dietary management itself is not sufficient to normalize glucose level, human insulin is administered.

Complications of diabetes mellitus

Acute complications

Diabetic ketoacidosis typically occurs in a person with type 1 diabetes. The lack of insulin leads to mobilization of fatty acids from adipose tissue because of the unsuppressed adipose cell lipase activity that breaks down triglycerides into fatty acids and glycerol. The increase in fatty acid levels leads to ketone production by the liver that exceeds cellular use and renal excretion of ketone.

Symptoms of diabetic ketoacidosis are polyuria, polydipsia, nausea, vomiting, and fatigue, with eventual stupor that can progress to coma. Presence of ketoacids leads to typical smell of breath.

Hyperosmolar hyperglycemic state is characterized by severe hyperglycemia, hyperosmolarity and dehydration, the absence of ketoacidosis, and depression of the sensorium. It is seen most frequently in people with type 2 diabetes, but may occur also in acute pancreatitis, severe infection, myocardial infarction and others. Symptoms are dehydration, neurologic signs and symptoms, and excessive thirst.

Hypoglycemia (see also next page) is caused by relative excess of insulin in the blood and is characterized by low blood glucose levels. It occurs in people treated with insulin injections, but may be caused by some oral hypoglycemic agents, too.

Onset of hypoglycemia is rapid, causing headache, difficulty in problem solving, disturbed or altered behavior, coma, and seizures may occur. Other symptoms are hunger, anxiety, tachycardia, sweating, and constriction of the skin vessels.

Chronic complications

In developed countries, diabetes is the leading cause of blindness, renal failure and lower limb amputation. It is also one of the leading causes of death through its effects on cardiovascular disease (70 - 80% of people with diabetes die of cardiovascular disease). About half of all the money spent on diabetes care goes towards the costs of managing diabetic complications.

Diabetic neuropathy affect both the somatic and autonomic nervous systems. They appear as a result of demyelinization of neurons. Somatic neuropathy is associated with diminished sensation of vibration, pain, and temperature. Autonomic neuropathy affects sympathetic and parasympathetic nervous system function, and leads to various problems including disorders of vasomotor function, impaired motility of the gastrointestinal tract, decreased cardiac responses, inability to empty the bladder, or erectile dysfunction.

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD). Early stages are characterized by microcirculation changes in glomeruli leading to increased albumin clearance (microalbuminuria stage). Microalbuminuria, which represents significant risk factor for diabetic nephropathy development, may be found in as much as 8% patients within 3 years after type 1 DM diagnosis. Microalbuminuria is found in 50 - 60% diabetic patients after 20 - 30 years of diabetes duration. This complication affects both type 1 and 2 diabetic patients.

Diabetic retinopathy is the leading cause of blindness in developed countries. Twenty years after the onset of diabetes, nearly all people with type 1 diabetes and more than 60% of people with type 2 diabetes have some degree of retinopathy. Poor glycemic control, elevated blood pressure, and hyperlipidemia are factors involved in retinopathy development.

Macrovascular complications as coronary heart disease, stroke, and peripheral vascular disease are leading cause of death in diabetic persons. Like in diabetic retinopathy, poor glycemic control, elevated blood pressure, and hyperlipidemia are the key factors involved in macrovascular complication development.

Diabetic foot ulcers may appear due to neuropathy and vascular insufficiency. Impaired pain sensation may keep unnoticed any damage of foot and, in extreme cases, the foot problems may lead to need for leg amputation.

Hypoglycemic conditions

Hypoglycemia is a condition when the level of glucose in blood is low. Principal problems arise from an inadequate supply of glucose to the brain, resulting in impairment of its function. Effects can range from mild dysphoria to more serious issues such as seizures, unconsciousness, and death.

