

Glucose Homeostasis – Mechanism and Defects

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1. Introduction

Glucose is an essential metabolic substrate of all mammalian cells. D-glucose is the major carbohydrate presented to the cell for energy production and many other anabolic requirements. Glucose and other monosaccharides are transported across the intestinal wall to the hepatic portal vein and then to liver cells and other tissues. There they are converted to fatty acids, amino acids, and glycogen, or are oxidized by the various catabolic pathways of cells.

Most tissues and organs, such as the brain, need glucose constantly, as an important source of energy. The low blood concentrations of glucose can cause seizures, loss of consciousness, and death. On the other hand, long lasting elevation of blood glucose concentrations, can result in blindness, renal failure, vascular disease, and neuropathy. Therefore, blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis. This is accomplished by the finely hormone regulation of peripheral glucose uptake, hepatic glucose production and glucose uptake during carbohydrate ingestion. This maintenance is achieved through a balance of several factors, including the rate of consumption and intestinal absorption of dietary carbohydrate, the rate of utilization of glucose by peripheral tissues and the loss of glucose through the kidney tubule, and the rate of removal or release of glucose by the liver and kidney. To avoid postprandial hyperglycemia (uncontrolled increases in blood glucose levels following meals) and fasting hypoglycemia (decreased in blood glucose levels during periods of fasting), the body can adjust levels by a variety of cellular mechanisms. Important mechanisms are conveyed by hormones, cytokines, and fuel substrates and are sensed through of cellular mechanisms.

Diabetes mellitus is one of the clinical manifestations of long-term metabolic abnormalities involving multiple organs and hormonal pathways that impair the body's ability to maintain glucose homeostasis. As a result of impaired glucose homeostasis is a hyperglycemia. Prolonged elevation of blood glucose concentrations causes a number of complications like blindness, renal failure, cardiac and peripheral vascular disease, neuropathy, foot ulcers, and limb amputation. Vascular complications represent the leading cause of mortality and morbidity in diabetic patients.

Hypoglycemia is abnormally low levels of sugar (glucose) in the blood. Low levels of sugar in the blood interfere with the function of much organ system. A person with hypoglycemia may feel weak, drowsy, confused, hungry, and dizzy. The other signs of low blood sugar are: paleness, headache, irritability, trembling, sweating, rapid heart beat, and a cold. The

most common cause of hypoglycemia is a complication of diabetes. Low level of glucose in the blood occurs most often in people who use insulin to lower their blood sugar. Hypoglycemia can occur as a side effect of some oral diabetes medication that increases insulin production. People with diabetes who reduce food intake to lose weight are more likely to have hypoglycemia.

2. Role of glucose in mammalian cells metabolism

2.1 Glucose as a source of cellular energy

Glucose is rapidly metabolized to produce ATP (adenosine triphosphate), a high energy end product. Glucose is oxidized through a large series of reactions that extract the greatest amount of possible energy from it. If glucose metabolism occurs in the presence of oxygen (aerobically), the net production are 36 molecules of ATP from one molecule of glucose, and 2 molecules of ATP, if glucose metabolism occurs in the absence of oxygen (anaerobically). For details see [Szablewski, 2011].

2.1.1 Glycolysis

Glycolysis is the first pathway which begins the complete oxidation of glucose to pyruvate. It takes place in the cytoplasm of the cell. Glycolysis occurs virtually in all tissues. This pathway is unique in the sense that it can proceed in both aerobic and anaerobic conditions. Glycolysis is the pathway which cleaves the six carbon glucose molecule into two molecules of the three carbon compound pyruvate. The end result of glycolysis is two molecules of ATP and two molecules of NADH+H⁺ (Nicotinamide adenine dinucleotide – reduced form). NAD is used as an electron acceptor. This cofactor is present only in limited amounts and once reduced to NADH+H⁺, as in this reaction, it must be re-oxidized to NAD to permit continuation of the pathway. This process occurs by the one of the two methods: aerobic metabolism of glucose or anaerobic glycolysis.

2.1.2 Oxidative decarboxylation

During aerobic metabolism of glucose in the mitochondria, pyruvate is oxidized. During this reaction NAD is uses as an electron and proton acceptor, and pyruvate is converted to acetyl coenzyme-A (abbreviated as "acetyl-CoA"). The carboxyl group of pyruvate leaves the molecule as CO₂ and the remaining two carbons become acetyl-CoA. This reaction occurs twice since each glucose (six carbons) produce 2 pyruvates (three carbons each). Consequently, these processes produce 2 NADH+H⁺, 2 Acetyl-CoA, and 2 CO₂.

2.1.3 Krebs cycle

Further series of reactions, all which occur inside mitochondria (mitochondrial matrix) of eukaryotic cells, is collectively called "Krebs Cycle", also known as the "Citric Acid Cycle" or the "Tricarboxylic Acid Cycle". In this cycle, acetyl-CoA is oxidized ultimately to CO₂. It is to note, that the molecules that are produced in these reactions can be used as building blocks for a large number of important processes, including the synthesis of fatty acids, steroids, cholesterol, amino acids, and the purines and pyrimidines. Fuel for Krebs cycle comes from lipids, carbohydrates, and proteins, which produce the molecule acetyl-CoA. While the Krebs cycle does produce CO₂, this cycle does not produce significant chemical energy in the form of ATP directly. This cycle produces NADH+H⁺ and FADH₂, which feed

into the respiratory cycle, also located inside mitochondria (inner mitochondrial membrane). It is electron transport chain that is responsible for production of large quantities of ATP. The electron transport chain converts $\text{NADH}+\text{H}^+$ and FADH_2 into reactants that the Krebs cycle requires to function. If oxygen is not present, the electron transport chain cannot function, which halts the Krebs cycle.

2.1.4 Electron transport chain

Oxidative phosphorylation is a series of reactions that utilize the energy from $\text{NADH}+\text{H}^+$ and FADH_2 electron carriers to produce more ATP. Embedded in the inner membrane of the mitochondria are the series of proteins that use the stored energy from $\text{NADH}+\text{H}^+$ and FADH_2 to pump protons into the membrane space. This results in an electrical and chemical gradient of protons. The enzyme ATP synthase (ATPase) uses the proton gradient to drive the reaction of producing ATP from ADP and inorganic phosphate. The electron transport chain consists of a series of proteins (called cytochromes) that are embedded in the inner mitochondrial membrane and an enzyme ATP synthase. There are four complexes, namely, I, II, III, and IV. In complex IV, the electrons are combined with protons and oxygen to form water, the final end-product. The oxygen acts as the final electron acceptor and without oxygen, so the reaction does not proceed and therefore only anaerobic respiration is possible. The end result of electron transport chain is three molecules of ATP, if a donor of protons and electrons is $\text{NADH}+\text{H}^+$ and one molecule of H_2O . If a donor of protons and electrons is FADH_2 , the end result of electron transport chain is two molecules of ATP and one molecule of H_2O .

2.1.5 The metabolism of lactate

The anaerobic glycolysis occurs in the absence of oxygen (anaerobically). During anaerobic glycolysis, earlier obtained pyruvate is reduced to a compound called lactate. This reduction of pyruvate to lactate is coupled to the oxidation of $\text{NADH}+\text{H}^+$ to NAD. Glycolysis and reduction of pyruvate to lactate are coupled to the net production of two molecules of ATP from one molecule of glucose. Accumulation of lactate also causes a reduction in intracellular pH. Therefore lactate is removed to other tissues and dealt with by one of the two mechanisms: 1) Lactate is converted back to pyruvate. This process is enzymatically catalyzed by lactate dehydrogenase. In this reaction, lactate becomes oxidized (loses two electrons) and is converted to pyruvate. The pyruvate then proceeds to be further oxidized by a second mechanism, the aerobic metabolism of glucose. 2) Conversion of lactate to glucose in the process of gluconeogenesis.

2.2 Gluconeogenesis

Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrate such as lactate, glycerol, and glucogenic amino acids. One common substrate is lactic acid formed in the skeletal muscle in the absence of oxygen. It may also come from erythrocytes, which obtain energy solely from glycolysis. The lactic acid is released to the blood stream and transported into liver. Here it is converted to glucose. The glucose is then returned to the blood for use by muscle as an energy source and to replenish glycogen stores. This cycle is termed the "Cori cycle". The gluconeogenesis of the cycle is net consumer energy, costing the body four moles of ATP more than are produced during glycolysis. Therefore, the cycle cannot be sustained indefinitely. The

process of gluconeogenesis uses some of the reactions of glycolysis (in reverse direction) and some reactions unique to this pathway to re-synthesize glucose. This pathway requires an energy input, but has a role of maintaining a circulating glucose concentration in the blood stream even in the absence of dietary supply. Fatty acids cannot be converted into glucose in animals with the exception of odd-chain acids, which yield propionyl-CoA, a precursor of succinyl-CoA. Glycerol, which is a part of all triacylglycerols, can also be used in gluconeogenesis. On the other hand, in humans and other mammals, in which glycerol is derived from glucose, glycerol is sometimes not considered a true gluconeogenic substrate, as it cannot be used to generate new glucose. For details see [Szablewski, 2011].

2.3 Glycogenesis

Glycogenesis is the process of glycogen synthesis in which glucose molecules are added to chains of glycogen to storage in liver and muscle. This process acts during rest periods following the Cori cycle, in the liver, and also activated by insulin in response to high glucose levels. For details see [Szablewski, 2011].

2.4 Glycogenolysis

When the blood sugar levels fall, glycogen stored in the tissue, especially glycogen of muscle and liver may be broken down. This process of breakdown of glycogen is called "Glycogenolysis" (also known as "Glycogenolysis"). Glycogenolysis occurs in the liver and muscle. Hepatocytes can consume glucose-6-phosphate in glycolysis, or remove the phosphate group and release the free glucose into the blood stream for uptake by other cells. Since muscle cells lack enzyme glucose-6-phosphatase, they cannot convert glucose-6-phosphate into glucose and therefore use the glucose-6-phosphate for their own energy demands. For details see [Szablewski, 2011].

2.5 Pentose phosphate pathway

The pentose phosphate pathway (also called "Phosphogluconate pathway" or "Hexose monophosphate shunt") is primarily a cytoplasmic anabolic pathway that converts the six carbons of glucose to five carbons (pentose) sugars and reducing equivalents. The primary functions of this pathways are: 1) To generate reducing equivalents (NADH+H⁺) for reductive biosynthesis reactions within cells; 2) To provide the cell with ribose-5-phosphate for the synthesis of the nucleotides and nucleic acids; 3) To metabolize dietary pentose sugars derived from the digestion of nucleic acids as well as rearrange the carbon skeleton of dietary carbohydrates into glycolytic/gluconeogenic intermediates. This pathway is an alternative to glycolysis. While it does involve oxidation of glucose, its primary role is anabolic rather than catabolic. It is to note, that 30% of the oxidation of glucose in the liver occurs via the pentose phosphate pathway. For details see [Szablewski, 2011].

2.6 Lipogenesis

Lipogenesis is the process by which simple sugars such as glucose are converted to fatty acids. Lipogenesis starts with acetyl-CoA and builds up by the addition of two carbon units. Fatty acids are subsequently esterified with glycerol to form triglycerides that are packed in very low-density lipoprotein (VLDL) and secreted from the liver. For details see [Szablewski, 2011].

3. Glucose homeostasis

3.1 Definition of glucose homeostasis

Most tissues and organs need glucose constantly, as an important source of energy. The low blood concentrations of glucose can cause seizures, loss of consciousness, and death. On the other hand, long lasting elevation of glucose concentrations, can result in blindness, renal failure, vascular disease etc. therefore, blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called “glucose homeostasis” [DeFronzo, 1988]. This is accomplished by the finely hormone regulation of peripheral glucose uptake, hepatic glucose production, and glucose uptake during carbohydrates ingestion. For details see [Szablewski, 2011].

