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CLASSIFICATION OF FASTING NORMOGLYCEMIA BASED ON REGULATORY, PSYCHOPHYSIOLOGICAL AND CLINIC-BIOCHEMICAL APPROACHES

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Abstract

Objective. To propose a new classification of capillary blood glucose level of a healthy adult on fasting with justification of the threshold values of normoglycemia levels on the basis of three approaches: regulatory, psychophysiological and clinical-biochemical.

Methods. Analysis of scientific data from the literature of international databases and the results of our own research in four areas: metabolism of glucose in the body and its level in the blood on fasting and after eating; glucose as a regulated and regulating indicator of homeostasis; relationship between the level of glycemia and the state of functional activity of the organism; level of glycemia as a predictor and / or an indicator of hyper- and hypo-glycemic conditions and / or diseases.

Results. Based on the three proposed approaches, the scientific data and the results of our own research have been analyzed for the relationship between blood glucose and indicators: mental capacity of the individual (psychophysiological approach to the development of a new classification); secretion of basic glucose-regulating hormones (regulatory approach - level of glycemia as a regulating factor for endocrine glands, liver, kidneys, nervous system). In the analysis of scientific data, clinical data on the levels of glycemia (clinical and biochemical approach) as predictors or indicators of hyper- or hypoglycemic conditions or diseases (including diabetes, neuroglycopenia, hyper- or hypoglycemic coma) are also taken into account.

Conclusion. A new, refined classification of normoglycemia in healthy adult was developed and proposed for examination at rest and functional activity: low (3.33-3.84 mmol / l and 3.33-4.44 mmol / l, respectively), optimal (3.85-4.44 mmol / l and 4.45-6.10 mmol / l), elevated (4.45-5.10 mmol / l, for rest only) and high (5.11-5.55 mmol / l and 6.11-6.67 mmol / l) normoglycemia. The substantiation of the classification of normoglycemia with regard to the physiological and biochemical mechanisms of its regulation as well as clinically significant risks of the onset of diabetes mellitus and hypoglycemic conditions is given.

Keywords: glucose, normoglycemia, classification, hormones, mental work

КЛАССИФИКАЦИЯ НОРМОГЛИКЕМИИ НАТОЩАК НА ОСНОВЕ РЕГУЛЯТОРНОГО, ПСИХОФИЗИОЛОГИЧЕСКОГО И КЛИНИКО-БИОХИМИЧЕСКОГО ПОДХОДОВ

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Резюме

Цель. Предложить новую классификацию содержания глюкозы в капиллярной крови здорового взрослого человека натощак с обоснованием пороговых значений уровней нормогликемии на основе трех подходов: регуляторного, психофизиологического и клинико-биохимического.

Методика. Анализ научных данных из литературных источников международных баз и результаты собственных исследований по четырём направлениям: обмен глюкозы в организме и её содержание в крови натощак и после приёма пищи; глюкоза как регулируемый и регулирующий показатель гомеостаза; взаимосвязь между уровнем гликемии и состоянием функциональной активности организма; уровень гликемии как предиктор и/или показатель гипер- и гипо-гликемических состояний и/или заболеваний.

Результаты. На основе трех предлагаемых подходов проанализированы научные данные и результаты собственных исследований на предмет взаимосвязей между содержанием глюкозы в крови и показателями: умственной работоспособности индивидуума (психофизиологический подход к разработке новой классификации); секреции основных глюкозорегулирующих гормонов (регуляторный подход – уровень гликемии как регулирующий фактор для эндокринных желез, работы печени, почек, нервной системы). При анализе научных данных учтены также клинические данные о уровнях гликемии (клинико-биохимический подход) как предикторах или показателях гипер- или гипогликемических состояний или заболеваний (в том числе сахарного диабета, нейрогликопении, гипер- или гипогликемической комы).

Заключение. Разработана и предлагается к рассмотрению новая, уточнённая классификация нормогликемии у здоровых взрослых людей натощак в покое и при функциональной активности: низкая (3,33-3,84 ммоль/л и 3,33-4,44 ммоль/л соответственно), оптимальная (3,85-4,44 ммоль/л и 4,45-6,10 ммоль/л), повышенная (4,45-5,10 ммоль/л, только для покоя) и высокая (5,11-5,55 ммоль/л и 6,11-6,67 ммоль/л) нормогликемия. Приведено обоснование классификации нормогликемии с учётом физиологических и биохимических механизмов её регуляции, а также клинически значимых рисков возникновения сахарного диабета и гипогликемических состояний.

