

Model of Diabetes Mellitus Type 2, T2DM

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Abstract

Nutrition and lifestyle have the principal role in etiology of diabetes mellitus type 2. T2DM is a disease that is caused by chronic energy excess that damaged the basic regulation systems. T2DM is not caused by a (relative or absolute) lack of insulin and it is not caused by inborn insulin resistance. The insulin "pseudo-resistance" is present; it is a sign of active intracellular defence. It is therefore temporarily influenceable. T2DM is caused by a collision of basic hormonal systems (insulin, glucagon, GLP1, adiponectin, cortisol, ACTH, epinephrine, amylin and other hormones), and intracellular regulatory system (AMPK and other "intracellular hormones"). The optimal therapy of the early stage of T2DM is probably not insulin administration, but drugs which have an anorectic effect (incretin mimetics, glucagon like peptide-1 analogs), drugs, which diminish the effectivity of metabolism (metformin), bariatric surgery, endobarrier or drugs, that directly remove the glucose (gliflozins). Adequate food intake and physical training have no dangerous side effect.

Keywords: Diabetes mellitus; T2DM; Insulin Resistance; Insulin Pseudo-Resistance

Introduction

Diabetes mellitus is one of the most widespread diseases in developed countries [1]. Diabetes mellitus is a disorder that is characterized by hyperglycemia, high blood sugar. Diabetes mellitus type 1 (T1DM) results from the autoimmune destruction of the insulin-producing beta cells in the pancreas and the subsequent lack of insulin. Diabetes mellitus type 2 (T2DM) is considered to be a metabolic disorder that is characterized by a relative lack of insulin and insulin resistance [2-6].

The most important function of insulin is to regulate the delivery of glucose into cells, to provide them with energy. Congenital hyperinsulinemia is associated with a considerable increase in weight and macrosomia [7,8]. Insulin resistance (IR) is a condition in which cells fail to respond to the actions of insulin. Insulin resistant cells cannot take in glucose. This disorder exists, but it is extremely rare: Donohue syndrome, leprechaunism [9,10]. The cause of the disease is the lack of a fully functional insulin receptor [11,12]. The mutant allele is not as effective as the normal receptor. Insulin-dependent cells starve.

A different situation is in case of the "insulin pseudo-resistance" (I-PR). Diabetes mellitus type 2 with obesity is characterized by excessive filling of cells by energetically rich substances [13]. The patients have intramyocellular lipid stores comparable to stores of endurance athletes [14] but they do not use them. A low energy output leads to the development of regulatory mechanism, which restricts further nutrient (glucose) uptake from blood into cells. Reaven's metabolic syndrome [3] is not a disorder of low energy utilization and storage, but it is a disorder of the lifestyle. Two principal causes of it are overeating and inactivity [15-17]. Abdominal (central) obesity is a sign of a high cell energy intake [18]. New clinical findings, new drugs forced us to find a new model, a different view to etiology and pathogenesis of T2DM.

Metformin and other drugs which influence energy exchange (nutrient exchange)

Metformin is the first-line drug of choice for the treatment of T2DM in obese people today. Primary site of metformin action is probably through direct inhibition of complex 1 of the respiratory chain. The membrane-potential-driven accumulation of this drug within the

mitochondrial matrix is slow and self-limited [19,20]. Limitation of aerobic metabolism is probably the main cure effect of metformin, not only the unwanted effect. Restricted energy income, restricted ATP production and increasing AMP concentration influence basic mechanism which define energetic of the cells, among others also AMP activated protein kinase (AMPK) [21]. Final effect is in increased income of glucose by a cell enabling repeated creation of ATP. This mechanism explains the fact that metformin decreases production of glucose by liver cells and restores glucose consumption by muscle cells from blood, even if they did not sufficiently react to insulin stimulated impulses. The other modern drugs – gliflozins – influence the glucose elimination [22]. They cause blood glucose to be eliminated through the urine. Others new drugs improve the T2DM syndrome such as cannabinoid receptor 1 antagonists or inverse agonists [23,24]. Incretins, which have an anorectic effect or metformin that diminish the effectivity of the metabolism and has an anorectic effect too, could solve the problem of hyperglycaemia in T2DM. Anyway, side effect of these drugs can be dangerous- Metformin-induced lactic acidosis, MILA, can be a lethal disorder. Adequate food intake and physical training have the same beneficial effect; they nevertheless have no dangerous side effect [25,26].

This paper brings a model of energy balance in our body. It describes the extracellular and the intracellular situation. Intracellular starvation is perceived as the most important sign of shortage of insulin. The glycaemia is not considered to be the most important sign of energy transport.