3.2 Mechanisms of glucose homeostasis

To avoid postprandial hypoglycemia and fasting hypoglycemia, the body can adjust glucose levels by secreting two hormones, insulin and glucagon that work in opposition to each other. During periods of hyperglycemia, the β -cells of the pancreatic islets of Langerhans secrete more insulin. Insulin is synthesized in β -cells of pancreas in response to an elevation in blood glucose and amino acid after a meal. The major function of insulin is to counter the concerned action of a number of hyperglycemia-generating hormones to maintain low blood glucose levels. It also plays an important role in the regulation of glucose metabolism. This hormone regulates glucose metabolism at many sites reducing hepatic glucose output, via decreased gluconeogenesis and glycogenolysis, facilitates the transport of glucose into striated muscle and adipose tissue, and inhibits glucagon secretion. Insulin is not secreted if the blood concentration is ≤ 3 mmol/L, but is secreted in increasing amounts as glucose concentrations increase beyond this threshold [Gerich, 1993]. When blood glucose levels increase over about 5 mmol/L the β -cells increase their output of insulin. The glucagon producing α -cells of the pancreatic islets of Langerhans remain quiet, and hold on their hormone. It is to note, that postprandially, the secretion of insulin occurs in two phases. An initial rapid release of preformed insulin, followed by increased insulin synthesis and release in response to blood glucose. Long-term release of insulin occurs if glucose concentrations remain high [Aronoff et al., 2004; Cryer, 1992]. On the other hand, during periods of hypoglycemia, the α -cells of the pancreatic islets of Langerhans secrete more glucagon. It is the principal hormone responsible for maintaining plasma glucose at appropriate levels during periods of increased functional demand [Cryer, 2002]. This hormone counteracts hypoglycemia and opposes insulin actions by stimulating hepatic glucose production. It induces a catabolic effect, mainly by activating liver glycogenolysis and gluconeogenesis, which results in the release of glucose to the bloodstream, thereby increasing blood glucose levels. The digestion and absorption of nutrients are associated also with increased secretion of multiple gut hormones that act on distal targets. There are more than 50 gut hormones and peptides synthesized and released from the gastrointestinal tract. These hormones are synthesized by specialized enteroendocrine cells located in the epithelium of the stomach, small bowel, and large bowel. It was demonstrated that ingest food caused a more potent release of insulin than glucose infused intravenously [Perley & Kipnis, 1967]. This effect, termed the “incretin effect” suggests that signals from the gut are important in the hormonal regulation of glucose disappearance. Incretin hormones are peptide hormones secreted from the gut and specific criteria have to be fulfilled for an agent to be called an incretin. They have a number of important biological effects, as for example,

release of insulin, inhibition of glucagon, maintenance of β -cells mass, and inhibition of feeding. Several incretin hormones have been characterized, but currently, GLP-1 (Glucagon-Like Peptide-1) and GIP (Glucose-Dependent Insulinotropic Polypeptide) are the only known incretins. Both GLP-1 and GIP are secreted in a nutrient-dependent manner and stimulate glucose-dependent insulin secretion. Gut hormones are secreted at low basal levels in the fasting state. The secretion of gut hormones is regulated, at least in part, by nutrients. Plasma levels of most gut hormones rise quickly within minutes of nutrient uptake and fall rapidly thereafter mainly because they are cleared by the kidney and are enzymatically inactivated [Drucker, 2007].

4. Defects in glucose homeostasis

4.1 Hyperglycemia

Hyperglycemia is the technical term for high blood glucose (sugar). It develops when there is too much sugar in the blood. High blood glucose happens when the body has too little insulin or when the body cannot use insulin properly. Hyperglycemia is a serious health problem for those with diabetes. In people with diabetes, there are two specific types of hyperglycemia that occur. Fasting hyperglycemia is defined as a blood sugar greater than 90 – 130 mg/dL (5 – 7.2 mmol/L) after fasting for at least 8 hours. Postprandial (after-meal hyperglycemia) is defined as a blood sugar usually greater than 180 mg/dL (10 mmol/L). Hyperglycemia in diabetes may be caused by: skipping or forgetting insulin or oral glucose-lowering medicine, eating too many grams of carbohydrates for the amount of insulin administered, eating too much food and having too many calories, infection, illness, increased stress, decreased activity or exercising less than unusual, strenuous physical activity. Early signs and symptoms of hyperglycemia include the following: increased thirst, headaches, difficulty concentrating, blurred vision, frequent urination, fatigue (weak, tired feeling), weight loss, blood sugar more than 180 mg/dL (10 mmol/L), high levels of sugar in the urine. Prolonged hyperglycemia in diabetes may result in: vaginal and skin infections, slow-healing cuts and sores, decreased vision, nerve damage causing painful cold or insensitive feet, stomach and intestinal problems. In people without diabetes postprandial or post-meal sugars rarely go over 140 mg/dL (7.8 mmol/L), but occasionally, after a large meal, a 1 – 2 hour post-meal glucose levels can reach 180 mg/dL (10 mmol/L). Blood glucose levels can vary from day to day. An occasional high level (above 10 mmol/L) is not problem, as long as it returns to normal (below 7 mmol/L; 126 mg/dL) within 12 – 24 hours. Persistently high blood glucose levels (above 15 mmol/L; 270 mg/dL) for more than 12 – 24 hours can result in the symptoms of hyperglycemia. For details see [Szablewski, 2011].

4.1.1 Impaired glucose tolerance and Impaired fasting glucose

There are two forms of pre-diabetes: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Impaired glucose tolerance is a transition phase between normal glucose tolerance and diabetes, also referred to as prediabetes. In impaired glucose tolerance, the levels of blood glucose are between normal and diabetic. People with IGT do not have diabetes. Each year, only 1 – 5% of people whose test results show IGT actually develop diabetes. Weight loss and exercise may help people with IGT return their glucose levels to normal. Impaired glucose tolerance is a combination of impaired secretion of insulin and reduced insulin sensitivity (insulin resistance). Fasting blood glucose levels are normal or moderately raised. IGT is diagnosed when: 1) plasma glucose, two hours after consuming 75 g

glucose, appears to be superior to 7.8 mmol/L (normal level) but remains inferior to 11.1 mmol/L (diabetes level). The level of plasma glucose is measured by means of an Oral Glucose Tolerance Test (OGTT). The procedure typically involves testing glucose levels after an eight hour fasting period, and measuring it again two hours after drinking a sugar solution. Generally, if the test shows blood glucose levels in the 140 and 199 mg/dL range, two hours after the drink, this could signify impaired glucose tolerance. 2) Fasting plasma glucose is less than 7.0 mmol/L (6.1 – 6.9 mmol/L), a level above normal, but below the threshold for diagnosis of diabetes. Impaired glucose tolerance is often affiliated with several other similar related risk factors such as high blood pressure (hypertension), increased LDL-cholesterol, reduced HDL-cholesterol. A person has impaired fasting glucose when fasting plasma glucose is 100 to 125 mg/dL. This level is higher than normal but less than the level indicating a diagnosis of diabetes. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia and is diagnosed by demonstrating any one of the following: fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL), plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test, symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/dL, glycated hemoglobin (HbA_{1c}) $\geq 6.5\%$.

4.1.2 Type 1 diabetes mellitus

Type 1 diabetes mellitus (previously known as juvenile or insulin-dependent diabetes) results due to autoimmune progressive destruction of insulin-producing β -cells by CD4+ and CD8+ T cells and macrophages infiltrating the islets [Foulis et al., 1991]. Although, the etiology of type 1 diabetes is believed to have a major genetic component, studies on the risk of developing type 1 suggest that environmental factor may be important etiological determinants. Evidence of an autoimmune etiology is found in about 95% of these cases and is classified as type 1A, and the remaining 5% lacks defined markers of autoimmunity and therefore are classified as type 1B, also termed idiopathic [Todd, 1999]. Type 1 diabetes is observed in approximately 10% of patients with diabetes mellitus [Gilespe, 2006]. Type 1 diabetes is a complex polygenic disorder. It cannot be classified strictly by dominant, recessive, or intermediate inheritance, making identification of diseases susceptibility or resistant gene difficult [Atkinson & Eisenbarth, 2001; Rabinovitch, 2000]. The lifetime of type 1 diabetes risk for a number of the general population is often quoted as 0.4%. Eight-five percent of cases of type 1 diabetes occur in individuals with no family of the disease. Differences in risk also depend on which parent has diabetes. The risk increases to 1 – 2% if the mother has diabetes and intriguingly to 3 – 7% if the father has diabetes [Haller & Atkinson, 2005; Warram et al., 1988]. The sibling risk is 6% [Risch, 1987]. Monozygotic twins have a concordance rate of 30 to 50%, whereas dizygotic twins have a concordance rate of 6 to 10% [Haller & Atkinson, 2005]. Disease susceptibility is highly associated with inheritance of the HLA (Human Leukocyte Antigen) alleles DR3 and DR4 as well as the associated alleles DQ2 and DQ8. More than 9% of patients with type 1 diabetes express either DR3DQ2 or DR4DQ8. Heterozygous genotypes DR3/DR4 are most common in children diagnosed with type 1 diabetes prior to the age of 5 (50%) [Atkinson & Eisenbarth, 2001]. Individuals with the HLA haplotype DRB1*Q302-DQA1*0301, especially when combined with DRB*10201-DQA1*0501 are highly susceptible (10 – 20-fold increase) to type 1 diabetes. On the other hand, HLA class II haplotypes such as DR2DQ6 confer dominant protection [Todd & Wicker, 2001]. Individuals with the haplotype DRB1*0602-DQA1*0102 rarely develop type

1 diabetes [Peakman, 2001]. Candidate genes studies also identified the insulin gene as the second most important genetic susceptibility factor [Bell et al., 1984]. Whole genome screen has indicated that there are at least 15 other loci associated with type 1 diabetes [Concannon et al., 1998; Cox et al., 2001]. To date, no single gene is either necessary or sufficient to predict the development of type 1 diabetes. Although type 1 diabetes is likely a polygenic disorder, epidemiological pattern of type 1 diabetes suggests that environmental factors are involved [Dorman & Bunker, 2000].

4.1.3 Type 2 diabetes mellitus

Type 2 diabetes mellitus, previously called non-insulin-dependent diabetes mellitus, is a complex heterogeneous group of metabolic disorders including hyperglycemia and impaired insulin action and/or insulin secretion. Current theories of type 2 diabetes include a defect in insulin-mediated glucose uptake in muscle, a dysfunction of the pancreatic β -cells, a disruption of secretory function of adipocytes, and an impaired insulin action in liver [Lin & Sun, 2010]. The etiology of human type 2 diabetes is multifactorial with genetic background and environmental factors of the modern world which favor the development of obesity. Several findings indicate that genetics is an important contributing factor. It has been estimated that 30 – 70% of type 2 diabetes risk can be attributed to genetics [Poulsen et al., 1999]. The lifetime risk of type 2 diabetes is about 7% in a general population, about 40% in offspring of one parent with type 2 diabetes, and about 70% if both parents have type 2 diabetes [Majithia & Florez, 2009]. Patterns of inheritance suggest that type 2 diabetes is both polygenic and heterogeneous – i.e. multiple genes are involved and different combinations of genes play a role in different subsets of individuals [Doria et al., 2008]. Genetic research effort have led to the identification of at least 27 type 2 diabetes susceptibility genes [Staiger et al., 2009] and most recent genome-wide association studies have identified 20 common genetic variants associated with type 2 diabetes [Ridderstrål & Groop, 2009]. Since skeletal muscle accounts for ~ 75% of whole body insulin-stimulated glucose uptake, defects in this tissue play a major role in glucose homeostasis in patients with type 2 diabetes [Bjornholm & Zierath, 2005]. Insulin resistance in skeletal muscle is among the earliest detectable defects in humans with type 2 diabetes [Mauvais-Jarvis & Kahn, 2000]. Type 2 diabetic patients are characterized by a decreased fat oxidative capacity and high levels of circulating free fatty acid [Blaak et al., 2000]. The latter is known to cause insulin resistance by reducing stimulated glucose uptake most likely via accumulation of lipid inside the muscle cell [Boden, 1999]. A reduced fat oxidative capacity and metabolic inflexibility are important components of skeletal muscle insulin resistance [Phielix & Mensink, 2008].

4.1.4 Gestational diabetes mellitus

Gestational diabetes mellitus is defined as “carbohydrate intolerance with onset or first recognition during pregnancy” [Metzger, 1991]. This definition includes pregnancies in which the following occur: insulin therapy is required, diabetes persists after delivery, and diabetes may have been present, but not recognized, prior to the pregnancy [Avery & Rossi, 1994]. Women at risk of type 2 diabetes are at risk of gestational diabetes mellitus [Cheung, 2009]. Gestational diabetes mellitus is a heterogeneous disorder in which age, obesity, and genetic background contribute to the severity of the disease. Multiparous women have a very high prevalence of gestational diabetes mellitus [Wagaarachchi et al., 2001]. There has

been relatively little research in the area of gestational diabetes genetics [Watanabe et al., 2007]. There is evidence for clustering of type 2 diabetes and impaired glucose tolerance in families with gestational diabetes mellitus [McLellan et al., 1995] and evidence for higher prevalence of type 2 diabetes in mothers of women with gestational diabetes [Martin et al., 1985]. The pathophysiology of gestational diabetes remains controversial. Gestational diabetes mellitus may reflect a predisposition to type 2 diabetes under the metabolic conditions of pregnancy or it may represent the extreme manifestation of metabolic alterations that normally occur in pregnancy [Butte, 2000]. Women with gestational diabetes have decreased insulin sensitivity in comparison with control groups. Gestational diabetes induces a state of dyslipidemia consistent with insulin resistance. During pregnancy, women with gestational diabetes do have high serum triacylglycerol concentrations but lower LDL-cholesterol concentrations than do healthy pregnant women [Koukkou et al., 1996]. During pregnancy, gestational diabetes is associated with a number of complications for child. Because insulin does not cross the placenta, the fetus is exposed to the maternal hyperglycemia. The fetal pancreas is capable of responding to this hyperglycemia [Scollan-Kolippoulos et al., 2006]. The fetus becomes hyperinsulinemic, which in turn promotes growth and subsequent macrosomia [Perkins et al., 2007]. Fetus born to mother with gestational diabetes has higher risk of developing macrosomia, neonatal hypoglycemia, hyperbilirubinemia, shoulder dystonia with its attendant risk of brachial injury and clavicle fracture, etc [Ecker et al., 1997; Hapo Study Group, 2008; Hod et al., 1991; Langer & Mazze, 1988; Persson & Hanson, 1998]. These complications have been reported with varying frequency [Garner, 1995]. Additionally, there are some data that suggest an increase in fetal malformation and perinatal mortality [Sepe et al., 1985]. Cesarean sections are also more common, and gestational diabetes mellitus is associated with a higher risk of pre-eclampsia [Hapo Study Group, 2008, Persson & Hanson, 1998]. Infant exposed to maternal diabetes in uterus have and increased risk of diabetes and obesity in childhood and adulthood [Silverman et al., 1998]. Studies indicate that the magnitude of fetal-neonatal risk is proportional to the severity of maternal hyperglycemia [Langer & Conway, 2000]. Gestational diabetes is one of the most common complications in pregnancy occurring in 2,2% - 8,8% of each year, dependent on the ethnic mix of the population and the criteria used for diagnosis.