Ключевые слова: глюкоза, уровни нормогликемии, классификация, гормоны, умственная работа

Introduction

Fasting normoglycemia is defined as the normal level of glucose in the blood, providing energy and plastic maintenance for body cells (primarily nervous tissue, etc.) at 8 h / (and more) after eating, at rest and / or functional activity, and also which is a predictor and / or an indicator of pathological conditions or diseases.

The importance of the concept of "normoglycemia" is due to a number of factors: 1) the greatest contribution of carbohydrates (glucose) to the energy supply for the vital activity of the organism (it makes up at least 50-60% in the daily energy production [9, 13, 18, 22]); 2) the leading role of glucose as a source of energy in the nutrition of cells of the nervous tissue, the medullary substance of the kidneys, erythrocytes and ensuring that these cells fulfill their functions [9, 10, 18, 21, 22, 29-30]; 3) the need for constant monitoring of the level of glycemia, when blood glucose is both a regulated parameter from the side of the nervous and endocrine systems, and a regulating factor of the functional and secretory activity of these systems [4, 8-10, 20, 22, 25, 37] ; 4) high rate of exchange of glucose and its metabolites between blood and tissues [10, 13, 22]. Thus, the daily intake of glucose, obtained from carbohydrates as a result of the hydrolysis of polysaccharides in the intestine or by converting other absorbed monosaccharides in the liver, averages about 250-400 g or 60-70% of the total mass of incoming organic substances. This amount of glucose gradually enters the bloodstream and further into the tissue. For a day, all blood glucose is completely renewed 50-80 times (with its average amount constituting 1 g/l or 5 g in all blood). Provided that the glucose enters the bloodstream uniformly and is distributed into the tissues, the rate of its exchange will be 174-278 mg/min or 3.48-5.56% of its content throughout the blood; 6) the fact that changes in the levels of glycemia is an important predictor or indicator of a number of diseases, primarily diabetes mellitus, hyper- or hypoglycemic coma caused by various causes [3, 6, 8, 13, 17, 20, 24, 27, 36-38].

The purpose of this analysis of the scientific data and the results of our own 10-year studies was to develop a new classification of glucose in the capillary blood of a healthy adult person on an empty stomach with the rationale for threshold values of normoglycemia levels based on three approaches: regulatory, psychophysiological and clinical-biochemical.

Methods

Analysis of scientific data from the literature sources of international databases "Scopus", "MedLine", "Thomas Reuters" and the results of our own research in four areas: metabolism of glucose in the body (its system balance or pathways and mechanisms of its entry and removal in the blood) and after eating food in conditions of rest and functional activity; glucose as an adjustable (from the endocrine system and autonomic nervous system) and regulating (the synthesis and secretion of hormones, the activity of enzymes and the work of internal organs) the index of homeostasis; the relationship between the level of glycemia and the state of functional activity (working capacity) of the body; the level of glycemia as a predictor and / or indicator of diabetes mellitus and / or hypoglycemic conditions.

Results and Discussion

Under normal conditions, the amount of glucose supplied to and from the systemic bloodstream is matched to one another and regulated by both this monosaccharide and a number of hormones and neurotransmitters [9, 10, 13, 22]. The latter can lower the blood glucose (insulin, insulin-like growth factors, acetylcholine - regulatory effect) and increase its level (glucagon, adrenaline, norepinephrine, etc. – counter-regulatory effect).

The flow of glucose into the bloodstream is possible from exogenous sources (with food) and through endogenous synthesis in the liver, kidneys and intestines (table 1). The outflow of glucose from the blood to the tissues is related to its continuous utilization by the cells of the nervous system (60-70%), the renal medulla (10%) and erythrocytes (about 10%) and variable utilization by other cells (muscle, fat, hepatocytes, etc.). By matching between the intake of glucose into the bloodstream and its outflow into the tissue, the systemic balance of glucose is maintained in order to prevent primarily hypoglycemia (to a lesser degree of hyperglycemia) and to ensure a continuous supply of glucose to the brain.