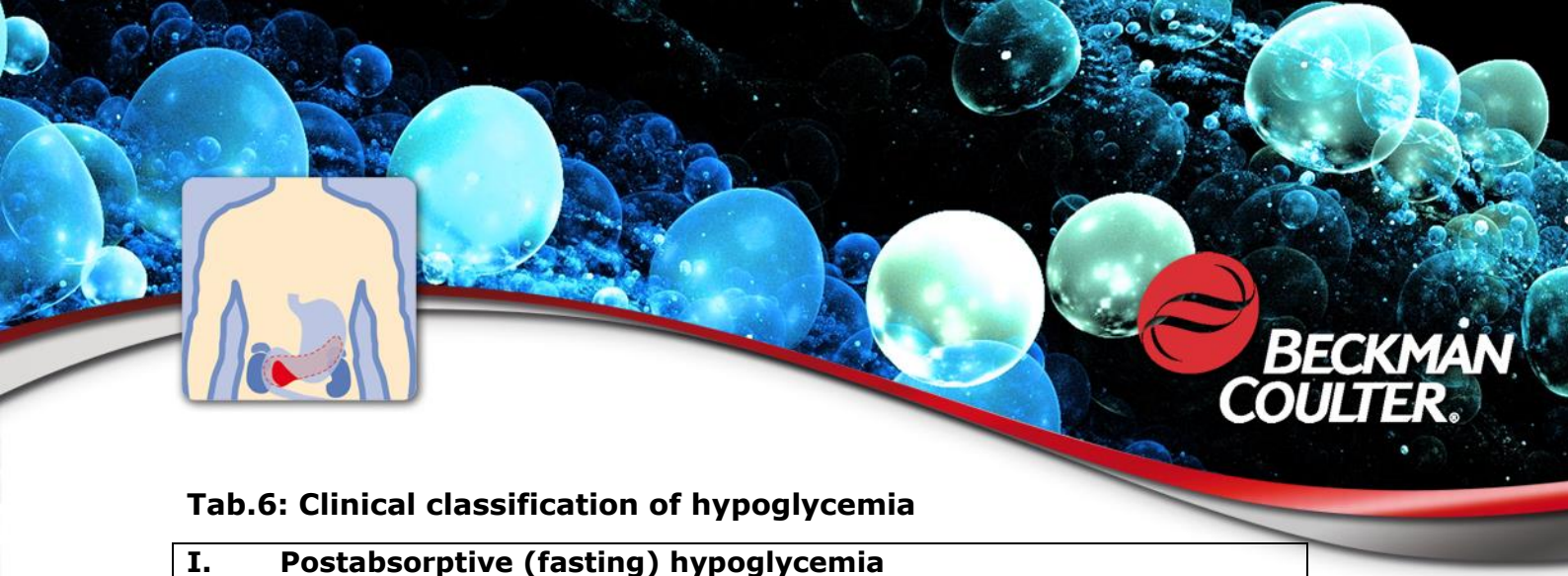
Hypoglycemia can occur at any age. The most common forms of hypoglycemia occur as a complication of treatment of diabetes mellitus with insulin or oral medications. Other possible causes are excessive insulin produced in the body (hyperinsulinemia), inborn error of metabolism, medications and poisons, alcohol, hormone deficiencies, prolonged starvation, alterations of metabolism associated with infection, and organ failure.

Hypoglycemia is treated by restoring the blood glucose level to normal, usually by oral administration of glucose. Intravenous administration of glucose or intramuscular administration of glucagon is possible if person is unconscious.

Various symptoms and manifestations may appear due to occurrence of counterregulatory hormones (epinephrine/adrenaline and glucagon) triggered by the falling glucose, or due to effects produced by the reduced brain sugar. Symptoms may be very mild, and not all of them appear in each case of hypoglycemia. Possible symptoms are listed in Tab.5, classification of hypoglycemic states is in Tab.6.

Tab.5: Symptoms of hypoglycemia

Counterregulatory hormone effects
Shakiness, anxiety, nervousness
Palpitations, tachycardia
Sweating, feeling of warmth
Pallor, coldness, clamminess
Dilated pupils
Hunger
Nausea, vomiting, abdominal discomfort
Headache
Brain affects
Abnormal mentation, impaired judgment
Nonspecific dysphoria, moodiness, depression, crying, exaggerated concerns
Feeling of numbness "pins and needles" (paresthesia)
Negativism, irritability, belligerence, combativeness, rage
Personality change, emotional lability
Fatigue, weakness, apathy, lethargy, daydreaming, sleepiness
Confusion, amnesia, lightheadedness or dizziness, delirium
Staring, "glassy" look, blurred vision, double vision
Flashes of light in the field of vision
Automatic behavior, also known as automatism
Difficulty speaking, slurred speech
Ataxia, incoordination, sometimes mistaken for "drunkenness"
Focal or general motor deficit, paralysis, hemiparesis
Paresthesia, headache
Stupor, coma, abnormal breathing
Generalized or focal seizures
Memory loss, amnesia



Tab.6: Clinical classification of hypoglycemia

I.	**Postabsorptive (fasting) hypoglycemia**
	A. Drugs
	1. Insulin, sulphonylureas, ethanol
	2. Pentamidine, quinine, salicylates, propranolol
	3. Others
	B. Critical organ failure
	1. Liver disease
	2. Renal failure
	3. Cardiac failure
	4. Sepsis
	5. Inanition
	C. Hormone deficiences
	1. Hypopituarism
	2. Adrenal insufficiency
	3. Glucagon and epinephrine deficiency
	D. Non-β–cell tumours
	E. Endogenous hyperinsulinism
	1. Insulinoma
	F. Autoimmune
	1. Autoantibodies to insulin
	2. Autoantibodies to insulin receptor
	G. Factitious
	1. Insulin
	1. Sulfonylureas
	H. Hypoglycemia in infancy and childhood
	1. Ketonic hypoglycemia
	2. Enzyme deficiencies in pathways of glycogenolysis and gluconeogenesis
	3. Defect in amino acid, fatty acid, and ketoacid metabolism
II.	**Postprandial (reactive) hypoglycemia**
	A. Alimentary hypoglycemia
	B. Idiopathic reactive hypoglycemia
	C. Deficiencies of carbohydrate metabolism enzymes
	1. Galactosemia
	2. Hereditary fructose intolerance