4.1.5 MODY

MODY (Maturity onset diabetes of young) is a monogenic and autosomal dominant form of diabetes mellitus. Disease was described in 1974 - 1975 and since then newer gene mutations and subgroups of MODY have been identified [Tattersall, 1974; Tattersall & Fajans, 1975]. To distinguish MODY from type 1 diabetes tests need to be done to establish the absence of diabetes antibodies (anti-insulin, anti-islet, anti-glutamic acid decarboxylase). In obese people, the absence of insulin resistance, will differentiate it from type 2 diabetes. MODY presents in children, adolescent or young adults and may account for up to 5% of diabetes cases [Johnson, 2007]. MODY patients have a strong family history of diabetes, suggestive of a primary genetic cause [Fajans et al., 2001; Mitchell & Frayling, 2002]. MODY is caused by changes to a single gene and if either one of the parents carriers this gene they have a 50% chance of passing it on to their child. Disease progression in MODY is thought to be largely independent of nongenetic factors other than time. A primary physiological defect caused [Fajans et al., 2001; Mitchell & Frayling, 2002]. Nine of genetic forms of MODY

have been identified to date, and these have been termed MODY 1 – 9. These rare diabetic disorders are associated with heterozygosity for mutations in single genes, including 7 transcription factors (MODY 1, 3, 4, 5, 6, 7 and 9) and 2 metabolic enzymes (MODY 2 and 8). In some cases, there are significant differences in the activity of the mutant gene product that contribute to variations in the clinical features of the diabetes.

4.1.6 Neonatal diabetes mellitus

Neonatal diabetes mellitus is defined as insulin-sensitive hyperglycemia occurring in the first months of life, lasting for more than 2 weeks and required insulin for management [Shield, 2000]. It is rare, with an incidence of approximately 1 in 500 000 births [von Muhlendahl & Herkenhoff, 1995]. Neonatal diabetes mellitus is considered distinct from autoimmune type 1 diabetes, which manifests after the first 3 to 6 months of life [Hathout et al., 2000]. In this disease, antibodies to insulin or islet cells and other markers of autoimmune type 1 diabetes are absent. There are two separate forms of neonatal diabetes mellitus that vary in the length of insulin dependency in the premature stage of disease. In about 50% of cases of neonatal diabetes mellitus, diabetes is transient and resolves at a median age of 3 months (Transient Neonatal Diabetes Mellitus). The other 50% of cases of neonatal diabetes mellitus are permanent (Permanent Neonatal Diabetes Mellitus) [Neve et al., 2005]. The etiology of neonatal diabetes mellitus is genetically heterogeneous, producing abnormal development or absence of pancreas or islets, decreased β -cell mass secondary to increased β -cell apoptosis, and β -cell dysfunction that limits insulin secretion [Aguilar-Bryan & Bryan, 2008]. Transient neonatal diabetes mellitus is a form of neonatal diabetes that appears in the first six weeks of life and usually ends by 18 months. It is characterized by intrauterine growth retardation, dehydration, small gestational age at birth, and failure to thrive. Permanent neonatal diabetes mellitus can occur alone or as a larger genetic syndrome. In permanent neonatal diabetes mellitus, diabetes develops within days to months after birth and persists throughout life. Intrauterine growth retardation, hyperglycemia, severe dehydration, osmotic polyuria, and failure to thrive are all associated with permanent neonatal diabetes mellitus.

4.2 Hypoglycemia

4.2.1 Definition of hypoglycemia

Normally, the body maintains the levels of sugar in the blood within a range of about 70 to 110 mg/dL, depending on when a person last ate. In the fasting state, blood sugar can occasionally fall below 60 mg/dL and even to below 50 mg/dL and not indicate a serious abnormality or disease. This can be seen in healthy women, particularly after prolonged fasting. Hypoglycemia, also called low blood glucose or low blood sugar, occurs when glucose drops below normal levels. Hypoglycemia is defined arbitrarily as blood glucose of less than 50 mg/dL (2.8 mmol/L) with neuroglycopenic symptoms or less than 40 mg/dL (2.2 mmol/L) in the absence of symptoms [Carroll et al., 2003]. The clinical manifestations of hypoglycemia are nonspecific. Therefore, clinically significant hypoglycemia is characterized by Whipple's triad: 1) symptoms of neuroglycopenia, 2) simultaneous blood glucose lower than 40 mg/dL (2.2 mmol/L), 3) relief of symptoms with the administration of glucose. All 3 criteria should be met to establish a diagnosis of hypoglycemia. Asymptomatic hypoglycemia with glucose levels as low as 30 mg/dL (1.7 mmol/L) can be seen during fasting in normal women and during pregnancy [Merimee & Tyson, 1974].

Asymptomatic patients may have artifactual hypoglycemia due to *in vitro* consumption of glucose by blood cell elements such as in leukemia or polycythemia [Carroll et al., 2003].

4.2.2 Signs and symptoms of hypoglycemia

Because of the effectiveness of the normal defenses against falling plasma glucose concentrations, hypoglycemia is an uncommon clinical event, except in persons who use drugs that lower plasma glucose levels, to treat diabetes mellitus [Cryer, 2004; Cryer et al., 2009; Guettier & Gorden, 2006]. According to Cryer and colleagues [Cryer et al., 2009], in healthy individuals, symptoms of hypoglycemia develop at a mean plasma glucose concentration of approximately 55 mg/dL (93.0 mmol/L). However, the glycemic threshold for this and other responses to hypoglycemia shift to lower plasma glucose concentrations in patients with recurrent hypoglycemia [Cryer, 2001 a, Cryer, 2009]. Documentation of Whipple's triad established that a hypoglycemic disorder exists. In a person who does not have diabetes mellitus an unequivocally normal plasma glucose concentration during a symptomatic episode indicates that symptoms are not the result of hypoglycemia [Cryer et al., 2009]. The clinical manifestations of hypoglycemia are nonspecific. The central nervous system relies primarily on glucose for generation of cellular energy, but has reserves sufficient for only a few minutes and cannot synthesize glucose. Furthermore, studies have demonstrated that glucose is an obligate metabolic fuel for the brain under physiological conditions. It is to note, that glucose is not the only fuel that can be utilized by the brain. The noninjured brain can also utilize ketone bodies, particularly during starvation [Robinson & Williamson, 1980]. On the other hand, the brain cannot use fuels others than glucose during acute hypoglycemia [Cryer, 2001 a; Cryer, 2007; Wahren et al., 1999]. When the brain is deprived of its supply of glucose, serious neurological dysfunction occurs [Carroll et al., 2003]. During severe hypoglycemia, glycogen stores appear to play a special role in maintaining brain function. Studies suggest that increasing brain glycogen stores protects neuronal activity [Wender et al., 2000]. Results obtained from human and animal studies showed that the most sensitive neuronal populations are the superficial layers of the cortex, the hippocampus, the caudate nucleus, and the subiculum [Auer et al., 1984; Auer et al., 1985]. Hypoglycemia induces neuronal death [Lacherade et al., 2009]. The neuronal death resulting from hypoglycemia is not a straightforward result of energy failure but instead results from a sequence of events initiated by hypoglycemia [Such et al., 2007]. These events include activation of neuronal glutamate receptors [Nellgard & Wieloch, 1992], production of mitochondrial reactive oxygen species [Singh et al., 2004], neuronal zinc release [Assaf & Chung, 1984], and extracellular release of excitatory amino acids (glutamate and aspartate) [Engelsen et al., 1986]. Activation of postsynaptic glutamate receptor and postsynaptic zinc accumulation induce a variety of mechanisms leading to neuronal death [Patockova et al., 2003; Singh et al. 2004]. According to Carroll and colleagues [Carroll et al., 2003], there are 4 pathophysiologic mechanisms capable of exceeding the body's counterregulatory capacity and causing severe hypoglycemia: excessive insulin effect, diffuse hepatic dysfunction, limited substrate for gluconeogenesis and excessive glucose consumption. More than one mechanism may be responsible, especially in ill patients. Symptoms of hypoglycemia are categorized as neuroglycopenic and neurogenic or autonomic. Symptoms of hypoglycemia may be nonspecific but tend to be similar for repeated episodes in the same individual. The symptoms associated with hypoglycemia are sometimes mistaken for symptoms caused by conditions not related to blood sugar. Unusual stress and anxiety can cause excess production of catecholamines, resulting in symptoms similar to those caused by

hypoglycemia but having no relation to blood sugar levels. Symptoms can be slowly or suddenly, progressing from mild discomfort to severe confusion or panic within minutes. If left untreated, hypoglycemia can get worse and cause confusion, clumsiness, or fainting. Severe hypoglycemia can lead to seizures, coma, and even death. General symptoms of hypoglycemia are: nausea, dizziness, collapse, weight gain. Neurogenic symptoms result from sympathetic discharge triggered by hypoglycemia. They include sweating, tremor, palpitations, tachycardia, agitation, nervousness, hunger [Towler et al., 1993]. Symptoms linked to neuroglycopenia are direct result of the lack of brain metabolic energy. Neuroglycopenic symptoms occur at glucose levels of approximately 45 mg/dL and impair the ability of affected individual to take corrective action to abort severe hypoglycemia [Carroll et al., 2003]. These symptoms include impairment of consciousness, mental concentration, vision, speech, memory. Blurred vision, fatigue, seizures, paralysis, ataxia, loss of consciousness, unusual or bizarre behavior, and emotional lability [Cryer, 2008; Guettier & Gorden, 2006; McAulay et al., 2001; Ng, 2010; Towler et al., 1993]. Coma may result from values below 40 - 50 mg/dL [Ben-Ami et al., 1999], and death in extreme cases. Hypoglycemia can also happen during sleep. Some signs of hypoglycemia during sleep include crying out or having nightmares, finding pajamas or sheets damp from perspiration, feeling tired, irritable, or confused after waking up. The symptoms of hypoglycemia rarely develop until the level of sugar in the blood falls below 60 mg/dL of blood. Some people develop symptoms at slightly higher levels, especially when blood sugar levels fall quickly, and some do not develop symptoms until the sugar levels in their blood are much lower. The body first responds to a fall in the level of sugar in the blood by releasing noradrenaline (epinephrine) from the adrenal glands. Hormone stimulates the release of sugar from body stores but also causes symptoms similar to those of an anxiety attack: sweating, nervousness, shaking, faintness, palpitations, and hunger. Sometimes people who are hypoglycemic are mistakenly thought to be drunk. In adults and children older than 10 years, hypoglycemia is uncommon except as a side effect of diabetes treatment. Hypoglycemia in people who do not have diabetes is far less common than once believed [Cryer, 2008; Guettier & Gorden, 2006; Service, 1995; Service, 1999]. It can occur in some people under certain conditions such as early pregnancy, prolonged fasting, and long periods of strenuous exercise. Hypoglycemia can also result, however, from other medications or diseases, hormone or enzyme deficiencies, or tumors.

4.2.3 Causes and types of hypoglycemia

Two types of hypoglycemia can occur in people who do not have diabetes: reactive hypoglycemia, also called postprandial hypoglycemia, occurs within 4 hours after meals and fasting hypoglycemia, also called postabsorptive hypoglycemia, is often related to an underlying disease [Cryer, 2008]. This classification has been criticised for being unhelpful diagnostically. According to Service [1995] some causes of hypoglycemia can present with both postabsorptive and postprandial (e.g. insulinoma). Other disorders can present with erratically occurring symptoms independent of food ingestion (e.g. factitious hypoglycemia). Patients with an insulinoma, who typically have postabsorptive hypoglycemia, may experience postprandial hypoglycemia, and post-gastric-bypass patients, who typically have postprandial hypoglycemia, may have symptoms when fasting. Indeed, some disorders, e.g. factitious hypoglycemia, are not readily classified as either postabsorptive or postprandial [Cryer et al., 2009]. Therefore, a more useful approach for clinicians is a classification based on clinical characteristics [Ng, 2010]. Symptoms of the both reactive and fasting

hypoglycemia are similar to diabetes-related hypoglycemia. Symptoms may include hunger, sweating, shakiness, dizziness, light-headedness, sleeping, confusion, difficulty speaking, anxiety, and weakness. The average age of a patient diagnosed with an insulinoma is the early 40s, but cases have been reported in patients ranging from birth to age 80 years [Garza, 2008].