Table 1. Systemic balance of glucose in fasting [10, 13, 18, 22]

Entry of glucose into the bloodstream	Disappearance of glucose from the bloodstream
Endogenous synthesis of glucose: glycogenolysis in the liver [1, 3, 4] ; gluconeogenesis: in liver [1, 3-5], in kidneys [1, 4], in intestine [1, 3, 4]	Continuous utilization of glucose: the brain (60%), renal medulla (10%) and red blood cells (10%) + Variable utilization by tissues (muscle, fat, etc.)[2, 6]

N/B: processes are regulated by hormones: 1 - ↓ insulin; 2 - ↑ insulin; 3 - ↑ glucagon; 4 - ↑ adrenaline; 5 - ↑ cortisol; 6 - ↓ cortisol

Expressed hyperglycemia in a healthy person usually occurs within 30-90 minutes after eating, especially meal rich in carbohydrates [10, 13, 22]. It is due to the high rate of entrance of exogenous glucose into the bloodstream and depends on the bioavailability of glucose in food, the rate of digestion of polysaccharides and the absorption of products of their hydrolysis in the intestine. When the exogenous glucose is absorbed, its endogenous production is inhibited, and the rate of utilization in the liver and muscles (glycolysis and glycogenesis), fatty tissue (glycolysis and lipogenesis) increases [18, 22]. This process is triggered by glucose itself due to metabolic regulation (activation of glucokinase first in pancreatic β cells and insulin secretion, then in hepatocytes and synthesis of glycogen in them), and maintained by the activity of the parasympathetic nervous system and is significantly enhanced by insulin; so the regulatory effect of glucose, acetylcholine and insulin on the level of glycemia is realized. If the level of glycemia exceeds the threshold of 8-10 mmol/l, glucose may appear briefly in significant amounts in the terminal urine [10, 22]. As a result of all the above processes, the content of glucose in the blood returns to its normal content.

Fasting is a condition associated with the use of endogenous sources of energy and nutrients. It can be caused by the lack of food intake for 6 hours or more and / or the active state of a person (work activity and the sharply increased energy demands of the body). In a healthy adult, after 8-10 hours of nocturnal fasting (the so-called "physiological postabsorptive state"), the glycemia level averages about 5 mmol / l with its fluctuations from 3.3 to 6.0 mmol/l [10, 22]. In the conditions of physiological fasting (8-10 hours to 16 hours after eating), the rate of synthesis of endogenous glucose and its use by tissues is approximately the same [10, 18, 22] and averages about 2.2±0.4 mg/kg/min (154±28 mg/min for a person weighing 70 kg). For infants, this value is 3 times higher, partly due to the greater weight of the brain. The only source of glucose in the blood during starvation (table 1) is its endogenous formation due to two processes: glycogenolysis in the liver and gluconeogenesis, primarily in hepatocytes and to a lesser extent

in cells of the kidneys and small intestine. In the liver, the reserves of glycogen that can be mobilized into the bloodstream are not large and amount to about 70 g (25-150 g) on average, which can maintain a sufficient level of glycemia for no more than 8 hours under physiological postabsorption conditions [10, 22]. With a longer starvation, the role of glycogenolysis in maintaining glycemia decreases, and gluconeogenesis constantly increases [9, 15]. In the conditions of functional activity (labor activity), the need for glucose from the working organs (brain, spinal cord, skeletal and cardiac muscles) increases significantly in comparison with the postabsorptive state at rest [9, 18, 22, 29-30]. Accordingly, the duration of the contribution of glycogenolysis is significantly shortened and the role of gluconeogenesis in maintaining the proper level of glycemia increases, and also increases in comparison with similar indices of blood glucose at rest. Preservation of the proper level of glycemia in conditions of dormancy during fasting and / or with functional activity is provided by counter-regulating influences of glucose itself (a decrease in its content inhibits the formation of glycogen in the liver, insulin secretion, and stimulates the release of counter-regulating hormones), inhibition of insulin secretion, increased activity of the sympathetic nervous system and the concentration of a number of hormones (glucagon, adrenaline, cortisol, somatotropin).

The normal level of glycemia is regulated by a variety of factors [9, 10, 13, 18, 22, 32-34]: metabolic (glucose itself and other metabolites / fatty acids, ketone bodies, amino acids /, and their transporters in cell membranes), hormonal (hormones of the pancreas, adrenal glands, pituitary gland, hypothalamus and their receptors) and nerve (receptor sensitivity and activity of the corresponding nerve centers in the organization of behavioral activity and the autonomic nervous system).

Glucose can act as a regulatory factor (with an increase in its content in the blood) and counter-regulating (with a decrease in its content) factor in the regulation of the level of glycemia (see above). Important in this regulation is not only the level of glycemia (to trigger the activity of certain sensors), but also the state of glucose transporters in cell membranes [1, 2, 5, 10, 13, 15, 22], some of which are considered as glucose sensors. Their throughput is associated with the activity of intracellular enzymes (e.g., glucokinase) and signaling pathways involving AMPK (adenosine / AMP / activated protein kinase whose β-subunit is sensitive to glycogen levels in muscle and glial cells [19]), PASK enzymes required for glucose-stimulated transcription of the insulin gene [11, 14]), hexosamine (which may be a factor in the modification of intracellular proteins, preventing the possibility of oncogenes to induce tumorigenesis [12], as well as general precursor of the synthesis of many amino acids [16]), among others.