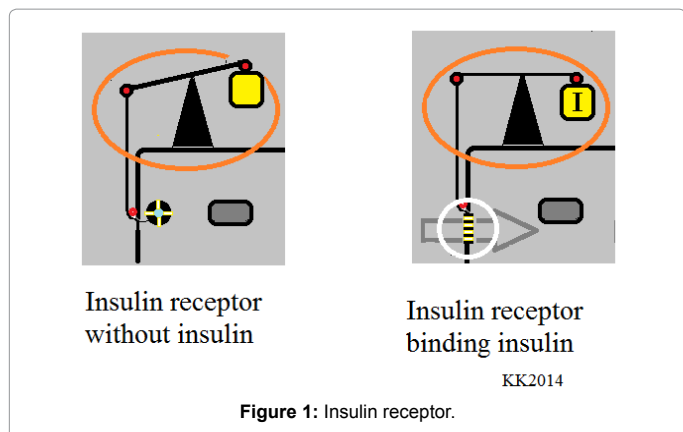
The insulin receptor is a Tran's membrane receptor which is activated by insulin. The receptor is in this picture illustrated as a two-

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pan balance in the red ellipse. Insulin receptor can bind this hormone and after that enables transport of cellular vesicles containing GLUT4 on the outer membrane of cell (white circle) (Figure 1).

Glucose transporter GLUT4 [27] is found in insulin-responsive tissues, in adipose tissue, skeletal and cardiac muscle (striated muscle). It is located intracellularly in the basal state (yellow-black circles in this picture, left). It could be transported from intracellular vesicles to the cell surface, where it can mediate the transport of glucose into the cell (yellow and black stripes in this picture - right) (Figure 2).

Eating, ingestion of food is the first principal step of energy transport. Food enters the mouth, passes through small and large intestine to blood. Transport from blood into a cell is nevertheless not the last step of energy transport. Intracellular metabolism, formation of intracellular energy transporter molecules (adenosine-triphosphate for example) and using them to metabolic reactions (synthesis of macromolecules, transport of ions, exocytosis, endocytosis, and shortening of actin and myosin filament) determine the need of glucose. Locomotion, muscle contraction, physical exercises are the last (most) important step of energy transport in the body (Figure 3).

Insulin receptor (red ellipse) and glucose transporter GLUT4 (white circle) (Figure 4).

The cell has its own regulatory system which determines the energy homeostasis. AMPK, 5' AMP- activated protein kinase is an important enzyme which plays the essential role in cellular energy homeostasis. It regulates the cellular uptake of glucose, regulates the beta-oxidation of fatty acids and the biogenesis of glucose transporter GLUT4. AMPK increases the glucose input in case of a lack of energy, intracellular starvation, high concentration of adenosine mono phosphate (AMP) and low concentration of adenosine triphosphate (ATP) (Figure 5).

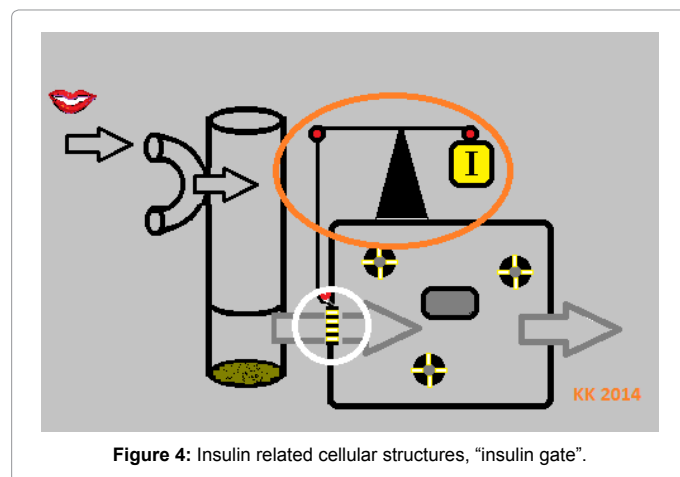
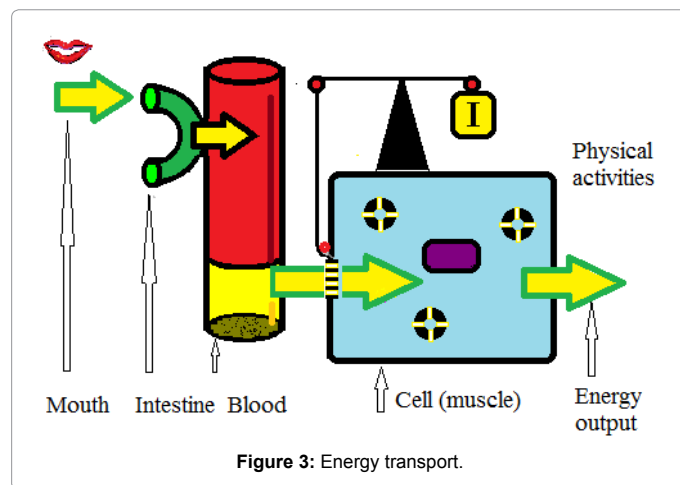
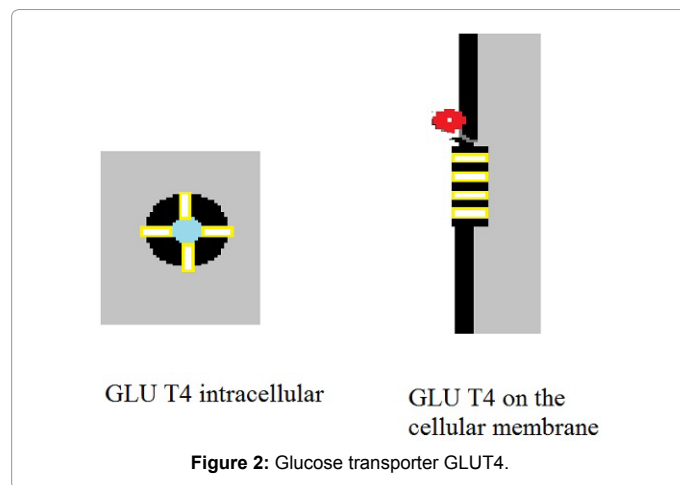
Food intake and energy expenditure are in the optimal correlation, low (red arrows), moderate (yellow arrows, green arrows) or high (violet arrows) (Figure 6).

