DIABETES MELLITUS: BIOCHEMISTRY, CLINICAL CORRELATION, AND DEVELOPMENT OF SYNTHETIC HYPOGLYCEMIC AGENT

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Abstract

Background.. *Glucose is the major energy substrate which has the major pathways of carbohydrate metabolisms begin or end. The body's sources of glucose are dietary carbohydrate and endogenous (principally hepatic) which produced by glycogenolysis and gluconeogenesis.*

Objective. *The aim of this study is to review the biochemistry of diabetes, biochemistry with clinical correlations, and the development of synthetic hypoglycemic agent.*

Method*. The review is used the 6 books and 5 articles related to the biochemistry of diabetes, biochemistry with clinical correlations, and the development of synthetic hypoglycemic agent.*

Result. *This article presents biochemistry of diabetes included major pathways of glucose utilization in cells; three possible catabolic fates of pyruvate formed in glycolysis; relationship of glucose to major pathways of carbohydrate metabolism; regulation of blood glucose; hormones involved in glucose homoeostasis; major characteristics of IDDM and NIDDM; diagnosis blood glucose concentrations; insulin production and action. The development of synthetic hypoglycemic agent from the beginning until now is also proposed.*

Conclusion*. It is concluded that glucose is the major energy substrate; therefore, the energy consumed and needed should be balanced. Food with a traditional style is better than the modern style.*

Key words : *Diabetes Mellitus, glycogenesis, glycogenolysis, glycolysis, hyperglycaemia.*

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INTRODUCTION

The term of Diabetes Mellitus (DM) was first given by Aretaeus in 200 BC. Diabetes means "continously flowing", and mellitus means "sweet". It was called as diabetes due to its continous drink in large quantities (polydipsia), which subsequently "continously flow" in the form of urine; It was called Mellitus because the urine contains sugar (sweet).Thus, DM or diabetic patients is due to insufficient insulin that cannot work normally (Tjokroprawiro, 1988).

In 2010, the number of diabetic patients in the world population is around 7.0 M and is predicted to increase to 8.4 M in 2030. In 2010, Indonesia was positioned as the ninth rank country in the world with diabetic patients (7.0 million people). Furthermore, in 2030, it is predicted to position as the sixth rank country with 12 million diabetic patients (IDF, 2009).

One of the causes of increasing in the number of dabetic patients is due to the diet that shifted from a traditional diet, which is containing of many carbohydrates and fiber from vegetables, to the diet-westerly, which is containing of protein, fat, sugar, salt, and less sugar. It was said in American proverbial that "you are what you eat" (Diehl, 1996). In other side, lifestyle is very busy with working from morning till evening, without movement or sports. This fact is almost happened on executives who also have lunch or dinner with westerly diet.

Lifestyle and diet as described above, could causes high frequency of diseases, such as: Dm, Coronary Heart Disease (CHD), hypertension, hyperlipidemia and stroke. The number of diabetic patients is increased and within fifteen years the increase is doubled. However, the treatment of diabetes mellitus is still not satisfactory (Diehl, 1996).

The other problem in Indonesia, DM is a disease with the highest cost of the 10 diseases, besides mental illness, heart disease, trauma, cancer, lung, hypertension, osteoarthritis, back pain, kidney, and diabetes (Anonim, 2009).

The aim of this study is to review the biochemistry of diabetes, biochemistry with clinical correlations, and the development of synthetic hypoglycemic agent.

METHOD

The review is used the 6 books and 5 articles related to the biochemistry of diabetes, biochemistry with clinical correlations, and the development of synthetic hypoglycemic agent.

RESULT AND DISCUSSION

Biochemistry of diabetic/glucose

The sources of glucose are: (1). Polysaccharides: starch (amylose and amilodektrin), Glycogen, Dextrin; (2). Disaccharides: Maltose, Lactose, Sucrose, trehalose, and (3). Monosaccharides: fructose, mannose, galactose, glucose.

Glucose is the major pathways of carbohydrate metabolisms begin or end.. Glucose may be stored as glycogen via glycogenesis. Furthermore, glucose is formed lactate via glycolysis, and lactate is formed glucose via gluconeogenesis.

The major pathway of glucose utilization in cells of higher animals are glucose will be stored as glycogen via glycogenesis. Then, It may be oxidized to 2 moles of pyruvate via glycolysis, and oxidized to the pentose phosphate (ribose 5-phosphate) via pentose phosphate pathway.