Glucose is a hydrophilic molecule, so it cannot passively diffuse through the bilipid membrane into the cell [2, 34]. It is transferred through the membrane into the cell or from the cell with the participation of the transporter protein (glucose transporter) or through the mechanism by exocytosis.

There are 2 main groups of glucose carriers. The first group of glucose transport proteins is sodium-dependent carriers. There are 6 types of these glucose transporters (table 2).

Table 2. Characteristics of sodium-dependent protein-glucose transporters [4-7, 9, 10, 13, 20, 22, 32-34]

Transporter	Gene / locus in chromosome	Localization of the transporter in the cells of organs, its functions
SGLT-1	SLC5A1 / 22q13.1	Intestine, kidney, trachea, heart, ovaries, prostate; cotransport sodium (2 molecules): glucose (1 molecule) or galactose (1 molecule): water (260 molecules)
SGLT-2	SLC5A2 / 16p11.2	Kidneys, brain, liver, thyroid, heart, skeletal muscles; cotransport sodium (1 molecule): glucose (1 molecule)
SGLT-3	SLC5A4 / 22p12	Intestine, lungs, uterus, brain, thyroid gland, testes; glucose sensor
SGLT-4	SLC5A9 / 1p32	Intestine, kidneys, lungs, liver, uterus, pancreas; transporter of sodium with glucose, fructose or mannose
SGLT-5	SLC5A10 / 17p11.2	Kidneys, intestines, liver, skeletal muscles; cotransport sodium with glucose or galactose
SGLT-6	SLC5A11 / 16p12-p11	Kidneys, intestines, brain and spinal cord: cotransport sodium with glucose, myoinositol, chiroinositol or xylose

N/B: Sodium-dependent glucose transporter types 1-6 (SGLT-1-6) belong to the family of co-transporters, which has at least 220 members (the corresponding carrier proteins transport myo-inositol, lipoate, pantothenate, choline, lactate, pyruvate, mannose, nicotinate, short chain fatty acids and a number of other substances in cells of different organs, including the brain, mammary glands, large intestine, esophagus, heart, kidneys, liver, lungs, skeletal muscles etc.). They are encoded by the corresponding genes (SLC5A - Solute Carrier Type 5A). SGLT uses the electrochemical energy generated by the operation of the Na + / K + pump, for transporting glucose against the concentration gradient

The most studied of sodium-dependent glucose transporters are SGLT-1 and SGLT-2 [4, 5, 7, 33, 34]. SGLT-1 is located on the apical membrane of intestinal epithelial cells or proximal tubules in the kidneys and provides joint transport of sodium, glucose and water (from the lumen of the intestine or tubule) to the interior (table 2). Its contribution to the absorption of glucose through the apical membrane of enterocytes in the intestine is integral, and to reabsorption of glucose in the kidneys does not exceed 10% (2-10%). The main contribution (90-98%) to the reabsorption of filtered glucose (and this is approximately 144 g/day) in the kidneys is due to another carrier – SGLT-2 [4, 35]. The invented inhibitors of this glucose transporter (SGLT-2) have been used as agents that reduce glycemia and body weight in patients with type 2 diabetes mellitus, and can be used also to correct high blood pressure, acting as osmotic diuretics [6, 7].

The second group of glucose carriers of the GLUT family (GLUcose-Transporter) uses mainly the mechanism of facilitated diffusion for the transport of hexoses (primarily glucose) and other small molecules (myoinositol, urates, etc.) through the cell membrane, often in both directions in and out of cells). Currently, 14 species of these GLUT-1-GLUT-14 carriers are known (table 3).