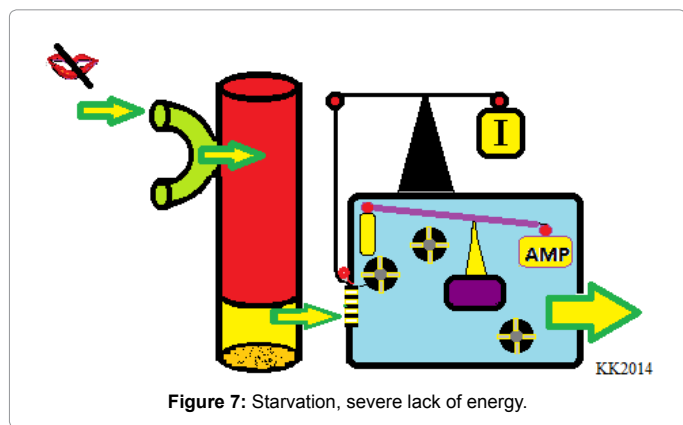
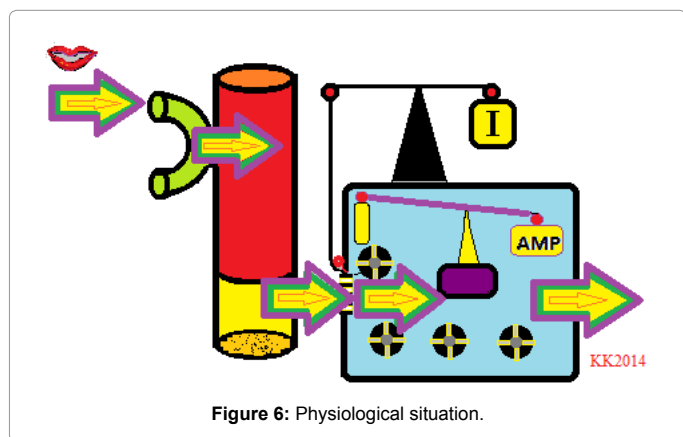
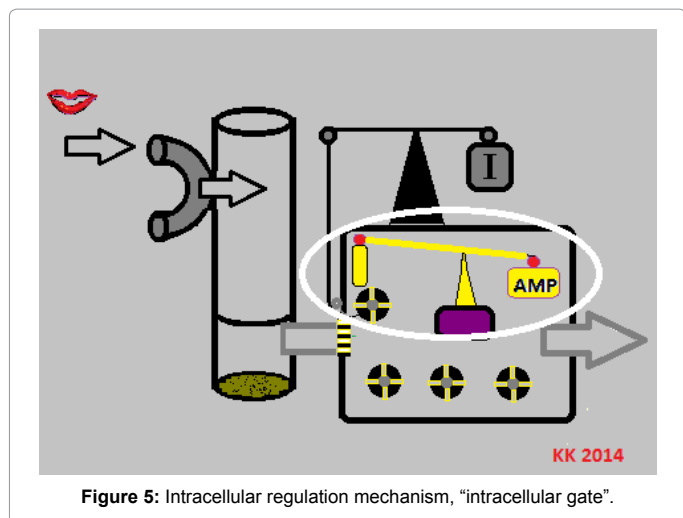
After 12- 24 hour of total starvation hepatic glycogen stores are exhausted and the liver produces ketones (acetoacetate, beta-hydroxybutyrate, acetone) to provide an energy substrate for peripheral tissues. Intracellular "gate system" is open, high level of AMP enables glucose input but the supply of glucose (from gut/liver to blood) is low. Acidosis (ketoacidosis) is a side effect of this alternative hepatic "fuel" production (Figure 7).