The three possible catabolic fates of pathway of the pyruvate formed in glycolysis are : 1. transformation into acetyl CoA and enter Krebb cycle; 2 Formation of under aerobic condition ethanol and CO2, and 3. Formation of lactate in anaerobic conditions (Nelson and Cox, 2004; Berg, et al., 2001).

Metabolic fates of pyruvate

The glucose formation to pyruvate glycolysis); pyruvate will be reducted to lactate; then it is oxidized and decarboxylated into acetyl CoA, then it is carboxylated into to oxaloacetate; and finally the formed via tranamination.

General precursors of acetyl CoA

The general precursors of acetyl CoA are glycogen; triglyceride; and protein. The glycogen is formed into glucose via glycogenolysis, then it will be oxidized into pyruvate, oxidized and decarboxylated to acetyl CoA. The triglyceride will be hydrolyzed into free fatty acid via lipolysis, then it will betaoxidized to acetyl CoA. Finally, the protein will be hydrolyzed into amino acid via proteolysis, then deaminized and oxidized into acetyl CoA.

Sources and fates of acetyl CoA.

The sources of acetyl CoA are pyruvate, amino acids, and fatty acids. Then the metabolic results are energy via tricarboxylic acid cycle, keton bodies, steroid & fatty acid.

Energy yielding metabolic pathway

Glycogen serves as a source of glucose for the energy yielding processes of glycolysis (2ATP/glucose molecule), the citric acid cycle (2ATP/glucose), and oxidative phosphorylation (26ATP/glucose).Lactate is formed from pyruvate under anaerobic condition..

Biochemistry of diabetic with clinical correlation

The diagnosis of DM is based on the occurrence hyperglycaemia.

There are two distinct types: type 1 (insulin-dependent diabetes mellitus –IDDM), which is related to the destruction of pancreatic cells resulted no adequate insulin secretion; type 2 (non insulin-dependent diabetes mellitus –NIDDM) which is related to the inadequate of insulin secretion or resistence to the insulin action.

Major characteristics of IDDM and NIDDM are shown in Table I (Marshall, 1995)

Table I. Major characteristics of IDDM and NIDDM (Marshall, 1995)

Feature	IDDM	NIDDM
typical age of onset	children, young adults	middle age
Onset	Acute	gradual
Habitus	Lean	often obese
weight loss	Usual	uncommon
ketosis-prone	Usually	usually not
plasma insulin concentration	low or absent	often normal; may be <
hamily history of diabetes	Uncommon	common
HLA	DR3, DR4	none

Insulin Stimulates Glycogenesis in Muscle and Liver (Marshall, 1995)

An increase in blood glucose signal release of insuline from beta cells of the pancreas. Insulin receptors on the plasma membranes of insulin-responsive cells will respond to insulin binding through a signaling cascade that promotes glucose use. Then the pancreas will respond to a decrease in blood glucose with less release of insulin and more release of glucagon.

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Glucagon is secreted by alfa-cells of pancreatic islets; its actions oppose those of insulin; it stimulates glycogenolysis and gluconeogenesis and promotes lipolysis and ketogenesis. The combined effects of insulin and glucagon are shown in Figure 1.

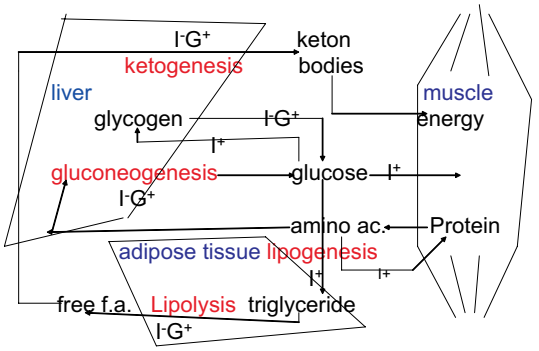

Figure 1. Effects of insulin n glucagon in liv, musc, adip

Insulin increases part of glucose utilization by promoting glycogenesis and inhibiting glycogenolysis in muscle and liver. Hormon whichare involved in glucose homoeostatis are shown in table II (Marshall, 1995).

Glucose is a major source of energy. The daily food which is contained of carbohydrate is a source of glucose, however endogenous sources of glucose is derived from glycogenolysis, which is resulted from decomposition of glycogen. Glycogen is stored in the liver. Gluconeogenesis is a source of glucose from lactate, amino acids, and glycerol.