Table 3. Characteristics of glucose transport-proteins of the family "GLUT" [1, 2, 9, 10, 13, 15, 20, 22, 26, 34]

Transporter	Gene / locus in chromosome	Localization of the transporter in the cells of organs, its functions
GLUT-1	SLC2A1 / 1p35-31.3	In many organs (especially a lot in erythrocytes and the brain), its synthesis is partially controlled by insulin. In addition to glucose, through it diffuse fructose, galactose, and mannose.
GLUT-2	SLC2A2 / 3q26.2-27; 3q26-1-q26.2	Liver, pancreatic β-cells, hypothalamus, small intestine; two-way transport of glucose, galactose, fructose, mannose into cells and from cells; a glucose sensor conjugated with glucokinase activity and intracellular signaling pathways
GLUT-3	SLC2A3 / 12p13.3	In many organs (especially in neurons and astrocytes). In addition to glucose, small amounts of maltose, xylose, mannose, galactose, dihydroascorbic acid
GLUT-4	SLC2A4 / 17p13	High expression in skeletal and cardiac muscles, adipose tissue, endothelium, endometrium, monocytes; ensures the absorption of 50% of all glucose by the cells, is controlled by insulin, except for glucose transports dehydroascorbic acid and glucosamine.
GLUT-5	SLC2A5 / 1p36.2	Kidneys, adipose tissue, skeletal muscles. It transports more than 90% of fructose. In the intestine can work as a sodium-dependent glucose transporter
GLUT-6	SLC2A6 / 9q34	Apical membranes of intestinal and renal cells; is present in the membranes of cells of the brain and spinal cord, spleen, and leukocytes. Carry out the transport of sodium with glucose
GLUT-7	SLC2A7 / 1p36.2	Extracellular and intracellular (membrane of endoplasmic reticulum) fructose and glucose transporter in the cells of the intestine, prostate and testes
GLUT-8	SLC2A8 / 9	Intracellular transporter of glucose in lysosomes, endosomes, endoplasmic reticulum in the cells of many organs and tissues (intestines, skeletal muscles, heart, etc.). Extracellular insulin-dependent glucose transporter in neurons.
GLUT-9	SLC2A9 / 4p15.3-16	Kidneys, adrenals, liver, intestines, lungs, placenta. The main conveyor of urate, also transports fructose and glucose
GLUT-10	SLC2A10 / 20q12-13.1	Kidneys, brain, fat and muscle tissues, lungs and airways. It transportsthe proton with glucose, galactose, myoinositol. It plays an important role in the removal of glucose from airways and alveoli, which prevents the growth of microorganisms in them.
GLUT-11	SLC2A11 / 22q11.2	Isoform A is present in skeletal muscle, kidney and heart, isoforms B and C in fat and muscle tissues, placenta. It transports glucose and fructose.
GLUT-12	SLC2A12 / 6q23.2	Fat and muscle tissues, chondrocytes, etc. It transports proton and glucose.
GLUT-13	SLC2A13 / 12q12	Brain, white adipose tissue. The proton is co-transported with myoinositol, less often with glucose. It is the leading pathway of transport of myoinositol to neurons and astrocytes.
GLUT-14	SLC2A14 / 12p13.3	Is present in the ovaries, present in the brain. It transports glucose.

Hormones are the most important glucose-regulating factors, the secretion of most of which is regulated by glucose itself.

Insulin is the main hormone that lowers blood glucose levels by stimulating its absorption, increasing its redundancy in the form of glycogen, increasing its utilization [10, 18, 22]. Insulin, through its receptors in muscle, fat and a number of other cells, increases the number of glucose transport proteins (primarily GLUT-4 and fewer GLUT-1 and GLUT-8) in the cell membrane (Table 3), which enhances glucose transport in these cells from blood (as well as the transport of glucose to intracellular organelles), in hepatocytes and myocytes increase glycogenesis, inhibit the breakdown of glycogen and the formation of glucose from other organic substances (gluconeogenesis) in the liver. Insulin reduces the production of glucose by the liver and kidneys, inhibiting the activity of gluconeogenesis enzymes. As a result, the concentration of glucose in the blood under the influence of insulin decreases (the regulatory action of insulin). At the same time, a decrease in insulin in a healthy body is accompanied by an increase in the production of glucose in the liver and kidneys, a decrease in the utilization of glucose by insulin-dependent tissues, which leads to an increase in glycemia (insulin counter-regulatory action). Increased insulin secretion is an important mechanism (factor) of protection against hyperglycemia, and inhibition of secretion is the first factor of protection from hypoglycemia [10]. Insulin is a powerful and critical hormone, a substantial deficit or a pronounced excess of which can be fatal to the body. The main regulator of insulin secretion is glucose entering the pancreatic β cells from the blood. The glycemic threshold (table 4), at which insulin secretion ceases (with a decrease in the glucose level in the blood) or glucose-dependent insulin secretion is activated (with the rise of glycemia), was taken as 4.45 mmol/l (4.4-4.7 mmol/l). Parasympathetic effects increase secretion of insulin, gastrin, secretin, glucose-dependent insulinotropic peptide (GIP, enterogastron), glucagon-like peptide (GLP-1, enteroglucagon), some amino acids (arginine, leucine). Insulin secretion is inhibited by sympathetic effects (norepinephrine via α-adrenoreceptors), hormones of the adrenal medulla and some other glands.