Diabetes mellitus type 1 (T1DM) results from the autoimmune destruction of the insulin-producing beta cells in the pancreas and the

subsequent lack of insulin. Insulin gate is closed. The most important symptoms are intracellular starvation, shortage of intracellular ATP, diabetic ketoacidosis. The usual clinical symptoms are polydipsia, polyphagia, hyperglycaemia and a weight loss. Administration of insulin is essential for the survival (Figure 8).

Insulin resistance (IR) is a condition in which cells fail to respond to the actions of the insulin. Insulin resistant cells cannot take in glucose,



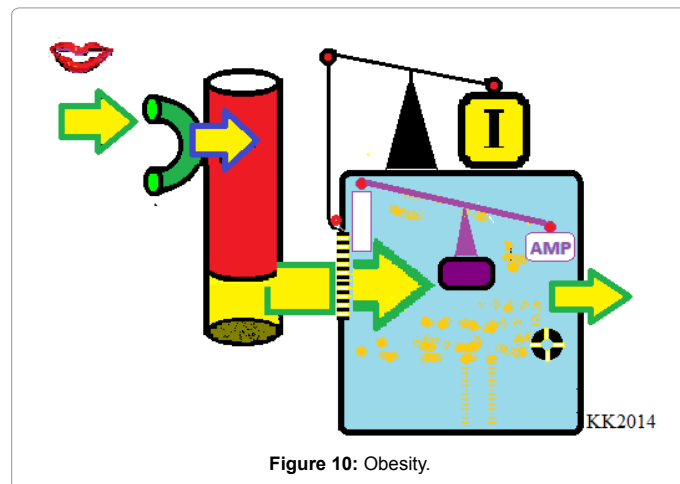
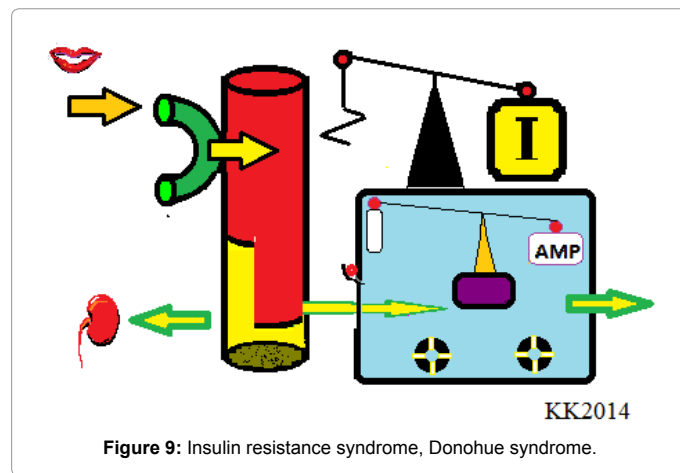
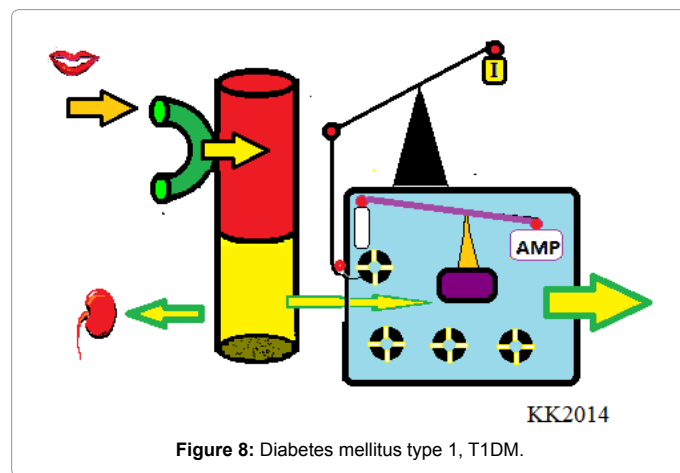


amino acids and fatty acids. The cause of the disease is the lack of a fully functional insulin receptor. The mutant allele is not as effective as the normal receptor. Subcutaneous adipose tissue is markedly diminished, muscle tissue too. Insulin-dependent cells starve. Subcutaneous adipose tissue is markedly diminished, it is not able to "puffer" glucose level, and there is a fluctuating glycaemia. Severe hypoglycemia can occur (Figure 9).

Food intake is long-time high. The Insulin production is high, unlimited (temporarily, for several years). Energy intake, intake of triacylglycerol, glucose and amino acids, is (temporarily) unlimited

too. Energy expenditure is relatively high but not sufficient. The glucose level is "normal" (Figure 10).