4.2.3.1 Reactive hypoglycemia (postprandial hypoglycemia)

A diagnosis of reactive hypoglycemia is considered only after possible causes of low blood sugar have been ruled out. Reactive hypoglycemia with no known cause is a condition in which the symptoms of low blood sugar appear 2 to 5 hours after eating foods, especially when meals contain high levels of simple carbohydrates (as for example glucose). Reactive hypoglycemia refers to hypoglycemia caused by external influences, like diet and medication use. This type is more amenable to management or cure. Reactive hypoglycemia can be seen in patients who have had surgical removal of the stomach and in patients who had other surgical procedures (gastrojejunostomy, vagotomy, pyloroplast). This type of hypoglycemia, alimentary hypoglycemia, is another form of hypoglycemia. In the absence of stomach, glucose in the meal is rapidly absorbed into the blood stream through the intestines, causing sudden hyperglycemia. In order to correct this sudden hyperglycemia, excessive amounts of insulin are released by the pancreas, which drives the blood glucose down, causing hypoglycemia. The reactive hypoglycemia in gastrectomy patients occurs early, usually within 1 hour after a meal. In hereditary fructose intolerance and galactosemia, an inherited deficiency of a hepatic enzyme causes acute inhibition of hepatic glucose output when fructose or galactose is ingested. In patients with leucine sensitivity in childhood leucine provokes an exaggerated insulin secretory response to a meal and reactive hypoglycemia. Reactive hypoglycemia can occur when blood glucose falls, stores of glucose from the liver are exhausted and an individual chooses not to eat. The body gradually adjusts to this situation by using muscle protein to feed glucose to brain and fat to fuel the other body cells, tissues and organs, but before this adjustment takes place, an individual may experience symptoms of glucose deprivation to the brain. Reactive hypoglycemia seldom causes glucose levels to drop low enough to induce severe neuroglycopenic symptoms; therefore, a history of true loss of consciousness is highly suggestive of an etiology other than reactive hypoglycemia. Reactive hypoglycemia has been suggested to be more common in people who are insulin-resistant, and it may be a frequent precursor to type 2 diabetes. Therefore patients who have a family history of type 2 diabetes or insulin-resistance syndrome, may be at higher risk of developing hypoglycemia. Reactive hypoglycemia often is treated successfully with dietary changes and is associated with minimal morbidity. Mortality is not observed. Reactive hypoglycemia is reported most frequently by women. It typically is in women aged 25 – 35 years. The average age of a patients diagnosed with an insulinoma is the early 40s, but cases have been reported in patients ranging from birth to age 80 years [Garza, 2009]. Idiopathic postprandial hypoglycemia is another form of reactive hypoglycemia [Ng, 2010]. It is a disorder in which autonomic and neuroglycopenic symptoms develop postprandially, accompanied by low plasma glucose [Brun et al., 2000]. This disease is due to various mechanisms, as for example: 1) high insulin sensitivity, 2) an exaggerated insulin response, either related to insulin resistance or to increased glucagon-like peptide 1, 3) renal glycosuria, 4) defects in glucagon response [Brun et al., 2000]. In idiopathic postprandial syndrome, autonomic symptoms, appear 2 – 5 hours after a meal. It is to note that plasma glucose concentration is

normal [Charles et al., 1981]. This phenomenon is due to enhanced catecholamine release following a meal or enhanced sensitivity to normal postprandial noradrenaline (norepinephrine) and adrenaline (epinephrine) release. This condition is also known as pseudohypoglycemia [Foster & Rubenstein, 1998].

4.2.3.2 Fasting hypoglycemia (postabsorptive hypoglycemia)

Fasting hypoglycemia, also called postabsorptive hypoglycemia, is diagnosed from a blood samples that shows a blood glucose level below 50 mg/dL after an overnight fast, between meals, or after physical activity. Fasting hypoglycemia occurs when the stomach is empty. It usually develops in the early morning when a person awakens. In otherwise healthy people, prolonged fasting (even up to several days) and prolonged strenuous exercise (even after a period of fasting) are unlikely to cause hypoglycemia. However, there are several conditions or diseases in which the body fails to maintain adequate levels of sugar in the blood after a period without food. Causes of fasting hypoglycemia include certain medications, alcoholic beverages, critical illnesses, hormonal deficiencies, some kinds of tumors, and certain conditions occurring in infancy and childhood. Drugs, including some used to treat diabetes, are the most common cause of hypoglycemia. Many other drugs have been reported to cause hypoglycemia, as for example: salicylates, sulfa medications, pentamidine, quinine [Cryer, 2008; Malouf & Brust, 1985; Murad et al, 2009]. In people who drink heavily without eating, alcohol can block the release of stored sugar from the liver. The body's break-down of alcohol interferes with the liver's efforts to raise blood glucose. The alcohol directly interferes with hepatic gluconeogenesis, but not glycogenolysis. The energy required for metabolism of alcohol is diverted from the energy needed to take up lactate. Patients who drink alcohol may become hypoglycemic after 12 - 24 hour when the glycogen stores are depleted. Hypoglycemia caused by excessive drinking can be serious and even fatal. Some illnesses that affect the liver, heart, or kidneys can cause hypoglycemia. Liver insufficiency/failure from any cause may result in deficient glycogen stores or inadequate gluconeogenesis. In advanced liver failure, the defects may be severe enough to cause hypoglycemia. The kidneys have the capacity to produce glucose by gluconeogenesis. Isolated renal failure is rarely associated with hypoglycemia. More often, renal failure is associated with hypoglycemia in patients who are on insulin or insulin secretagogues as insulin is cleared by the kidney. Sepsis is other cause of hypoglycemia. In this case, hypoglycemia can occur due to decreased gluconeogenesis. Hormonal deficiencies may cause hypoglycemia in very young children, but rarely in adults. Certain endocrine deficiencies are associated with poor gluconeogenesis, poor glycogenolysis, or both. These include: adrenal insufficiency, hypopituitarism, isolated growth hormone deficiency, hypothyroidism, isolated glucagon deficiency, and sympathetic nervous system defects. Shortages of cortisol, growth hormone, glucagon or epinephrine can lead to fasting hypoglycemia. Mesenchymal tumors, hepatocellular carcinoma, adrenocortical tumors, carcinoid tumors, leukemia and lymphomas are nonislet cell tumors most commonly associated with hypoglycemia [Diaz et al., 2008; Guettier & Gorden, 2006; Jayaprasad et al., 2006; Ng, 2010]. Although the pathogenesis is incompletely understood, it is believed that these tumors may secrete an insulin like substance that may be biologically active. An alternative hypothesis is that these tumors are so large that they require a significant amount of glucose the liver/kidney are unable to match. Insulinomas can cause hypoglycemia by raising insulin levels too high in relation to the blood glucose level. These tumors are rare and do not normally spread to other parts of the body. The estimated

incidence is 1 case per 250 000 patients-years [Service et al., 1991]. It is characterized by neuroglycopenia spells and occurs primarily in a fasting state, and only occasionally in a postprandial period [Kar et al., 2006]. Approximately 60% of patients with insulinoma are female. Insulinomas are uncommon in persons younger than 20 years and are rare in those younger than 5 years. The median age at diagnosis is about 50 years. In some people, an autoimmune disorder lowers sugar levels in the body by changing insulin secretion or by some other means. Hypoglycemia due to anti-insulin antibody is a rare disorder occurring in people often with a history of autoimmune disease [Ng, 2010]. Pregnancy is associated with lower glucose level because of decreased gluconeogenesis due to decreased substrate supply [Pugh et al., 2009]. Inborn errors of carbohydrate metabolism are rare and present during the first days of life [Gustafsson, 2009; Menhesha et al., 2007]. Infants present with fasting hypoglycemia, especially at night. Children rarely develop hypoglycemia and causes may include the following: brief intolerance to fasting, often during an illness that disturbs regular eating patterns, hyperinsulinism, which can result in temporary hypoglycemia in newborns, which is common in infants of mothers with diabetes, enzyme deficiencies that affect carbohydrate metabolism and hormone deficiencies.

5. Hypoglycemia in diabetes mellitus

Hypoglycemia occurring as a complication of therapy for diabetes is common [Chen, 2010; Ito et al., 2010; Swinnen et al., 2010]. Mild hypoglycemia occurs in more than half of all patients with diabetes who are in therapy. Hypoglycemia can occur as a side effect of some diabetes medications, including insulin and oral diabetes medications that increase insulin production. Rapid-acting insulin analogues may decrease the frequency of hypoglycemia associated with regular insulin administration. Insulin lispro has been shown to decrease postprandial glucose excursions and to result in less hypoglycemia in the postabsorptive state [Holleman et al., 1997]. Long-acting analogues, such as glargine, may decrease the frequency of hypoglycemia in both type 1 and type 2 diabetic patients [Pieber et al., 2000; Rosenstock et al., 2001]. Several studies have demonstrated a reduction in hypoglycemic events during continuous subcutaneous insulin infusion using a portable electromechanical pump when compared with multiple injection regimens [Pickup & Keen, 2002]. The effect of normal aging may contribute to the risk for severe hypoglycemia in older diabetic patients treated with sulfonylureas and insulin. Glycemic control in the pregnant diabetic women has major consequence on maternal and fetal morbidity and mortality. The strict control that is recommended during pregnancy leads to a high risk for hypoglycemia, the incidence reported as high as 72% in several studies [Coustan et al., 1986; Rosenn et al., 1995]. The majority of episodes occur during the first 20 weeks of gestation [Kimmerle et al., 1992]. Factors that may contribute to the occurrence of hypoglycemia during pregnancy include anorexia, changes in hormonal counterregulation or the development of altered hypoglycemic awareness [Bjorklund et al., 1998; Dagogo-Jack et al., 1993]. Exercise is an important mode of therapy in both type 1 and type 2 diabetes. High levels of insulin resulting from therapy may prevent the increased mobilization of glucose normally induced by exercise, and hypoglycemia may ensue. Exercise may cause immediate, early, and delayed hypoglycemia, particularly in type 1 diabetic patients and in patients with type 2 diabetes on insulin or sulfonylurea therapy. In general, hypoglycemia during exercise tends to be less of a problem in this population. Injection of insulin into the arm or abdomen decreases the hypoglycemic effect of exercise by 57% and 89%, respectively, in comparison

with injection of insulin into the leg [Koivisto & Felig, 1978]. Nonselective β -blockers attenuate some components of the autonomic response to hypoglycemia and could increase the risk of hypoglycemia. In study with elderly diabetic patients, no significant impact on the rate of hypoglycemia could be associated with any particular class of antihypertensives [Shorr et al., 1997]. Although in general in type 2 diabetes mellitus there is less hypoglycemia risk versus type 1 diabetes mellitus, the frequency of hypoglycemia increases with increased diabetes and insulin treatment duration in type 2 diabetes mellitus [Cryer, 2008 b]. Recent clinical trials have better quantified the risk of hypoglycemia in both type 1 and type 2 diabetes [Leese et al., 2003; Pramming et al., 2000]. Severe hypoglycemia is operationally defined as an episode that the patient cannot self-treat, so that external help is required, regardless of the glucose concentration. Mild or moderate hypoglycemia refers to episodes that the patient can self-treat, regardless of the severity of symptoms, or when blood glucose levels are noted to be lower than 60 mg/dL. The incidence of mild or moderate hypoglycemia episodes is difficult to determine accurately because they are rarely reported, although they are common in insulin-treated patients [Gabriely & Shamoon, 2004]. Representative event rates for severe hypoglycemia in type 1 diabetes mellitus are from 62 to 170 episodes per 100 patient-years [MacLeod et al., 1993]. These reported during aggressive insulin therapy of type 2 diabetes mellitus range from 3 to 73 episodes per 100 patient-years [MacLeod et al., 1993]. When glucagon responses to hypoglycemia are deficient, epinephrine and autonomic warning symptoms become critical for the integrity of glucose counterregulation. Iatrogenic hypoglycemia attenuates the magnitude of adrenaline and autonomic symptom responses to a subsequent hypoglycemic episode [de Galan et al., 2006]. Any hypoglycemia can provoke this phenomenon [Bolli et al., 1984; Davis & Shamoon, 1991; White et al., 1983]. Consequently, a downward vicious cycle of worsening counterregulation and recurrent hypoglycemia may ultimately lead to hypoglycemia unawareness. Clinical syndrome of hypoglycemia unawareness is defined as onset of neuroglycopenia before the appearance of autonomic warning symptoms and typified clinically by the inability to perceive hypoglycemia by symptoms [de Galan et al., 2006]. Patients with hypoglycemia unawareness are unable to manifest adequate behavioral defenses against developing hypoglycemia, therefore, hypoglycemia unawareness is also associated with a high frequency of severe iatrogenic hypoglycemia [Gold et al., 1994]. These patients are at a specifically high risk for severe disabling hypoglycemia (e. g. complicated by coma or seizures) that requires external assistance [Gold et al., 1994]. Hypoglycemia unawareness is generally thought to be the result of reduced sympathoadrenal responses and the resultant reduced neurogenic symptom responses to a given level of hypoglycemia [Cryer, 2002; Hepburn et al., 1991]. According to de Galan and colleagues [de Galan et al., 2006], various terms are used for the combination of defective hormonal counterregulation and hypoglycemia unawareness, as for example: counterregulatory failure, hypoglycemia-associated autonomic failure (HAAF), and hypoglycemia unawareness syndrome. A reduced sympathoadrenal response is the key feature of hypoglycemia-associated autonomic failure and, thus, the pathogenesis of iatrogenic hypoglycemia in diabetes [Cryer, 2006]. According to suggestion described by Cryer [Cryer, 2005] "The concept of HAAF in type 1 [Dagogo-Jack et al., 1993] and advanced type 2 [Segel et al., 2002] diabetes posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing epinephrine responses to a given level of subsequent hypoglycemia in the setting of absent decrements in insulin and absent increments in glucagon) and hypoglycemia unawareness (by reducing