Glucagon, adrenaline, cortisol and somatotropin are insulin antagonists and increase blood glucose levels [10, 18, 22]. Glucagon maintains a normal concentration of glucose in the blood between meals to ensure a constant supply of energy to brain cells, erythrocytes, etc. It is believed that the hormone acts primarily on hepatocytes, stimulating the processes of glycogenolysis and gluconeogenesis. In the cells, formation of glucose increases, and it enters the blood. Glucagon-induced hyperglycemia is short-lived because of increased secretion of insulin with it. The secretion of glucagon is stimulated by amino acids (especially, alanine and arginine, which are formed from cleavage of proteins) that are absorbed after eating; hypoglycaemia (a decrease in the level of glycemia less than 3.6-3.9 mmol/l), for example, due to fasting or prolonged physical and / or mental stress; sympathetic influences. In condition of hyperglycemia, secretion of glucagon is inhibited under the influence of somatostatin.

The mechanism of hyperglycemic action of adrenaline - the hormone of adrenal medulla is more complex; The resulting increase in blood glucose is persistent and prolonged. The activation of the active secretion of the hormone into the blood is stimulated by the sympathetic nervous system, for example, activation of the sympathetic adrenal system under stress, or with a decrease in blood glucose content of less than 3.6-3.9 mmol/l against fasting or high mental and physical exertion. Adrenaline through β2-adrenoreceptors increases glycogenolysis and gluconeogenesis in the liver, and also mobilizes precursors of gluconeogenesis in lipocytes (as a result of lipolysis, the formation and release of glycerol and unesterified fatty acids increases) and myocytes (glycolysis and the release of lactate and alanine are stimulated). Adrenaline stimulates the synthesis and secretion of glucagon (via β-adrenoreceptors) and inhibits the release of insulin (via α-adrenoreceptors); it also inhibits the utilization of glucose in insulin-dependent tissues.

Cortisol and somatotropin cause a hyperglycemic effect only a few hours after increasing their concentration in the blood. Cortisol reduces glucose consumption by cells of muscle and fatty tissues, increases the activity of gluconeogenesis in hepatocytes and lipolysis in lipocytes, which causes an increase in the concentration of glucose in blood after 2-3 hours. The growth hormone initially causes a decrease in blood glucose levels due to the release of insulin-like growth factors in hepatocytes and chondrocytes. With more prolonged action, somatotropin limits the consumption of glucose by tissues, promotes the synthesis and secretion of glucagon, and increases the destruction of insulin by hepatocytes due to the activation of insulinase, which is followed by 3-4 hours after the rise in the level of glycemia. Synthesis and secretion of these hormones is regulated by many factors, an important place among which belongs to glucose. Reducing its content in the blood less than 3.5-3.8 mmol/l increases the secretion of cortisol (regardless of the influence of hormones of the pituitary and hypothalamus) and somatotropin (regardless of the effect of somatoliberin or other factors).

A sufficient level of glucose in the blood is vital for the functioning of brain cells and, consequently, for the successful functioning of the whole organism. It is provided by many factors: the consumption of carbohydrates with food, endogenous synthesis of glucose, the rate of its utilization, the action of metabolites, hormones and neurotransmitters. The content of glucose in the blood is constantly monitored for its correction in accordance with the needs of the body. Table 4 presents the threshold values for blood

glucose (glycemic thresholds) at which physiological responses are triggered to prevent or correct hypoglycemia or hyperglycemia.

Table 4. Physiological responses to changes in the concentration of glucose in the blood [10, 13, 18, 21, 22, 28]