Food intake is long-time high. The Insulin production is limited, high but progressively falling. The cell capacity to ingest triacylglycerol, glucose and amino acids is high, but limited, falling too. Energy expenditure is not sufficient, it is relatively low. The glucose level is high and progressively rising. There are no signs of intracellular starvation. The insulin "pseudo-resistance" is present; it is a sign of active



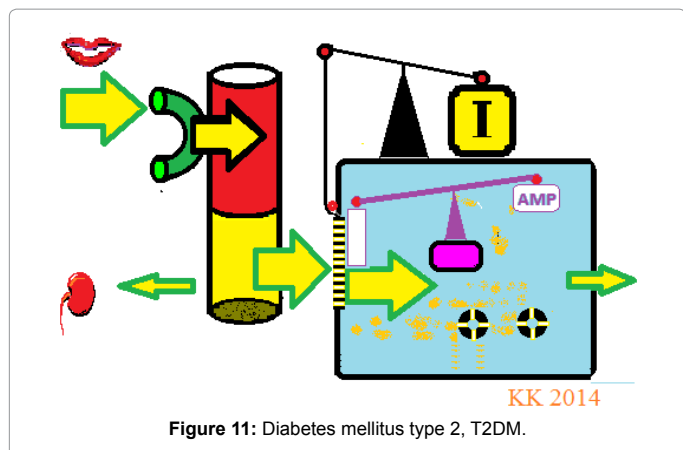


Figure 11: Diabetes mellitus type 2, T2DM.

intracellular defense, not a sign of an inborn disorder. It is nevertheless (temporarily) influenceable [28] (Figure 11).

Food intake is such high and energy expenditure is such low, the cells are such overloaded that intracellular mechanism reduces the glucose intake. Inner gate is significantly “closed”. Glucose intake is still greater than the energy expenditure. The insulin “pseudo-resistance” in obese patients causes a high blood glucose level. Glycosuria occurs. The only possibility of glucose elimination is via the urine. There is no other way how to eliminate glucose out of the body (Figure 12).

Hyperglycemia is the only similarity of T1DM and T2DM (Figure 13).

The plasma insulin concentration is maintained at a constant level by a continuous infusion of insulin. The plasma glucose concentration is sustained at a constant level by a variable glucose infusion. The glucose infusion rate equals glucose uptake by the tissues (Figure 14).

Induction of “comparable” conditions in clamp studies leads to paradoxical results. During relative hypoglycemia and hypo-insulinemia (as compared with “usual” conditions) the tissues of the diabetic patient take up a smaller amount of glucose than tissues of non-diabetic subject (although under “normal”, usual, conditions the glucose uptake is higher). This phenomenon is called “Paradox of insulin resistance” [29] (Figure 15).

Giving high doses of insulin (or sulfonylurea derivatives administration) solves the problem of hyperglycemia. It enables to overwhelm the intracellular defense mechanism. It can cause an extreme obesity. The situation (result of the biochemical blood analysis: normo-glycemia) seems to be optimal. Cardiovascular mortality is nevertheless high [30] (Figure 16).

Normo-glycemia is achieved through a different way: restriction of energy input (overeating). Food intake restriction is achieved by reducing the size of stomach (gastric band, sleeve gastrectomy) and/or by resecting the small intestines (biliopancreatic diversion, gastric bypass). Bariatric surgery can achieve full remission of the T2DM syndrome [31,32] (Figure 17).

Endobarrier is a thin plastic sleeve which lines the first 60 cm of the small intestine, causing food not to be (fully) absorbed (Figure 18).

Gliflozins are the sodium-glucose cotransporter 2 inhibitors. They act blocking reabsorption glucose in the renal proximal tubule. About 70 g of glucose are lost in the urine per day, 250 kg per ten years. Food is absorbed, but the glucose is removed afterwards in conditions of

normo-glycemia. These drugs enable the “desirable”, “pleasant” high food intake (Figure 19).

Adequate food intake, “eu-nutrition” and physical training have the best effect (Figure 20).

- Transport from A to B is possible. (Normal, physiological situation.)

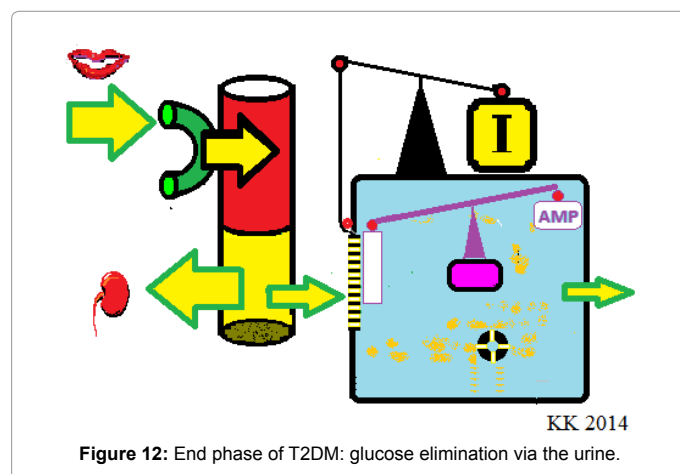


Figure 12: End phase of T2DM: glucose elimination via the urine.