The production of insulin and glucagon by pancreatic beta cells and alpha is the blood sugar regulation. If the blood sugar increase, insulin will be produced by pancreatic beta cells and will stimulate glycogenesis so that the blood sugar levels remain normal. If the blood sugar will go decrease, the glucagon will be stimulated, so that the decomposition of glycogen into

Table II. Hormones involved in glucose homoeostatis (Marshall, 1995)

Hormones	Principal action	Organ
Insulin	Increases: cellular glucose uptake	M, A
	Glycogen synthesis	L, M
	Protein synthesis	L, M
	Fatty acid and triglyceride Synthesis	L, A
	Decreases: gluconeogenesis	L
	Ketogenesis	L
	Lipolysis	A
	Proteolysis	M
Glucagon	Increases: glycogenolysis	L
	Gluconeogenesis	L
	Ketogenesis	L
	Lipolysis	A
Adrenaline	Increases: glycogenolysis	L, M
	Lipolysis	A
Growth hormones	Increases: glycogenolysis	L, M
	Lipolysis	A
Cortisol	Increases: gluconeogenesis	L
	Glycogen synthesis	L
	Proteolysis	M
	Decreases: cellular glucose uptake	M, A

L = Liver, M = skeletal muscle, A = adipose tissue

glucose will occure. This mechanism is called glycogenolysis, so that the blood sugar remain normal (IDF, 2009).

The high levels of glucose in the blood, stimulate the beta cells of Langerhans (pancreas) to produce insulin, the glycogen synthesis will increases, so that the synthesis of protein,

fatty acids and triglycerides will be increased.

This simultaneous mechanism will maintain the normal blood glucose levels, the glucose will be stored for supply / reserves in the form of glycogen in the liver.

Insulin also has action to reduce gluconeogenesis (glucose synthesis from lactate, amino acids and glycerol), ketogenesis (synthetic substances ketone / ketone bodies), lipolysis (decomposition of fat into fatty acids) and proteolysis (protein decomposition to amino acids).

If blood glucose levels in decreases, stimulate the alfa cells (pancreas) to produce glucagons, which works to increase glycogenolysis (glycogen decomposition yield glucose), gluconeogenesis (glucose synthesis from lactate, amino acids and glycerol).

Clinical correlation Diabetes Mellitus Type 1 (Harris, 2002)

Type 1 DM usually appears in childhood or in the teens.

Type 1 diabetes is characterized by hyperglycemia, hypertriglyceridemia (chylomicrons and VLDL), and episodes of severe ketoacidosis. Thus, there is severe derangement of carbohydrate, lipid, and protein metabolism. The hyperglycemia results from the inability of insulin-dependent tissue to take up glucose and from accelerated hepatic gluconeogenesis from amino acids derived from muscle protein.

The ketoacidosis is results from the increased lipolysis in adipose tissue and the acceleration of fatty acid oxidation in liver. Hyperchylomicronemia is results from low lipoprotein lipase activity in adipose tissue capillaries, an enzyme dependent on insulin for its synthesis.

Ketoacidosis in diabetes is caused by lipolysis which results in plasma free fatty acids that cause the occurrence ketonaemia ketogenesis then cause vomiting and loss of water with sodium and potassium ions, hipovolaemia and thirsty. Hiperglicaemia can cause osmotic diuresis glikosurea which will be continued to the occurance of dehydration (loss of water with sodium and potassium ions), causing hipovolaemia, and thirst (Marshall, 1995; Taylor and Agius, 1988).

In the presence of insulin deficiency, the decreased of glucose use by cells will cause hyperglycemia, then glycosurea, osmotic diuresis, dehydration, hemoconcentration, thrombosis, atherosclerosis etc, which could affect the macrovascular and microvascular. Macrovascular can affect the heart and cerebral infarction with miocard, stroke, furthermore, the extremity gangrene could be occured. The microvascular effect on the retina and kidney. Disorders of the kidney occur nefromati and subsequent renal failure(Artanto,2009).

With a deficiency of insulin, glucagon will stimulate gluconeogenesis which will raise the metabolism of blood urea nitrogen. In addition to protein metabolism also increase fat metabolism that causes ketogenesis and decreas of pH or blood acidosis which can lead to coma and death (Artanto, 2009).