Glycemic threshold (limit fluctuations), mmol/l	Physiological reactions and their role in preventing or correcting the development of hyperglycemia and hypoglycemia
3.85-4.44 (3.6-4.7)	basal secretion of the main regulatory (insulin - the first defense against hypoglycemia) and counter-regulating (glucagon, adrenaline, cortisol - the first defense against hyperglycemia) the level of glycemia of hormones
4.45 (4.4-4.7) and ↑	↑ (threshold) of insulin secretion (↑ influx of glucose in tissues, glycogenesis in the liver and muscles, lipogenesis in lipocytes) - the second line of protection against hyperglycemia
6.68 (6.4-6.8) and ↑	direct insulin-independent activation of glucose (threshold) synthesis of glycogen in the liver - the third line of protection against hyperglycemia
10.0 (8.0-11.0) and ↑	the appearance of glucose in the final urine (the threshold of reabsorption of glucose in the kidneys) - the fourth line of protection against hyperglycemia
11.0 (10.0-12.0) and ↑	symptoms of hyperglycemia and diabetes mellitus (increased diuresis, etc.). Treatment of diabetes
15.0-25.0 and ↑	reduction of cognitive abilities, disorders of behavior, threat of death
3.84 (3.6-3.9) and ↓	↑ (threshold) of glucagon secretion (↑ speed of glucose synthesis in the liver through stimulation of glycogenolysis and gluconeogenesis) - second line defense against hypoglycemia (short-term)
3.84 (3.6-3.9) and ↓	↑ (threshold) of adrenaline secretion (↑ rate of glucose synthesis in the liver, ↑ formation of substrates for gluconeogenesis) - the third line of protection against hypoglycemia (long-term, persistent)
3.60 (3.5-3.8) and ↓	↑ (threshold) of the secretion of cortisol and somatotropin (complex mechanism, uncritical)
3.00 (2.9-3.1) and ↓	symptoms of hypoglycemia (headache, etc.) leading to food intake (↑ intake of exogenous glucose) - the fourth line of protection against hypoglycemia (rapid behavioral protection)
2.80 (1.5-3.0) and ↓	reduction of cognitive abilities, disorders of behavioral protection, the threat of death

It should be noted that there is currently a wide range of values on threshold values of normal blood glucose and, accordingly, the boundaries of hyper- and hypoglycemia, as well as the limits of glycemia values with an increased risk of these conditions. So, for example, the modern criteria for fasting normoglycemia, adopted in endocrinology, is 3.3-5.5 mmol/l for whole venous and capillary blood [3, 8, 10, 20, 24, 27, 36, 37]. At the same time, in a number of works, researchers provide convincing evidence that the fasting glycemia level above 5.1 mmol/l can be considered as a predictor of diabetes mellitus [21, 36], and the blood glucose concentration in the range 3.0-3.9 mmol/l suggests the possibility of hypoglycemia [10, 22]. In connection with this, it is now important to develop a classification of normoglycemia similar to how it was done for indicators of normal arterial blood pressure.

Classification of normoglycemia, threshold values of glucose. Three approaches are proposed for the classification of normoglycemia: 1) regulatory (or physiological-biochemical) – the effect of a certain concentration of glucose (biochemical index and, accordingly, biochemical approach to classification) as a regulating factor on the work of the endocrine glands (primarily the pancreas and adrenal glands) other (liver) organs (physiological mechanism and, accordingly, physiological approach to classification) [10, 13, 18, 22]; 2) psychophysiological (mechanism and, accordingly, psychophysiological approach to the classification of normoglycemia) – the relationship between the level of glycemia and the capacity of increase in the number of erroneous actions [13, 21, 28-31,]; 3) Clinical and biochemical - the level of glycemia as a predictor or indicator of hyper- and hypo-glycemic states (under stress, alcohol effects, etc.) and / or endocrine and other diseases or their complications (diabetes, alcoholism, hyper- or hypoglycemic coma and others) [3, 8, 10, 17, 20, 24, 25, 27, 36, 37, 38].

In accordance with these approaches, the following levels of fasting normoglycemia can be distinguished (table 5): low (physiological hypoglycemia); optimal; increased; high (including physiological hyperglycemia on an empty stomach, especially with functional activity).

Table 5. Classification of fasting normoglycemia

Levels of normoglycemia	Содержание глюкозы в цельной капиллярной крови натощак, мМоль/л Glucose content in whole capillary blood on an empty stomach, mmol / l	
	rest	functional load
low (functional hypoglycemia)	3.33-3.84	3.33-4.44
optimal	3.85-4.44	4.45-6.10
elevated	4.45-5.10	
high (functional hyperglycemia)	5.11-5.55	6.11-6.67