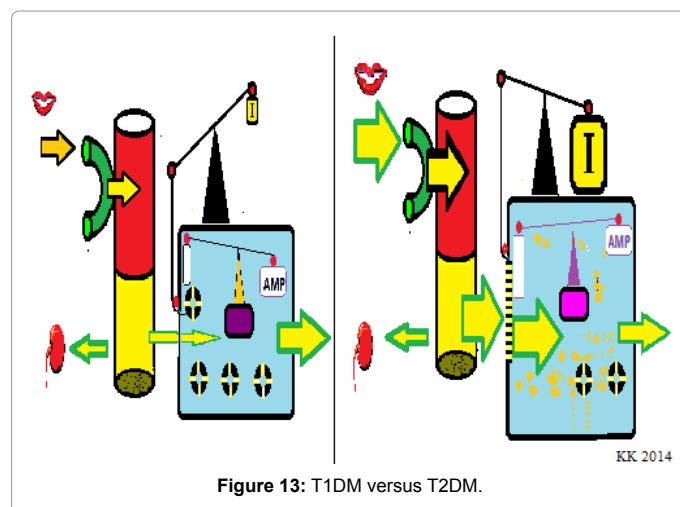


Figure 13: T1DM versus T2DM.

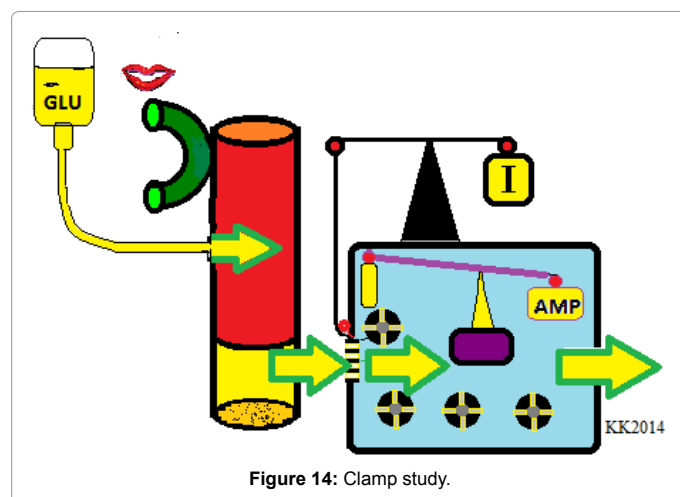


Figure 14: Clamp study.

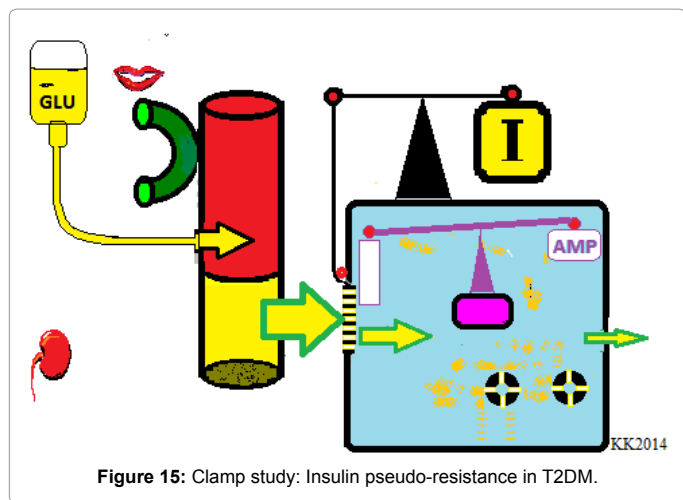


Figure 15: Clamp study: Insulin pseudo-resistance in T2DM.

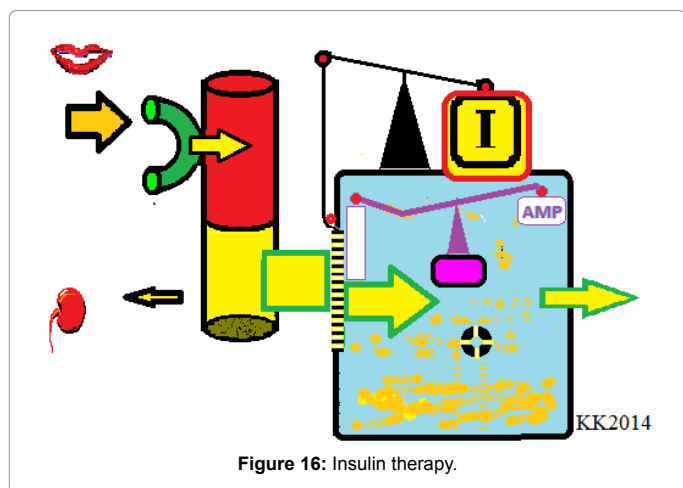


Figure 16: Insulin therapy.