sympathoadrenal and the resulting neurogenic symptom responses to a given level of subsequent hypoglycemia) a thus a vicious cycle of recurrent hypoglycemia". Reduced sympathoadrenal actions play a key role in the pathogenesis of both defective counterregulation and hypoglycemia unawareness and thus HAAF in diabetes [Cryer, 2004]. The mediators and mechanisms of HAAF are largely unknown [Cryer, 2005]. Different hypotheses are discussed [Cryer, 2001; Cryer, 2005; Cryer, 2006; Cryer et al., 2003; Cryer et al., 2009]. It is suggested that there are three causes of HAAF in diabetes: the originally recognized hypoglycemia-related HAAF, exercise-related HAAF, and sleep-related HAAF [Cryer, 2004]. The clinical impact of HAAF is well established in type 1 diabetes and it is less established in type 2 diabetes [Cryer, 2004]. Patients with iatrogenic hypoglycemia causes recurrent morbidity in most people with type 1 diabetes and many with type 2 diabetes, and it is sometimes fatal. Iatrogenic hypoglycemia often causes recurrent physical morbidity, recurrent or persistent psychosocial morbidity, or both and sometimes causes death [Cryer et al., 2003]. A direct relation between hypoglycemia and death has been proposed in the "dead-in-bed" syndrome [de Galan et al., 2006]. According to Maran et al. [1994] and Veneman et al. [1994], the dead-in-bed syndrome is rare disorder characterized by an unexpected death in young, previously healthy, tightly controlled patients with type 1 diabetes. Death in this syndrome is thought to be result of a fatal ventricular arrhythmia caused by hypoglycemia-induced lengthening of the QT interval [Bischof et al., 2004]. Corrected QT interval prolongation and increased QT dispersion have been demonstrated during acute-insulin-induced hypoglycemia in healthy subjects [Laitinen et al., 2008], in patients with type 1 and type 2 diabetes [Landstedt-Hallin et al., 1999; Rothenbuhler et al., 2008] or during nocturnal hypoglycemia in patients with type 1 diabetes [Murphy et al., 2004]. Myocardial cells can use either fatty acids or glucose oxidation as their source of energy [Stanley & Chandler, 2002]. Under normal conditions, the oxidation of fatty acids is prominent and in diabetic patients, the use of fatty acids is predominant [Lacherade et al., 2009]. During acute insulin-induced hypoglycemia or during nocturnal hypoglycemia in type 1 diabetes have been observed: cardiac rate and rhythm disturbances (tachycardia and bradycardia), and ventricular and atrial ectopy [Fisher et al., 1990; Gill et al., 2009; Laitinen et al., 2008]. Ventricular repolarization abnormalities appear to be the main feature observed during episodes of hypoglycemia [Lacherade et al., 2009]. It is not yet known to what extent hypoglycemia contributes to mortality in type 2 diabetes mellitus [Lacherade et al. 2009]. Hospitalization is required in a minority of patients, usually for observation of neurologic signs during hypoglycemia, such as seizures, obtundation, coma, or focal neurologic signs. The need for hospitalization arises most commonly in diabetic patients, although hypoglycemia is frequently identified in patients with malnutrition and associated alcohol consumption, mental illness, or severe underlying medical illness [Hart & Frier, 1998]. Hypoglycemia occurs in 1.2% of hospitalized patients and is of somewhat more diverse etiology [Fischer et al., 1986]. Hypoglycemia in diabetes is fundamentally the result of treatments that raise insulin levels and thus lower plasma glucose concentration.

5.1 Recommendations and prevention

Cryer and colleagues [Cryer et al., 2009] recommend "1) that both the conventional risk factors and those indicative of compromised defenses against hypoglycemia be considered in a patient with recurrent treatment-induced hypoglycemia, and 2) with a history of hypoglycemia unawareness, a 2- to 3-wk period of scrupulous evidence of avoidance of

hypoglycemia". Patients with diabetes become concerned about the possibility of developing hypoglycemia when the self-monitored blood glucose concentration is falling rapidly or is no greater than 70 mg/dL [Cryer et al., 2009]. Therefore diabetic patients need to be well informed about: the symptoms of hypoglycemia, the physiologic factors that come into play, the time course of the drugs they use; how to prevent and treat episodes of hypoglycemia, how to monitor their blood glucose levels, and the warning symptoms of hypoglycemia [Gabriely & Shamoon, 2004]. One of the most important things to prevent hypoglycemia is to educate the patient. Patients should always have a rapidly available source of glucose with them to treat hypoglycemia at the first sign of low glucose. Briscoe & Davis [2006] suggest that: 1) if blood glucose is < 70 mg/dL, give 15 - 20 g of quick-acting carbohydrate; 2) if test blood glucose 15 minutes after treatment is still < 70 mg/dL, re-treat with 15 g of additional carbohydrate; 3) if blood glucose is not < 70 mg/dL but is > 1 hour until the next meal, have a snack with starch and protein; 4) keep glucagon injection kit available for patients who are unconscious or unable to take in oral carbohydrate. It is to note, that insulin preparations have different onsets of action, times of peak effect, and effective duration of action. These differences affect both glycemic control and hypoglycemic episodes. Therefore, these factors must be considered when adjusting the treatment. A history of recurrent hypoglycemia should be investigated.

5.2 Hypoglycemia in type 1 diabetes mellitus

5.2.1 Pathophysiology

Secretion of the three main counterregulatory hormones normally responsible for rapid reversal of hypoglycemia is severely disrupted in type 1 diabetes. Insulin secretion is either insignificant or absent and glucagon release during hypoglycemia is also impaired soon after the onset of diabetes. The plasma glucagon concentration does not increase as it should during hypoglycemia [Gerich et al., 1973]. This is because the pancreatic α -cell glucagon secretory response to hypoglycemia is irreversibly lost [Cryer, 2001 b; Cryer et al., 2003]. The mechanism of the absent glucagon response to hypoglycemia that characterizes established type 1 diabetes is not known [Cryer et al., 2003]. Epinephrine is the main defense against hypoglycemia in patients with type 1 diabetes of > 5 years duration [Briscoe & Davis, 2006]; however, epinephrine release during hypoglycemia becomes progressively defective in type 1 diabetes [Amiel et al., 1988; Bolli et al., 1983]. It is to note, that epinephrine secretory response to falling glucose levels is typically attenuated in type 1 diabetes [Amiel et al., 1988; Dagogo-Jack et al., 1993]. HAAF in type 1 diabetes apparently results from antecedent episodes of mild hypoglycemia that further degrade the counterregulatory response [Dagogo-Jack et al., 1993]. Patients with type 1 diabetes already have a reduced counterregulatory response, therefore HAAF may play a role in the vicious circle of hypoglycemia begetting hypoglycemia. It is to note, that avoidance of hypoglycemia in type 1 diabetes can improve the epinephrine response [Crauston et al., 1994]. Iatrogenic hypoglycemia in diabetes is the result of treatments that raise insulin levels and thus lower plasma glucose concentration. In type 1 diabetes iatrogenic hypoglycemia is the result of the interplay of relative or absolute insulin excess and compromised glucose counterregulation [Cryer, 2001]. It is suggested [Cryer, 2001] that absolute or relative insulin excess occurs when insulin or insulin secretagogue or sensitizer doses are excessive, exogenous glucose delivery is decreased, endogenous glucose production is decreased, glucose utilization is increased, sensitivity to insulin is increased, and insulin clearance is decreased. It is to note, that the conventional risk factors for iatrogenic hypoglycemia are based on the premise that

absolute or relative insulin excess is the sole determinant of risk [Cryer, 2001]. In patients with type 1 diabetes, treated with insulin, insulin levels are unregulated and do not decrease until the subcutaneous depot is depleted, even though the plasma glucose levels may have started to fall. Insulin injected subcutaneously enters the circulation much slower and therefore elevated insulin levels persist considerably longer. Differences in insulin absorption may explain why a dose of insulin to maintain normoglycemia at one time may be too much at other times and creating a risk for hypoglycemia.

5.2.2 Frequency

In type 1 diabetes, the Diabetes Control and Complications Triad reported 62 severe hypoglycemic episodes per 100 patient-years [The DCCT Research Group, 1993]. Population-based studies in northern Europe reported 100 to 160 patient-years [Leese et al., 2003]. The average patient with type 1 diabetes suffers two episodes of symptomatic hypoglycemia per week, and one episode of temporarily disabling hypoglycemia (often with seizure or coma) per year [Cryer et al., 2009]. An estimated 2 to 4% of patients with type 1 diabetes die from hypoglycemia [Cryer et al., 2009]. In most instances, death cannot be attributed directly to hypoglycemia, but relates to the circumstances under which the hypoglycemic event involved, e.g. in traffic, during swimming etc.

5.3 Hypoglycemia in type 2 diabetes mellitus

5.3.1 Pathophysiology

Type 2 diabetes is characterized by a range of metabolic disorders: chronic hyperglycemia, declining β -cell effectiveness resulting in the absence of first-phase insulin response to nutrient ingestion, insulin insensitivity in fat and muscle cells, and hepatic glucose production in the prandial state [Aronoff, 2004; DeFronzo, 2004]. The traditional primary defects responsible for the development and progression of type 2 diabetes are impaired insulin secretion, increased hepatic glucose production and decreased peripheral glucose utilization. Insulin secretion may be increased early in the course of type 2 diabetes, as the pancreas attempts to compensate for the elevated fasting plasma glucose concentration and underlying insulin resistance. Insulin resistance is a key pathologic defect that is characteristic feature of type 2 diabetes [DeFronzo, 2009]. The liver, muscle and adipose tissue are severely resistant to the action of insulin. The current type 2 diabetes disease model supports more aggressive treatment later in the course of disorder and less aggressive treatment in its earlier stages [Stolar, 2010]. Hypoglycemia is a major barrier to care for physicians and their patients with type 2 diabetes. Certain agents prescribed for type 2 diabetes significantly increase the risk of hypoglycemia, whereas others are associated with a lower occurrence of hypoglycemia [DeFronzo, 2010; Kushner, 2011]. Exogenous insulin preparations have all been associated with hypoglycemia. Injected insulin can produce absolute or relative insulin excess largely because of dosing and pharmacokinetics [Briscoe & Davis, 2006; Gabriely & Shamon, 2004]. Oral antidiabetic medications can be a source of iatrogenic hypoglycemia in patients with type 2 diabetes. Sulfonylurea drugs enhance insulin secretion and are associated with hypoglycemia, especially in the elderly [Nathan et al., 2009]. Most reported cases of severe hypoglycemia were in patients taking chlorpropamide or glyburide [Gordon et al., 2009; Nathan et al., 2009]. Sulfonylurea drugs can interact with other agents to cause severe hypoglycemia. For example, the additive or possibly synergistic effects during combined insulin and

sulfonylurea therapy account for an increasing number of such episodes. Metformin monotherapy is usually not associated with hypoglycemia. The frequency of severe hypoglycemia is lower with metformin than with sulfonylureas or insulin [Kushner, 2011; Gabriely & Shamoon, 2004]. Thiazolidinediones, that increase sensitivity of muscle, fat, and liver to endogenous and exogenous insulin, are associated with a low occurrence of hypoglycemia [Kushner, 2011]. However, these drugs, as monotherapy do not increase the risk for hypoglycemia, may cause hypoglycemia when insulin is used concomitantly [Gabriely & Shamoon, 2004]. α -Glucosidase inhibitors slow the rate of polysaccharide digestion in the small intestine, are not associated with hypoglycemia [Nathan et al., 2009]. The incretins and dipeptidyl peptidase-4 (DPP-4) inhibitors increase insulin secretion via a glucose-dependent mechanism. These agents do not increase the risk for hypoglycemia. Nonsulfonylurea insulin secretagogues, such as glinide, stimulate insulin secretion, and are known to increase the risk of hypoglycemia [Kushner, 2011]. Counterregulatory responses to hypoglycemia have been investigated less systematically in type 2 diabetes than in type 1 diabetes [Cryer, 2002; Gerich, 1988; Zammitt & Frier, 2005]. Although various counterregulatory hormone deficiencies have been described in type 2 diabetes, these were mostly mild, and epinephrine secretion was invariably preserved. The studies have shown that counterregulatory hormonal release occurs at higher blood glucose levels than in non-diabetic subjects and patients with type 1 diabetes [Levy et al., 1998; Spyer et al., 2000]. On the other hand, in type 2 diabetes, residual β -cell function largely preserves the first-line defence against hypoglycemia. Consequently, the glucagon response is retained, hypoglycemic risk is limited and further counterregulatory defects are prevented [Veneman et al., 1993].