Clinical correlation Diabetes Mellitus Type 2 (Harris, 2002)

Type 2 diabetes mellitus usually occurs in middle aged to older obese people and is

characterized by hyperglycemia, often hypertriglyceridemia. The ketoacidosis characteristic of type 1 diabetes is usually not observed, although some patient can develop transient episodes of ketoacidosis. Increased levels of VLDL are probably the result of increased hepatic triacylglycerol synthesis stimulated by hyperglycemia and hyperinsulinemia.

Insulin is present at normal to elevated level in this form of the disease. Obesity often precedes the development of type 2 diabetes . Obese patients are usually hiperinsulinemic and have high levels of free fatty acids which due to the impairement of insulin action. Recent data implicates the increased level of tumor necrosis factor alfa (TNFalfa) and a new protein called resistin and reduction of adiponectin secretion by adipocytes of obese individuals as a cause of insulin resistance.

The development of synthetic hypoglycemic agent/sulfonylurea (Cutler, 2011)

At the beginning of 1918, guanidine show can lower blood sugar. The discovery that tripanosoma require a large blood sugar and will die if blood sugar is reduced or depleted. Then obtained galegin that can lower blood sugar and used as a weak tripanosidal. Subsequently found a very strong tripanosidal like bisamidin, diisotiourea, bisguanidin, and others. Synthalin and pentamidine is an active tripanosidal.

p-aminobenzenesulfonamidoisopropyl-thiadiazole:

It is an antibacterial sulfonamide, it is found to produce hypoglycemia

This result stimulated research for development of synthetic hypoglycemic agent.

Sulfonylurea

These are urea derivates with an arylsufonyl group in the 1-position and aliphatic group at the 3-position. The aliphatic group, R', confers lipophilic properties to the molecule. Maximal activity result when R' consists of three to six carbon atoms, as in chlorpropamide, tolbutamide, and acetohexamide.

Aryl group at R' generally give toxic compounds. The R group on the aromatic ring primarily in fluences the duration of action of the compound.

Tolbutamide disappears quite rapidly from the bloodstream by being metabolizedto the inactive carboxy compound, which is excreted rapidly. Chlorpropamide, however , is metabolized more slowly and persists in the blood much longer.

The mechanism of action of sulfonylureas is to stimulate the release of insulin from the functioning beta cells of the intact pancreass. Other actions, inhibition of secretion of glucagon and action at postreceptor intracellular sites to increase insulin activity

The preparation of synthetic hypoglycemic agent/derivats of sulfonylurea (Cutler, 2011).

Tolbutamide, USP

Struturnya 1-butyl-3-(p-tolylsulfonyl) urea (Orinase). This drug is rapidly absorbed and lowers blood sugar in diabetic dasien. Blood sugar dropped to 5-8 hours minimum. Metabolized to 1-butyl-3-(p-karboksifenil) sulfonurea, is inactive, readily soluble in water ekkresi through urine. Used for adult diabetic patients.

Sodium Tolbutamide,

Very easily soluble in water, used as an intravenous injection.

Chlorpropamide (Diabenes),

The structure is 1 - [(p-klorofenil) sulfonyl]-3-propilurea. Insoluble in water, its action is longer than the Tolbutamide. Hydroxy metabolites occurs at position 2 of the propyl.

Tolazamid USP

The structure is 1 - (1H-azepin-hexahidro-1-yl) -3 - (p-tolilsulfonil) urea, it works like Tolbutamide.

Asetohexamid USP

The structure is 1 - [(p-acetyl phenyl) sulfonyl]-3-sikloheksilurea. (Dymelorr)

It acts to stimulate insulin secretion

Glipizide

The structure is 1-siklohexil-3-[{p-(2 (metilpirazinkarboksamid) ethyl] phenyl] sulfonylureas]. (Ghicotrol). Effect as lowering blood sugar 12-24 hours.

Glyburide

The structure is 1 - [[p-(2 ??-(5-chloro-o-anisamido) ethyl] phenyl] sufonil]-3-sikloheksilurea (DiaBeta, Micronase, Glynase), a second generation oral hipoglikenik agent. Other preparations: Glipizide; Glimepirid; and Gliclazid

CONCLUSION

It is concluded that glucose is the major energy substrate; therefore, the energy consumed and needed should be balanced. Food with a traditional style is better than the westerly style. It has been explained the development agent. It is expected to benefit the reader.

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