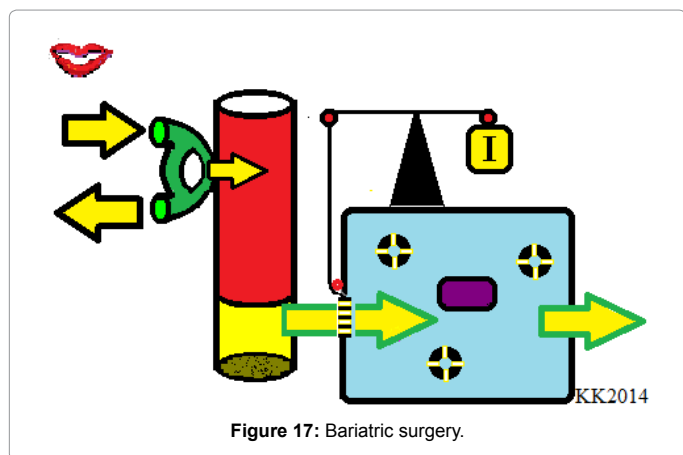


Figure 17: Bariatric surgery.

- Transport from C to D is impossible. The gate is closed. (T1DM. Lack of insulin or a (real) insulin resistance.)
- Transport from E to F is impossible. The gate is open, but there is no free space, (T2DM with obesity Insulinpseudo-resistance) (Figure 21).

There are many hormones that control starting and stopping a meal (hormones such as leptin, GLP-1) and hormones that control glucose

metabolism (insulin, amylin, glucagon, GLP-1). T2DM occurs when the extracellular system collides with the intracellular system (Figure 22).

Interpretation of the model: This model suggests that T2DM, diabetes mellitus type 2 with obesity, is a metabolic disorder that is not caused by relative or absolute lack of insulin and it is not caused by inborn insulin resistance. T2DM is a disease that is caused by chronic excess of energy intake that damaged the basic regulation systems. T2DM is caused by inadequate lifestyle, which does not comply with genetic predisposition of the major proportion of the population [33], population with thrifty genotype [34].

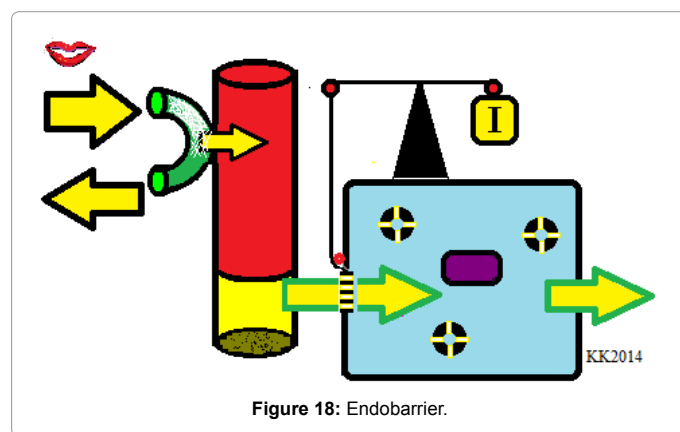


Figure 18: Endobarrier.

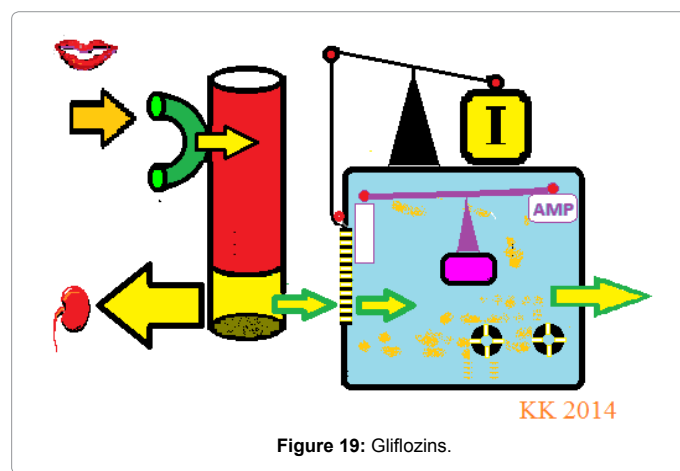


Figure 19: Gliflozins.