5.3.2 Frequency

Episodes of severe hypoglycemia are much less frequent in patients with intensively treated type 2 diabetes than with type 1 diabetes [MacLeod et al., 1993]. Obtained results indicate that 8 to 31% of insulin-treated patients with type 2 diabetes report having trouble in correctly identifying hypoglycemic events [Hepburn et al., 1990]. These patients have a nine fold higher risk for severe iatrogenic hypoglycemia than patients with normal hypoglycemic awareness [Bottini et al., 1997]. A study of patients with sulfonylureas and/or metformin observed that 20% of those taking sulfonylureas had experience symptoms of hypoglycemia in the preceding 6 months [Jennings et al., 1989]. Frequency of hypoglycemia in type 2 diabetic patients in dependence on age, mode of therapy, nationality, sex etc. is described in details by Zammitt & Frier [2005]. To note, according to Rodbard and colleagues [Rodbard et al., 2009] "For some patients, the risk of hypoglycemia may warrant specific choices of therapy and reevaluation of therapeutic goals. These patients include those who have a duration of diabetes greater than 15 years and advanced macrovascular disease, hypoglycemia unawareness, limited life expectancy, or other serious comorbidities".

6. References

- Aguilar-Bryan L., & Bryan J. (2008). Neonatal diabetes mellitus. *Endocrine Reviews*, Vol.29, No.3, pp. 265-291, ISSN 0163-769X

- Amiel S.A., Sherwin R.S., Simons D.C. & Tamborlane W.V. (1988). Effect of intensive insulin therapy on glycemic threshold for counterregulatory hormone release. *Diabetes*, Vol.37, No.3, pp. 901-907, ISSN 0012-1797
- Aronoff S.L. (2004). Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectrum*, Vol.17, No.3, pp. 183-189, ISSN 1040-9165
- Aronoff S.L., Berhowitz K., Shreiner B. & Want L. (2004). Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectrum*, Vol.17, No.3, pp. 183-190, ISSN 1040-9165
- Assaf S.Y. & Chung S.H. (1984). Release of endogenous Zn^{2+} from brain tissue during activity. *Nature*, Vol.308, No.5961, pp. 734-736, ISSN 0028-0836
- Atkinson M.A. & Eisenbarth G.S. (2001). Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet*, Vol.358, No.9277, pp. 221-229, ISSN 1040-6736
- Auer R., Hugh J., Cosgrove E. & Curry B. (1989). Neuropathologic findings in three cases of profound hypoglycemia. *Clinical Neuropathology*, Vol.8, No.2, pp. 63-68, ISSN 0722-5091, Kalimo H., Olsson Y. & Siesjo B.K. (1985). The temporal evolution of hypoglycemic brain damage. I. Light- and electro-microscopic findings in the rat cerebral cortex. *Acta Neuropathologica*, Vol.67, No.1-2, pp. 13-24, ISSN 0001-6322
- Auer R.N., Kalimo H., Olsson Y. & Siesjo B.K. (1984). Hypoglycemic brain injury in the rat. Correlation of density of brain damage with EEG isoelectric time: a quantitative study. *Diabetes*, Vol.33, No.1, pp. 1090-1098, ISSN 0012-1797
- Avery M.D. & Rossi M.A. (1994). Gestational diabetes. *Journal of Nurse-Midwifery*, Vol.39, No.2, Suppl., pp. 9S-19S, ISSN 0730-7659
- Bell G.I., Horita S. & Karam J.H. (1984). A polymorphic locus near the insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes*, Vol.33, No.2, pp. 176-183, ISSN 0012-1797
- Ben-Ami H., Nagachandran P., Mendelson A. & Edoute Y. (1999). Drug-induced hypoglycemic coma in 102 diabetic patients. *Archives of Internal Medicine*. Vol.159, No.3, pp. 281-284, ISSN 0003-9926
- Bischof M.G., Mlynarik V., Brehm A. et al. (2004). Brain energy metabolism during hypoglycemia in healthy and type 1 diabetic subjects. *Diabetologia*, Vol.47, No.4, pp. 648-651, ISSN 0012-186X
- Bjorklund A., Adamson U., Andreasson K. et al. (1998). Hormonal counterregulation and subjective symptoms during induced hypoglycemia in insulin-dependent diabetes mellitus patients during and after pregnancy. *Acta Obstetrica et Gynecologica Scandinavica*, Vol.77, No.6, pp. 625-634, ISSN 0001-6349
- Bjornholm M. & Zierath J. (2005). Insulin signal transduction in human skeletal muscle: identifying the defects in type 2 diabetes. *Biochemical Society Transactions*, Vol.33, No.Pt2, pp. 354-357, ISSN 0300-5127
- Black E.E., Wagenmakers A.J., Glatz J.F. et al. (2000). Plasma FFA utilization and fatty acid-binding protein content are diminished in type 2 diabetic muscle. *American Journal of Physiology – Endocrinology and Metabolism*, Vol.279, No.1, pp. E146-E154, ISSN 0193-1849
- Boden G. (1999). Free fatty acids, insulin resistance, and type 2 diabetes mellitus. *Proceedings of the Association of American Physicians*, Vol.111, No.3, pp. 241-248, ISSN 1081-650X
- Bolli G., de Feo P., Compagnucci P. et al. (1983). Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and

- impaired glucagon and epinephrine secretion. *Diabetes*, Vol.32, No.2, pp. 134-141, ISSN 0012-1797
- Bolli G.B., De Feo P., Cosmo S. et al. (1984). A reliable and reproducible test for adequate glucose counterregulation in type 1 diabetes. *Diabetes*, Vol.33, No.8, pp. 732-737, ISSN 0012-1797
- Bottini P., Boschetti E., Pampanelli S. et al. (1997). Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycemia in IDDM: evidence for a nonselective defect. *Diabetes*, Vol.46, No.5, pp. 814-823, ISSN 0012-1797
- Briscoe V.J. & Davis S.N. (2006). Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology, and management. *Clinical Diabetes*, Vol.24, No.3, pp. 115-121, ISSN 0891-8929
- Brun J.F., Fedou C. & Mercier J. (2000). Postprandial reactive hypoglycemia. *Diabetes and Metabolism (Paris)*, Vol.26, No.5, pp.337-351, ISSN 1262-3636
- Butte N.F. (2000). Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *The American Journal of Clinical Nutrition*, Vol.71, 5Suppl, pp. 1256S-1261S
- Carroll M.F., Burge M.R. & Schade D.S. (2003). Severe hypoglycemia in adults. *Reviews in Endocrine and Metabolic Disorders*, Vol.4, No.2, pp. 149-157, ISSN 1389-9155
- Charles M.A., Hofeldt F., Shackelford A. et al. (1981). Comparison of oral glucose tolerance tests and mixed meals in patients with apparent idiopathic postabsorptive hypoglycemia. *Diabetes*, Vol.30, No.6, pp.465-470, ISSN 0012-1797
- Chen L.A. (2010). A literature review of intensive insulin therapy and mortality in critically ill patients. *Clinical Nurse Specialist*, Vol.24, No.2, pp. 80-86, ISSN 0887-6274
- Cheung N.W. (2009). The management of gestational diabetes. *Vascular Health and Risk Management*, Vol.5, pp. 153-164, ISSN 1178-2048
- Concannon P., Gogolin-Ewans K.J., Hinds D.A. et al (1998). A second-generation screen of the human genome for susceptibility to insulin-dependent diabetes mellitus. *Nature Genetics*, Vol.19, No.3, pp. 292-296, ISSN 1061-4036
- Couston D.R., Reese E.A., Sherwin R.S. et al. (1986). A randomized clinical trial of insulin pump vs. intensive conventional therapy in diabetic pregnancies. *Journal of the American Medical Association*, Vol.255, No.5, pp. 631-636, ISSN 0002-9955
- Cox N.J., Wapelhorst B., Morrison V.A. et al. (2001). Seven regions of the genome show evidence of linkage to type 1 diabetes in a consensus analysis of 767 multiplex families. *American Journal of Human Genetics*, Vol.69, No.4, pp. 820-830, ISSN 0002-9297
- Cranston I., Lomas J., Maran A., Macdonald I. & Amiel S.A. (1994). Restoration of hypoglycemia unawareness in patients with long-duration insulin-dependent diabetes mellitus. *The Lancet*, Vol.344, No.8918, pp. 283-287, ISSN 0140-6736
- Cryer P.E. (1992). Glucose homeostasis and hypoglycemia. In: *William's Textbook of Endocrinology*. J.D. Wilson, D.W. Foster (Ed.), 1223-1253, ISBN 0-7216-9514-0, Philadelphia, Pa
- Cryer P. (2001 a). The prevention and correction of hypoglycemia. In: *Handbook of physiology: Section 7, the endocrine system. Vol.II. The endocrine pancreas and regulation of metabolism*. Jefferson L., Cherrington A., Goodman H. (Eds.), 1057-1092, ISBN 0195113268, New York: Oxford University Press
- Cryer P.E. (2001 b). Hypoglycemia risk reduction in type 1 diabetes. *Experimental and Clinical Endocrinology & Diabetes*, Vol.109, Suppl.2, pp. S412-S423, ISSN 0947-7349

- Cryer P.E. (2002). Hypoglycemia: the limiting factor of Type I and Type II diabetes. *Diabetologia*, Vol.45, No.7, pp. 937-948, ISSN 0012-186X
- Cryer P.E. (2004). Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *The New England Journal of Medicine*, Vol.350, No.22, pp. 2272-2279, ISSN 0028-4793
- Cryer P.E. (2005). Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes*, Vol.54, No.12, pp. 3592-3601, ISSN 0012-1797
- Cryer P.E. (2006). Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. *The Journal of Clinical Investigation*, Vol.116, No.6, pp. 1470-1473, ISSN 0021-9738
- Cryer P.E. (2007). Hypoglycemia, functional brain failure, and brain death. *The Journal of Clinical Investigation*, Vol.117, No.4, pp. 868-870, ISSN 0021-9738
- Cryer P. (2008 a). Glucose homeostasis and hypoglycemia. In: *Williams Textbook of Endocrinology* Kronenberg H., Melmed S., Polonsky K. et al (Eds.), 1503-1533, ISBN 978-1-4160-2911-3, Philadelphia: Saunders Elsevier
- Cryer P.E. (2008 b). Hypoglycemia: still the limiting factor in the glycemic management of diabetes. *Endocrine Practice*, Vol.14, No.6, pp. 750-756, ISSN 1530-891X
- Cryer P.E., Axelrod L., Grossman A.B. et al. (2009). Evaluation and management of adult hypoglycemic disorders: and endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, Vol.94, No.3, pp. 709-728, ISSN 0021-972X
- Cryer P.E., Davis S.N. & Shamooh H. (2003). Hypoglycemia in diabetes. *Diabetes Care*, Vol.26, No.6, pp. 1902-1912, ISSN 0149-5992
- Dagogo-Jack S.E., Craft S. & Cryer P.E. (1993). Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. *The Journal of Clinical Investigation*, Vol.91, No.3, pp. 819-828, ISSN 0021-9738
- Davis M.R. & Shamooh H. (1991). Counterregulatory adaptation to recurrent hypoglycemia in normal humans. *Journal of Clinical Endocrinology and Metabolism*, Vol.73, No.5, pp. 995-1001, ISSN 0021-972X
- DeFronzo R.A. (1988). The triumvirate: beta cell, muscle, liver – a conclusion responsible for NIDDM. *Diabetes*, Vol. 37, No.6, pp. 667-684, ISSN 0012-1797
- DeFronzo R.A. (2004). Pathogenesis of type 2 diabetes mellitus. *Medical Clinics of North America*, Vol.88, No.4, pp. 787-835, ISSN 0025-7125
- DeFronzo R.A. (2009). From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus [Banting Lecture]. *Diabetes*, Vol. 58, No.4, pp. 773-795, ISSN 0012-1797
- DeFronzo R.A. (2010). Overview of newer agents: where treatment is going. *The American Journal of Medicine*, Vol.123, No.3A, pp. S38-S48, ISSN 0002-9343
- de Galan B.E., Schouwenberg B.J.J.W., Tack C.J. & Smits P. (2006). Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *The Netherlands Journal of Medicine*, Vol.64, No.8, pp. 269-279, ISSN 0300-2977
- Diaz R., Aparicio J., Mendizábal A., Faus M. et al. (2008). Paraneoplastic hyperinsulinism and secondary hypoglycemia in a patient with advanced colon cancer: A rare association. *World Journal of Gastroenterology*, Vol.14, No.12, pp. 1952-1954. ISSN 1007- 9327
- Doria A., Patti M-E. & Kahn C.R. (2008). The emerging genetic architecture of type 2 diabetes. *Cell Metabolism*, Vol.8, No.3, pp. 186-200, ISSN 1550-4131