Functional tests of endocrine pancreas function

Test for characterisation of hyperglycemic conditions

Oral glucose tolerance test (OGTT):
- peroral administration of 75 g of glucose
- determination of glucose, but also insulin, C-peptide in time zero (fasting level) and 120 minutes after administration (optionally: time zero, 60, 120 and 180)
- in pregnant women, 100 g of glucose, The determination of glucose (insulin, C-peptide) at time zero and after 60, 120 and 180 minutes recommended

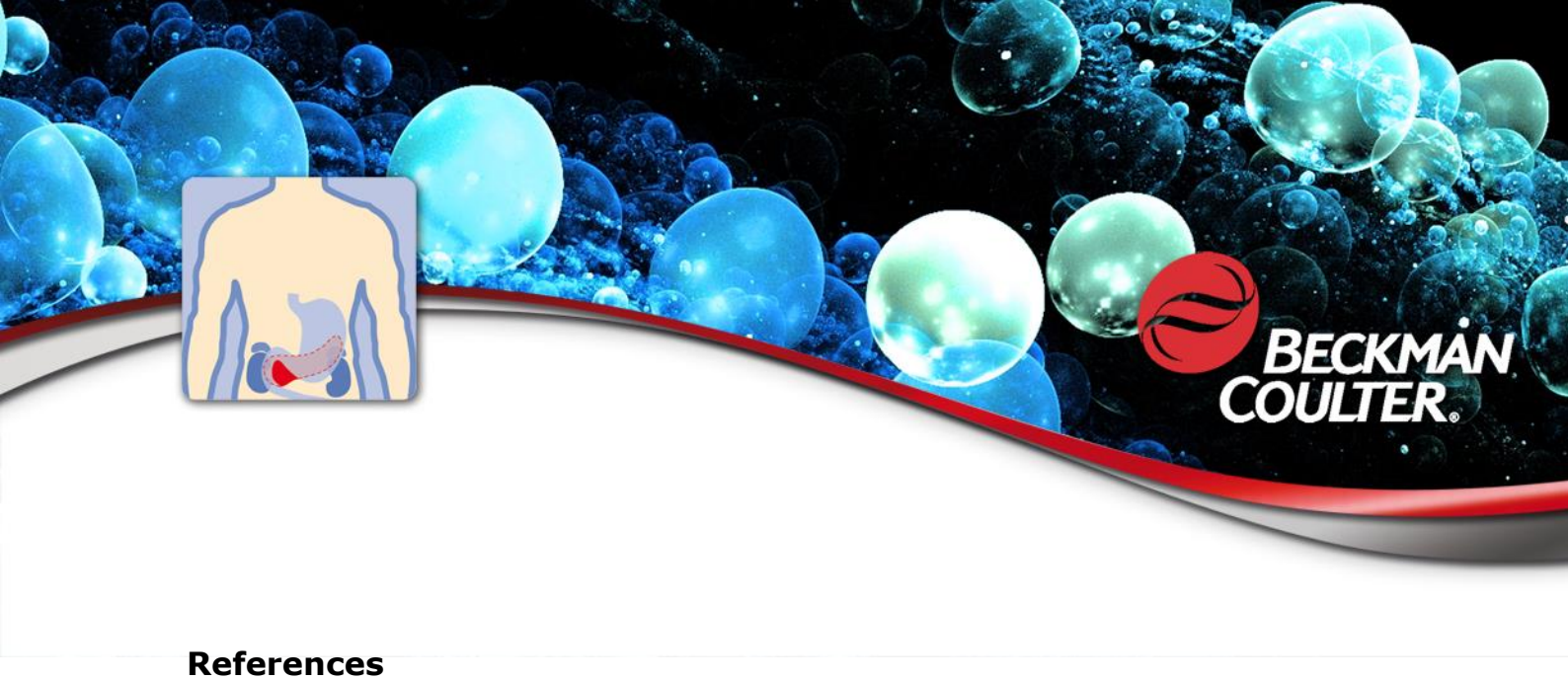
Intravenous glucose tolerance test (IGTT):
- intravonous administration of glucose, 0.5 g/kg
- determination of glucose, but also insulin, C-peptide in time zero (fasting level) and 3, 5, 10, 20, 30, 45 and 60 minutes after infusion

Postprandial glucose:
- determination 2 hours after meal

Glucose clamp techniques:
- for quantification of insulin secretion and resistance
- Hyperglycemic clamp evaluates rapidity of β-cell response to glucose. The plasma glucose is increased to 125 mg/dL (6.9 mmol/L) above basal levels by a continuous infusion of glucose and held stable. The glucose infusion amount reflects rate of insulin secretion and glucose metabolism.
- Hyperinsulinemic-euglycemic clamp evaluates sensitivity of the tissue to insulin. The plasma insulin concentration is increased to 100 μU/mL by a continuous infusion of insulin. Meanwhile, the plasma glucose concentration is held stable at basal levels by a variable glucose infusion. When the steady-state is achieved, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue insulin sensitivity and resistance.

Test for characterisation of hypoglycemic conditions

72-hour fasting test:
- no caloric intake for 72 hours
- determination of glucose, insulin and C-peptide. Low levels of glucose and high insulin and C-peptide is a prove of insulinoma



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