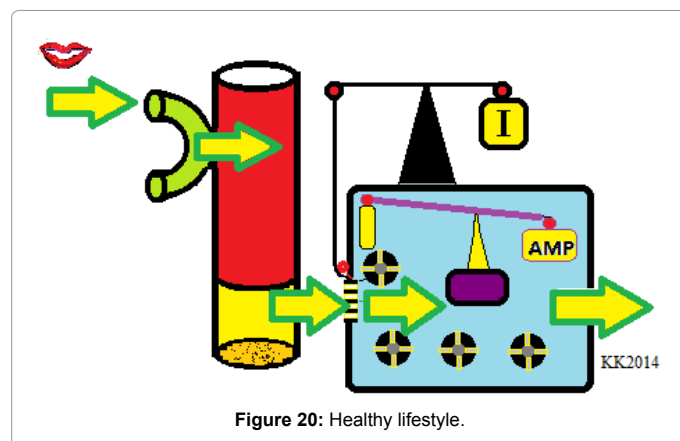
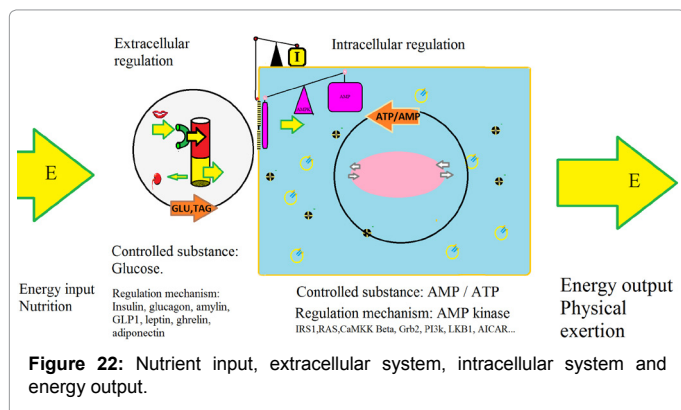
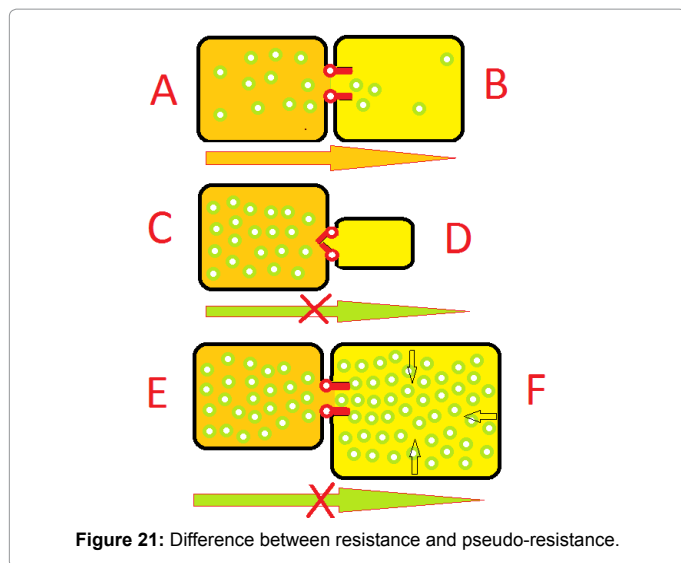


Figure 20: Healthy lifestyle.



T2DM is in many cases the result of the maladaptive habits, eating and exercise habits which could be corrected by the application of learning principles, by the behavioral treatment. T2DM is caused by excess of energetically rich substances [35], by excess of food, and lack of the physical exercise. T2DM is caused by collision of basic (extracellular) hormonal systems (insulin and other hormones) and intracellular regulatory system (AMPK and other “intracellular hormones”).

From this point of view there are three groups of diabetes mellitus types: Type with absolute lack of insulin (T1DM, LADA), relatively frequent (5%-10%). Type 2, caused due to overeating (T2DM with obesity), very frequent, (80%-90%) and other types, which are nevertheless very rare. Types such as type with a real relative lack of insulin, type with a severe or moderate insulin resistance. MODY, glucokinase defect, Kir6.2/SURI, HNF-4α, HNF-1α, Neuro D1 defect, KCNJ11 mutation, Congenital lipodystrophy Berardielli-Seip, Donohue syndrome, Rabson Mendenhall syndrome, ... hyperaldosteronism, Cushing’s syndrome, end stage of T2DM, combined disorders, sepsis, hepatitis C and many other syndromes and diseases (5%).

The differentiation between real “insulin resistance” and the “pseudo-resistance” is possible: we need to evaluate the capability of the insulin to provide cells with nutrient. Mathematically: The HOMA-IR Index ($k \cdot \text{fasting plasma glucose} \cdot \text{fasting plasma insulin}$) should be divided by the mass of the visceral fat, by the weight of the visceral fat.

Undernourishment as well as “over-nourishment” is dangerous. According to the Food and Agriculture Organization about 805 million people are estimated to be chronically undernourished in 2012-2014, 11.3 percent [36]. Global prevalence of diabetes is estimated to be 366 million people in 2030, 4.4 percent [37]. The prevalence of DM in the Czech Republic (2011) is 825 000 people, more than 8 percent.

Conclusion

Major proportion of the population is unable to tolerate the present over-nutrition and sedentary lifestyle without developing the T2DM. T2DM is a disease that is caused by chronic energy excess that damaged the basic regulation systems. The optimal therapy of early stage of T2DM is probably not insulin administration, but drugs which have an anorectic effect (incretin mimetics, glukagon like peptide-1 analogs), drugs, that diminish the effectivity of metabolism (metformin) or drugs, that directly remove the glucose (gliflozins). The adequate nutrition is the essential condition for our health.

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