- Dorman J.S. & Bunker C.H. (2000). HLA-DQ locus of the human leucocyte antigen complex and type 1 diabetes mellitus: a HUGE review. *Epidemiological Reviews*, Vol.22, No.2, pp. 218-227, ISSN 0193-936X
- Drucker D.J. (2007). The role of gut hormones in glucose homeostasis. *The Journal of Clinical Investigation*, Vol.117, No.1, pp. 24-30, ISSN 0021-9738
- Ecker J.L., Greenberg J.A., Norwitz E.R. et al. (1997). Birth weight as a predictor of brachial plexus injury. *Obstetrics and Gynecology*, Vol.89, No.5Pt1, pp. 643-647, ISSN 0029-7844
- Engelsen B., Westerberg E., Fonnum F. & Wieloch T. (1986). Effect of insulin-induced hypoglycemia on the concentrations of glutamate and related amino acids and energy metabolism in the intact and decorticated rat neostriatum. *Journal of Neurochemistry*, Vol.47, No.5, pp. 1634-1641, ISSN 0022-3042
- Fajans S.S., Bell G.I. & Polonsky K.S. (2001). Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *The New England Journal of Medicine*, Vol.345, No.13, pp. 971-980, ISSN 0028-4793
- Fischer K.F., Lees J.A. & Newman J.H. (1986). Hypoglycemia in hospitalized patients. Causes and outcomes. *The New England Journal of Medicine*, Vol.315, No.20, pp. 1245- 1250, ISSN 0028-4793
- Fisher J.M., Gillen G., Hepburn D.A., Dargie H.J. & Frier B.M. (1990). Cardiac responses to acute insulin-induced hypoglycemia in humans. *American Journal of Physiology. Heart and Circulatory Physiology*, Vol.258, No.6 Pt 2, pp. H1775-H1779, ISSN 0363-6135
- Foster D.W. & Rubenstein A.H. (1998). Hypoglycemia. In: *Harrison's Principles of Internal Medicine* 14th ed. Fauci A.S., Braunwald E., Isselbacher K.J. (Eds.), 2081-2087, ISBN 0-07-020291, New York: McGraw-Hill
- Foulis A.K., Mc Gill M. & Farquharson M.A. (1991). Insulinitis in type 1 (insulin-dependent) diabetes mellitus in man – macrophages, lymphocytes, and interferon-gamma containing cells. *The Journal of Pathology*, Vol.165, No.2, pp. 97-103, ISSN 1096-9896
- Gabriely I. & Shamoon H. (2004). Hypoglycemia in diabetes: common, often unrecognized. *Cleveland Clinic Journal of Medicine*, Vol.71, No.4, pp. 335-347, ISSN 0891-1150
- Garner P. (1995). Type 1 diabetes mellitus and pregnancy. *Lancet*, Vol.346, No.8968, pp. 157-161, ISSN 0140-6736
- Garza H. (2009). Minimizing the risk of hypoglycemia in older adults: a focus on long-term care. *The Consultant Pharmacist*, Vol.24, Suppl.B, pp. 18-24, ISSN 0888-5109
- Gerich J.E. (1988). Glucose counterregulation and its impact on diabetes mellitus. *Diabetes*, Vol.37, No.12, pp. 1608-1617, ISSN 0012-1797
- Gerich J.E. (1993). Control of glycemia. *Baillier's Best Practice and Research in Clinical Endocrinology & Metabolism*, Vol.7, No.3, pp.551-586, ISSN 0145-7217
- Gerich J.E., Langlois M., Noacco C., Karam J.H. & Forsham P.H. (1973). Lack of glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha cell defect. *Science*, Vol.182, No.4108, pp. 171-173, ISSN 0036-8075
- Gilespe K.M. (2006). Type 1 diabetes: pathogenesis and prevention (Review). *Canadian Medical Association Journal*, Vol.175, No.2, pp. 165-170, ISSN 0820-3946
- Gill G.V., Woodward A., Casson J.F. & Weston P.J. (2009). Cardiac arrhythmia and nocturnal hypoglycemia in type 1 diabetes – the “dead in bed” syndrome revisited. *Diabetologia*, Vol.52, No.1, pp. 42-45, ISSN 0012-186X
- Gold A.E., MacLeod K.M. & Frier B.M. (1994). Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. *Diabetes Care*, Vol.17, No.7, pp. 697-703, ISSN 0149-5992

- Gordon M.R., Flockhart D., Zawadzki J.K., Taylor T., Ramey J.N. & Eastman R.C. (1988). Hypoglycemia due to inadvertent dispensing of chlorpropamide. *The American Journal of Medicine*, Vol.85, No.2, pp. 271-272, ISSN 0002-9343
- Guettier J.M. & Gorden P. (2006). Hypoglycemia. *Endocrinology and Metabolism Clinics of North America*, Vol.35, No.4, pp. 753-766, ISSN 0889-8529
- Gustafsson J. (2009). Neonatal energy substrate production. *Indian Journal of Medical Research*, Vol.130, No.5, pp. 618-623, ISSN 0019-5340
- Haller M.J., Atkinson M.A. & Schatz D. (2005) Type 1 Diabetes Mellitus: Etiology, presentation and management. *Pediatric Clinics of North America*, Vol.52, No.6, pp. 1553-1578, ISSN 0031-3955
- Hapo Study Cooperative Research Group. (2008). Hyperglycemia and adverse pregnancy outcomes. *The New England Journal of Medicine*, Vol.358, pp. 1991-2002, ISSN 0028-4793
- Hart S.P. & Frier B.M. (1998). Causes, management and morbidity of acute hypoglycemia in adults requiring hospital admission. *QJM: An International Journal of Medicine*, Vol.91, No.7, pp. 505-510, ISSN 1460-2725
- Hathout E.H., Sharkey J., Racine M. et al. (2000). Diabetic autoimmunity in infants and preschoolers with type 1 diabetes. *Pediatric Diabetes*, Vol.1, No.3, pp. 131-134, ISSN 1399-543X
- Hepburn D.A., Patrick A.W., Brash H.M., Thomson L. & Frier B.M. (1991). Hypoglycemia unawareness in type 1 diabetes: a lower plasma glucose is required to stimulate sympathoadrenal activation. *Diabetic Medicine*, Vol.8, No.10, pp. 934-945, ISSN 1464-5491
- Hepburn D.A., Patrick A.W., Eadington D.W., Ewing D.J. & Frier B.M. (1990). Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. *Diabetic Medicine*, Vol.7, No.8, pp. 711-7117, ISSN 0742-3071
- Hod M., Merlob P., Friedman S. et al. (1991). Gestational diabetes mellitus: A survey of perinatal complications in the 1980s. *Diabetes*, Vol.40, Suppl.2, pp. 74-78, ISSN 0012-1797
- Holleman F., Schmitt H., Rottiers R., Rees A., Symanowski S. & Anderson J.H (1997). Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. The Benelux-UK Insulin Lispro Study Group. *Diabetes Care*, Vol.20, No.12, pp. 1827-1832, ISSN 0149-5992
- Ito T., Otsuki M., Igarashi H. et al. (2010). Epidemiological study of pancreatic diabetes in Japan in 2005: A nationwide study. *Pancreas*, Vol.39, No.6, pp. 829-835, ISSN 0885-3177
- Jayaprasad N., Anees T., Bijin T. & Madhusoodanan S. (2006). Severe hypoglycemia due to poorly differentiated hepatocellular carcinoma. *The Journal of the Association of Physicians of India*, Vol.54, pp. 413-415, ISSN 0004-5772
- Jennings A.M., Wilson R.M. & Ward J.D. (1989). Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care*, Vol.12, No.3, pp. 203-207, ISSN 0149-5992
- Johnson J.D. (2007). Pancreatic beta-cell apoptosis in maturity onset diabetes of the young. *Canadian Journal of Diabetes*, Vol.31, No.1, pp. 67-74, ISSN 1499-2671
- Kar P., Price P., Sawers S., Bhattacharya S., Reznick R.H. & Grossman A.B. (2006). Insulinomas may present with normoglycemia after prolonged fasting but glucose-

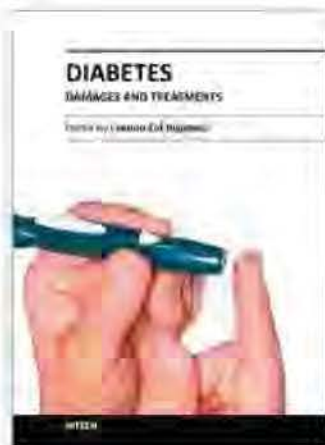
- stimulated hypoglycemia. *The Journal of Clinical Endocrinology and Metabolism*, Vol.91, No.12, pp. 4733-4736, ISSN 0021-972
- Kimmerle R., Heinemann L., Delecki A. et al. (1992). Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care*, Vol.15, No.8, pp. 1034-1037, ISSN 0149-5992
- Koivisto V.A. & Felig P. (1978). Effects of leg exercise on insulin absorption in diabetic patients. *The New England Journal of Medicine*, Vol.298, pp. 79-83, ISSN 0028-4793
- Koukkou E., Watts G.F. & Lowy C. (1996). Serum lipid, lipoprotein and apolipoprotein changes in gestational diabetes mellitus: a cross-sectional and prospective study. *Journal of Clinical Pathology*, Vol.49, pp. 634-637, ISSN 0021-9746
- Kushner P. (2011). Minimizing the risk of hypoglycemia in patients with type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, Vol.3, pp. 49-53, ISSN 1178-7007
- Lacherade J-C, Jacqueminet S. & Preiser J-C. (2009). An overview of hypoglycemia in the critically ill. *Journal of Diabetes Science and Technology*, Vol.3, No.6, pp. 1242-1249, ISSN 1932-2968
- Laitinen T., Lyyra-Laitinen T., Huopio H. et al. (2008). Electrocardiographic alterations during hyperinsulinemic hypoglycemia in healthy subjects. *Annals of Noninvasive Electrocardiology*, Vol.13, No.2, pp. 97-105, ISSN 1082-720X
- Landstedt-Hallin L., Euglund A., Adamson U. & Lins P.E. (1999). Increased QT dispersion during hypoglycemia in patients with type 2 diabetes mellitus. *Journal of Internal Medicine*, Vol.246, No.3, pp. 299-307, ISSN 1365-2796
- Langer O. & Conway D.L. (2000). Level of glycemia and perinatal outcome in pregestational diabetes. *Journal of Maternal-Fetal Medicine*, Vol.9, No.1, pp. 35-41, ISSN 1476-4954
- Langer O. & Mazze R. (1988). The relationship between large-for-gestational age infants and glycemic control in women with gestational diabetes. *American Journal of Obstetrics and Gynecology*, Vol.159, No.6, pp. 1478-1483, ISSN 0002-9378
- Leese G.P., Wang J., Broomhall J. et al. (2003). Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population based study of health service resource use. *Diabetes Care*, Vol.26, No.4, pp. 1176-1180, ISSN 0149-5992
- Levy C.J., Kinsley B.T., Bajaj M. & Simons D.C. (1998). Effect of glycemic control on glucose counterregulation during hypoglycemia in NIDDM. *Diabetes Care*, Vol.21, No.8, pp. 1330-1338, ISSN 0149-5992
- Lin Y. & Sun Z. (2010). Current views on type 2 diabetes. *Journal of Endocrinology*, Vol. 204, pp. 1-11, ISSN 0022-0795
- MacLeod K.M., Hepburn D.A. & Frier B.M. (1993). Frequency and morbidity of severe hypoglycemia in insulin-treated diabetic patients. *Diabetic Medicine*, Vol.10, No.3, pp. 238-245, ISSN 0742-3071
- Majithia A.R. & Florez C.J. (2009). Clinical translation of genetic predictors for type 2 diabetes. *Current Opinion in Endocrinology, Diabetes and Obesity*, Vol.16, No.2, pp. 100-106, ISSN 1072-296X
- Malouf R. & Brust J.C.M. (1985) Hypoglycemia: causes, neurological manifestations, and outcome. *Annals of Neurology*, Vol.17, No.5, pp. 421-430, ISSN 0364-5134
- Maran A., Cranston I., Lomas J., Macdonald I. & Amiel S.A. (1994). Protection by lactate of cerebral function during hypoglycemia (see comments). *The Lancet*, Vol.343, No.8888, pp. 16-20, ISSN 0140-6736