The optimal level of fasting normoglycemia is characterized by a minimal release (at the basal level) of the main hormones [10, 13, 18, 22] regulating the exchange of glucose-insulin and its antagonists (glucagon, adrenaline, cortisol, growth hormone) in a state of functional dormancy (Table 5). In the case of blood sampling for research from a worked person or working person (the accredited biochemical laboratories take blood for analysis until 12 noon, i.e., blood sampling is possible for a working person), the parameters of the optimal level of fasting glycemia for functional activity differ from those in the state of functional rest (Table 5). This is due to the fact that in an operating or working organism (up to 1 h after work), it is required to provide adequate energy supply of the nervous system through an increase in the level of glycemia (according to our data, the maximum increase in glucose in the capillary blood is 6.1 mmol/l) by activating the processes of glycogenolysis in the liver and / or gluconeogenesis in the liver, kidneys, intestines with the help of counterinsular hormones, the secretion of which increases. An increase in the level of glycemia above 4.45 mmol/l leads to an increase in the secretion of insulin by β-cells of the pancreas. A sufficient level of glucose with optimal fasting normoglycemia during operation or work (usually within 4.45-6.10 mmol/l) provides adequate energy supply to the nervous tissue and good and / or high working capacity of the human body with a minimum number of erroneous actions [13, 28-31]. According to clinical observations, the risk of developing diabetes mellitus or the appearance of symptoms of hypoglycemic conditions with the optimal level of normoglycemia is absent or minimal [3, 8, 10, 17, 20, 24, 25, 27, 36-38].

Elevated levels of fasting normoglycemia at rest differ from the optimal level only by higher glucose levels (table 5). Physiological and clinical parameters correspond to those at the optimal level of fasting normoglycemia. A high level of normoglycemia is characterized by a high fasting glucose content of more than 5.1 mmol / l at rest (table 5); while the risk of diabetes is elevated. So according to E.A. Zalutsky and T.V. Mokhort (2001) 47.2% of people older than 30 years with this level of fasting glycemia are further diagnosed with type 2 diabetes mellitus. A high level of glycemia can be caused by an increased synthesis of glucose in the liver under the influence of counter-regulating hormones (glucagon, adrenaline and cortisol), the secretion of which is determined by the high tone of the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis of the adrenal gland; this is especially characteristic for periods of functional activity. The lower limit of high fasting glycemia in functional activity was taken as 6.11 mmol/l (table 5), as we observed the maximum increase in glucose during work up to 6.10 mmol/l [21, 28-30], the upper limit was taken for 6.67 mmol/l. This is due to the fact that this level of glucose in the blood is a threshold for the stimulation of glycogen synthesis reactions in the liver (table 4), which contradicts the task of maintaining the level of glycemia to ensure a maintained work of the brain. In our studies, none of the subjects showed an increase in fasting glycemia during prolonged mental work above 6.1 mmol/l [21, 28-30].

Low level of normoglycemia is characterized by low glucose content in the human blood at rest and its insufficient endogenous synthesis during periods of functional load (Table 5). At the same time, the amount of glucose in the blood is such that direct activation of the secretion of not only glucagon (the second line of protection against hypoglycemia [10, 22]) but also stress hormones - adrenaline and cortisol (the third line of protection against hypoglycemia [10, 22]) occurs. At a given level of glucose in the blood, the number of erroneous actions in tasks is significantly increased and the effectiveness of mental activity is reduced [21, 28-30], which will make it possible to observe the state of functional hypoglycemia.

Conclusion

The substantiated classification of levels of normoglycemia based on the analysis of psychophysiological and clinical-biochemical data is given, taking into account physiological and biochemical mechanisms of its regulation, as well as clinically significant risks of the onset of diabetes and hypoglycemic conditions.

For the optimal level of normoglycemia on fasting at rest is proposed to be 3.85-4.44 mmol/l, at which the minimal release of the main hormones of its regulatory, namely, insulin and its antagonists (glucagon, adrenaline, cortisol , growth hormone); and there is either no or minimal risk of developing hyper- or

hypoglycemic conditions. In conditions of working on fasting the parameters of the optimal level of glycemia are proposed to increase to 4.45-6.10 mmol/l. This is due to the need for adequate energy supply to the nervous system.

Elevated levels of fasting normoglycemia differ from the optimal level only by higher glucose levels at rest.

A high level of fasting normoglycemia in a state of functional dormancy is characterized by a glucose content of more than 5.1 mmol/l (5.11-5.55 mmol/l), which is accompanied by an increased risk of diabetes, especially in people over 30 years old.

Low level of normoglycemia is characterized by a low level of glucose in the blood of a person at rest (3.33-3.84 mmol/l) and during a functional load (3.33-4.4 mmol/l). This causes a direct activation of the synthesis and secretion of the counterinsulin hormones glucagon, adrenaline and cortisol, and is accompanied by a significant decrease in efficiency of labor and increased risk of neuroglycopenia or hypoglycemic coma.

The proposed classification of normoglycemia will be useful for diagnosing hyperglycemic and hypoglycemic conditions in a fasting adult with regard to its functional state, as well as for objective biochemical monitoring of the working capacity of the organism.

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