- Martin A.O., Simpson J.L., Ober C. & Freinkel N. (1985). Frequency of diabetes mellitus in mothers of probands with gestational diabetes: possible maternal influence on the predisposition to gestational diabetes. *American Journal of Obstetrics and Gynecology*, Vol.151, No.4, pp. 471-475, ISSN 0002-9378
- Mauvais-Jarvis F. & Kahn C.R. (2000). Understanding the pathogenesis and treatment of insulin resistance and type 2 diabetes mellitus: what can we learn from transgenic and knockout mice? *Diabetes Metabolism (Paris)*, Vol.26, No.6, pp. 433-448, ISSN 0338-1684
- McAulay V, Deary I.J. & Frier B.M. (2001). Symptoms of hypoglycaemia in people with diabetes. *Diabetic Medicine*, Vol.18, No.9, pp. 690-705, ISSN 0742-3071
- McLellan J.A., Barrow B.A., Levy J.C. et al. (1995). Prevalence of diabetes mellitus and impaired glucose tolerance in parents of women with gestational diabetes. *Diabetologia*, Vol. 38, No.6, pp. 693-698, ISSN 0012-186X
- Mengesha Y., Frezghi E. & Gebremichael A. (2007). A neonate with persistent hypoglycemia and seizures. *Journal of the Eritrean Medical Association*, Vo.2, No.1, pp. 35-37, ISSN 1998-6017
- Merimee T.J. & Tyson J.E. (1974). Stabilization of plasma glucose during fasting. Normal variation in two separate studies. *The New England Journal of Medicine*, Vol.291, No.24, pp. 1275-1278, ISSN 0028-4793
- Metzger B.E. (1991). 1920 overview of GDM. Accomplishment of the last decade-challenges for the future. *Diabetes*, Vol.40, Suppl.2, pp. 1-2, ISSN 0012-1797
- Mitchell S.M. & Frayling T.M. (2002). The role of transcription factors in maturity-onset diabetes of the young. *Molecular Genetics and Metabolism*, Vol.77, No.1-2, pp. 35-43, ISSN 1096-7192
- Murad M.H., Coto-Yglesias F., Wang A.T. et al. (2009). Drug-induced hypoglycemia: a systematic review. *The Journal of Clinical Endocrinology and Metabolism*, Vol.94, No.3, pp. 741-745, ISSN 0021-972
- Murphy N.P., Ford-Adams M.E., Ong K.K. et al. (2004). Prolonged cardiac repolarisation during spontaneous nocturnal hypoglycemia in children and adolescent with type 1 diabetes. *Diabetologia*, Vol.47, No.11, pp. 1940-1947, ISSN 0012-186X
- Nathan D.M., Buse J.B., Davidson M.B. et al. (2009). Medical management of hypoglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, Vol.32, No.1, pp. 193-203, ISSN 0149-5992
- Nellgard B. & Wieloch T. (1992). Cerebral protection by AMPA- and NMDA-receptor agonists administered after severe insulin-induced hypoglycemia. *Experimental Brain Research*, Vol.92, pp. 259-266, ISSN 0014-4819
- Neve B., Fernandez-Zapico M.E., Ashkenazi-Katalan V. et al. (2005). Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proceedings of the National Academy of Sciences, USA*, Vol.102, No.13, pp. 4807-4812, ISSN 0027-8424
- Ng C.L. (2010). Hypoglycemia in nondiabetic patients. *Australian Family Physician*, Vol.39, No.6, pp. 399-404, ISSN 0300-8495
- Patockova J., Marhol P, Tumova E. et al. (2003). Oxidative stress in the brain tissue of laboratory mice with acute post insulin hypoglycemia. *Physiological Research*, Vol.52, No.1, pp. 131-135, ISSN 0862-8408

- Peakman M. (2001). Advance in understanding the immunopathology of type 1 diabetes mellitus. *CPD Bulletin of Immunology and Allergy*, Vol.2, No.1, pp. 23-26, ISSN 1367-8949
- Perkins J.M., Dunn J.P. & Jagasia S.M. (2007). Perspectives in gestational diabetes mellitus: a review of screening, diagnosis, and treatment. *Clinical Diabetes*, Vol.25, No.2, pp. 57-62, ISSN 0891-8929
- Perley M.J. & Kipnis D.M. (1967). Plasma insulin response to oral and intravenous glucose studies in normal and diabetic studies. *The Journal of Clinical Investigation*, Vol.46, No.12, pp. 1954-1962, ISSN 0021-9738
- Persson B. & Hanson U. (1998). Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care*, Vol.21, Suppl.2, pp. B79-B84, ISSN 0149-5992
- Phielix E., & Mensink M. (2008). Type 2 diabetes mellitus and skeletal muscle metabolic function. *Physiology & Behavior*, Vol.94, No.2, pp. 252-258, ISSN 0031-9384
- Pickup J. & Keen H. (2002). Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care*, Vol.25, No.3, pp. 593-598, ISSN 0149-5992
- Pieber T.R., Eugene-Jolchine I. & Derobert E. (2000). Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. *Diabetes Care*, Vol.23, No.2, pp. 157-162, ISSN 0149-5992
- Poulsen P., Kyvik K.O., Vaag A. & Beck-Nielsen H. (1999). Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study. *Diabetologia*, Vol.42, No.2, pp. 139-145, ISSN 0012-186X
- Pramming S., Pedersen-Bjergaard U., Heller S.P. et al. Severe hypoglycemia in unselected patients with type 1 diabetes: a cross sectional multicentre survey. *Diabetologia*, Vol.43, Suppl.1, A194, ISSN 0012-186X
- Pugh S.K., Doherty D.A., Maganu E.F., Chauhan S.P., Hill J.B. & Morrison J.C. (2009). Does hypoglycemia following a glucose challenge test identify a high risk pregnancy. *Reproductive Health*, Vol.6, No10, ISSN 1742-4755
- Rabinovitch A. (2000). Autoimmune diabetes mellitus. *Science and Medicine*, Vol.7, No.3, pp. 18-27, ISSN 1087-3309
- Ridderstrale M. & Groop L. (2009). Genetic dissection of type 2 diabetes. *Molecular and Cellular Endocrinology*, Vol.297, No.1-2, pp. 10-17, ISSN 0303-7207
- Risch N. (1987). Assessing the role of HLA-linked and unlinked determinants of disease. *American Journal of Human Genetics*, Vol.40, No.1, pp. 1-14, ISSN 0002-9297
- Robinson A.M. & Williamson D.H. (1980). Physiological roles of ketone bodies as substrate and signals in mammalian tissues. *Physiological Reviews*, Vol.60, No.1, ISSN 0031-9333
- Rodbard H.W., Jellinger P.S., Davidson J.A. et al. (2009). Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: and algorithm for glycemic control. *Endocrine Practice*, Vol.15, No.6, pp. 540-558, ISSN 1530-891X
- Rosenn B., Miodovnik M., Holcberg G., Khoury J.C. & Siddigi T.A. (1995). Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin dependent diabetes mellitus. *Obstetrics and Gynecology*, Vol.85, No.3, pp. 417-422, ISSN 0029-7844
- Rosenstock J., Schwartz S.L., Clark C.M. et al. (2001). Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care*, Vol.24, No.4, pp. 631-636, ISSN 0149-5992

- Rothenbuhler A., Bibal C.P., Le Fur S. & Bougneres P. (2008). Effects of controlled hypoglycemia test on QTc in adolescent with Type 1 diabetes. *Diabetic Medicine*, Vol.25, No.12, pp. 1483-1485, ISSN 0742-3071
- Scollan-Kolippoulos M., Guadagno S. & Walker E. (2006). Gestational diabetes management: guidelines to a healthy pregnancy. *Nurse Practitioner*, Vol.31, No.6, pp. 14-19, ISSN 0361-1817
- Segel S.A., Paramore D.S. & Cryer P.E. (2002). Hypoglycemia-associated autonomic failure and advanced in type 2 diabetes. *Diabetes*, Vol.51, No.3, pp. 724-733, ISSN 0012-1797
- Sepe S.J., Connell F.A., Geiss L.S. et al. (1985). Gestational diabetes: Incidence maternal characteristics and perinatal outcome. *Diabetes*, Vol.34, Suppl.2, pp. 13-16, ISSN 0012-1797
- Service F.J. (1995). Hypoglycemic disorders. *The New England Journal of Medicine*, Vol.332, No.17, pp. 1144-1152, ISSN 0028-4793
- Service F.J. (1999). Classification of hypoglycemic disorders. *Endocrinology and Metabolism Clinics of North America*, Vol.28, No.3, pp. 501-517, ISSN 0889-8529
- Service F.J., McMahan M.M., O'Brien P.C. et al. (1991). Functioning insulinoma: incidence, recurrence, and long-term survival of patients. *Mayo Clinic Proceedings*, Vol.66, No.7, pp. 711-719, ISSN 0025-6196
- Shield J.P. (2000). Neonatal diabetes: new insights into aetiology and implications. *Hormone Research*, Vol.53, Suppl.1, pp. 7-11, ISSN 0301-0163
- Shorr R.I., Ray W.A., Daugherty J.R., Griffin M.R. (1997). Antihypertensives and the risk of serious hypoglycemia in older persons using insulin and sulfonylureas. *Journal of the American Medical Association*, Vol.278, No.1, pp. 40-43, ISSN 0002-9955
- Singh P., Jain A. & Kaur G. (2004). Impact of hypoglycemia and diabetes on CNS: correlation of mitochondrial oxidative stress with DNA damage. *Molecular and Cellular Biochemistry*, Vol.260, No.1-2, pp. 153-159, ISSN 0300-8177
- Spyer G., Hattersley A., Macdonald I.A., Amiel S. & MacLeod K.M. (2000). Hypoglycemic counterregulation at normal blood glucose concentrations in patients with well controlled type 2 diabetes. *The Lancet*, Vol.356, No.9246, pp. 1970-1974, ISSN 1470-2045
- Staiger H., Machicao F., Fritsche A. & Häing H-U. (2009). Pathomechanisms of type 2 diabetes genes. *Endocrine Reviews*, Vol.30, No.6, pp. 557-585, ISSN 0163-769X
- Stanley W.C. & Chandler M.P. (2002). Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart Failure Reviews*, Vol.7, No.2, pp. 115-130, ISSN 1382-4147
- Stolar M. (2010). Glycemic control and complications in type 2 diabetes mellitus. *The American Journal of Medicine*, Vol.123, No.3A, pp. S3-S11, ISSN 0002-9343
- Suh S.W., Gum E.T., Hamby A.M., Chan P.H. & Swanson R.A. (2007). Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADH oxidase. *The Journal of Clinical Investigation*, Vol.117, No.4, pp. 910-918, ISSN 0021-9738
- Swinnen S.G., Dain M.P., Aronson R. et al. (2010). A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*, Vol.33, No.6, pp. 1176-1178, ISSN 0149-5992
- Szablewski L. (2011). *Glucose homeostasis and insulin resistance*, Bentham E-Books, eISBN 978-1-60805-189-2, 2011
- Tattersal R.B. (1974). Mild familial diabetes with dominant inheritance. *Quarterly Journal of Medicine*, Vol.43, No.170, pp. 339-357, ISSN 1460-2725

- Tattersal R.B. & Fajans S.S. (1975). A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes*, Vol.24, No.1, pp. 44-53, ISSN 0012-1797
- The DCCT Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine*, Vol.329, No.14, pp. 977-986, ISSN 0028-4793
- Todd J.A. (1999). From genome to aetiology in a multifactorial disease type-1 diabetes. *BioEssays*, Vol.21, No.2, pp. 164-173, ISSN 0265-9247
- Todd J.A. & Wicker L.S. (2001) Genetic protection from the inflammatory disease type 1 diabetes in humans and animal models. *Immunity*, Vol.15, No.3, pp. 387-395, ISSN 1074-7613
- Towler D.A., Havlin C.E., Craft S. et al. (1993). Mechanisms of awareness of hypoglycemia: perception of neurogenic predominately cholinergic rather than neuroglycopenic symptoms. *Diabetes*, Vol.42, No.12, pp. 1791-1798, ISSN 0012-1787
- Van Staa T., Abenhaim L. & Monette J. (1997). Rates of hypoglycemia in users of sulfonylureas. *Journal of Clinical Epidemiology*, Vol.50, No.6, pp. 735-741, ISSN 0895- 4356
- Veneman T., Mitrakou A., Mokan M., Cryer P. & Gerich J. (1993). Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes*, Vol.42, No.9, pp. 1233-1237, ISSN, 0012-1797
- Veneman T., Mitrakou A., Mokan M., Cryer P. & Gerich J. (1994). Effect of hyperketonemia and hyperlactacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone response during hypoglycemia in normal humans. *Diabetes*, Vol.43, No.11, pp. 1311-1317, ISSN, 0012-1797
- von Muhlendahl K.E. & Herkenhoff H. (1995). Long-term course of neonatal diabetes. *The New England Journal of Medicine*, Vol. 333, No.11, pp. 704-708, ISSN 0028-4793
- Wagaarachchi P.T., Fernand L., Premachadra P. & Fernand D.J.S. (2001). Screening based on risk factors in an Asian population. *Journal of Obstetrics and Gynecology*, Vol.21, No.1, pp. 32-34, ISSN 0144-3615
- Wahren J., Ekberg K., Fernquist-Forbes E. & Nair S. (1999). Brain substrate utilization during acute hypoglycemia. *Diabetologia*, Vol.42, No.7, pp. 812-818, ISSN 0012-186X
- Warram J.H., Krolewski A.S. & Kahn C.R. (1988). Determinants of IDDM and perinatal mortality in children of diabetic mothers. *Diabetes*, Vol.37, No.10, pp. 1328-1334, ISSN 0012-1797
- Watanabe R.M., Black M.H., Xiang A.H., Allayee H., Lawrance J.M. & Buchanan T.A. (2007). Genetics of gestational diabetes mellitus and type 2 diabetes. *Diabetes Care*, Vol.30, Suppl.2, pp. S134-S140, ISSN 0149-5992
- Wender R., Brown A.M., Fern R., Swanson R.A., Farrell K. & Ransom B.R. (2000). Astrocytic glycogen influences axon function and survival during glucose deprivation in central white matter. *The Journal of Neuroscience*, Vol.20, No.18, pp. 6804-6810, ISSN 0270- 6474
- White N.H., Skor D.A., Cryer P.E., Levandoski L.A., Bier D.M. & Santiago J.V. (1983). Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *The New England Journal of Medicine*, Vol. 308, No.9, pp. 485-491, ISSN 0028-4793
- Zammitt N.N. & Frier B.M. (2005). Hypoglycemia in type 2 diabetes. Pathophysiology, frequency and effects of different treatment modalities. *Diabetes Care*, Vol.28, No.12, pp. 2948-2961, ISSN 0149-5992



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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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