

Reassessment of the Treatment of Diabetes Based on Harmonization of Traditional Chinese Medicine and Western Medicine

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If a disease is sufficiently well understood and drugs for treatment are developed, the number of patients with the disease will decrease. Insulin was discovered about 100 years ago, and a Nobel prize was given to the discoverer. Since then, oral antidiabetic drugs have been developed one after another. However, the number of patients with type II diabetes has increased rapidly despite the development of many drugs, and diabetic patients have already exceeded 2% of the world's population. What is the cause of this phenomenon? Under such circumstances, we should reassess our understanding and treatment of diabetes. I would like to briefly express my views on the basis of harmonization of Western medicine and traditional Chinese medicine, which emphasize diagnosis of specific diseases and holistic analysis/balance, respectively.

Sugar is Essential for Life

Carbohydrates are the most abundant organic compounds on earth. The main type of carbohydrate is cellulose, but there are also polysaccharides, oligosaccharides, monosaccharides, etc. The base unit of each carbohydrate is a monosaccharide,

and all other more complex carbohydrates are aggregates of monosaccharides. Cellulose is the largest aggregate and it can only be broken down in the intestines of herbivorous animals. Humans mainly utilize carbohydrates that have a smaller number of chains than cellulose. Starch and oligosaccharides are broken down to monosaccharides (glucose, fructose, and galactose) by digestive enzymes, and then absorbed from the small intestine for transport to the liver. All of the monosaccharides are metabolized to glucose in the liver and then released into the systemic circulation, so only glucose is detected in the blood. Energy is consumed by all the activities of an organism. Adenosine triphosphatase (ATP) is a high-energy phosphate compound that acts as a very important energy source in the body. ATP is produced by the mitochondria of cells. Carbohydrate, fats, and proteins can all be utilized as energy sources for producing ATP. However, since the central nervous system, erythrocytes, and other tissues that are important for maintaining life cannot directly utilize fats and proteins, glucose is their only source of ATP. The metabolism of this energy source is unrelated to insulin. The blood glucose level normally remains in the range of 72-100 mg/dL (4-5.6 mmol/L) between meals to 130 mg/dL (7.2 mmol/L) after meals. If the blood glucose level decreases below 70 mg/dL, autonomic nervous symptoms develop, such as palpitations. If the glucose level decreases below 45 mg/dL, symptoms of

encephalopathy occur, including convulsions, paresthesia, dyskinesia, transient hemiparesis, and ataxia, and serious complications may develop like cerebral infarction, myocardial infarction, arrhythmia, or ocular vitreous hemorrhage. In severe cases, hypoglycemic coma and even death may occur. Except for the recent period of history, humans have faced the risk of starvation for most of their existence. Therefore, hypoglycemia has long been an important factor that can threaten life. At present, however, more attention is focused on iatrogenic hypoglycemia induced by overdosage of antidiabetic drugs.

Mechanisms of Glycemic Control

Since the body is composed of the same substances as its energy sources, energy intake naturally exceeds energy consumption in children. In adults, blood glucose levels are fundamentally kept stable by maintaining the balance between the intake of energy and its consumption. Since the body is always consuming energy, while food is not always being eaten, it is necessary to store energy somewhere in the body. Sugar is mainly stored at three sites, which are the liver, muscles, and fat. In particular, the liver plays an important role in the maintenance of normal blood glucose levels. It takes up and stores approximately 40% of the carbohydrates absorbed after a meal, synthesizes new carbohydrates from metabolites

like lactic acid and glycerol (gluconeogenesis) that are produced by the muscles and fat tissue, and releases glucose into the blood to supply it to the organs and tissues of the body during periods of fasting. The blood glucose level is usually quite stable and fluctuates within a narrow range. Excessively high or low blood glucose levels are problematic. An excessive total intake of energy, carbohydrate storage disorders, or decreased carbohydrate utilization by the tissues may lead to hyperglycemia, resulting in the onset of diabetes. The "total intake of energy" is defined as "the total calories derived from carbohydrates, fats, and proteins." For the same quantity, the effective energy derived from carbohydrates is equal to that from proteins, while the effective energy from fats is 2.25-fold higher than that from carbohydrates. If the intake of fat or protein is excessive, utilization of sugars is limited. Insulin is necessary for the uptake of glucose by the liver, muscles, and adipose tissue. In other words, glucose cannot be stored without insulin. If the action of insulin becomes weak, blood glucose levels will increase, resulting in the onset of diabetes. Needless to say, diabetes is not caused by changes of insulin alone. It can also be induced when the storage role of the liver is impaired by conditions like fatty liver and cirrhosis. **An excessive increase of fat** tends to be a cause of diabetes, while excessive lipotrophy may also lead to hyperglycemia because there is insufficient storage for

glucose.

Concept of Diabetes

Diabetes is characterized by a chronic increase of the blood glucose level. This disease was named "diabetes" because sugar is excreted in the urine when blood glucose levels become too high or renal dysfunction occurs (blood glucose levels could not be measured when the disease was discovered).

When blood glucose increases after a meal, etc., the hormone insulin is normally released from the β -cells in the islets of Langerhans in the pancreas. Since glucose is incorporated into various tissues, including the liver, fat, and muscles, by the action of insulin, the blood glucose level does not increase excessively and remains in the normal range. If the β -cells are destroyed, it becomes necessary to supply insulin from an exogenous source, because endogenous insulin will no longer be secreted and blood glucose will increase. This state is called insulin-dependent diabetes (type I diabetes). Non-insulin dependent diabetes (type II diabetes) is different because insulin is still secreted and its production may even be higher than in healthy persons, but the blood glucose level is not controlled due to insulin resistance of the tissues that results in decreased utilization of glucose. There is also gestational diabetes and other types of diabetes, including that induced by steroids or oral contraceptives and diabetes secondary to

pancreatitis. Among all diabetics, approximately 3% have type I diabetes, while type II diabetes accounts for more than 95% and attracts much more attention.

Drugs for Diabetes

Diabetes is mainly treated by using insulin preparations, sulfonamides that promote insulin secretion, biguanides that inhibit aerobic metabolism while promoting anaerobic metabolism and inhibiting hepatic gluconeogenesis, α -glucosidase inhibitors that block the enzymes degrading maltose to glucose, and troglitazone (a thiazolidine derivative) that improves insulin resistance (adverse drug reactions are common, including fatal hepatopathy). The objective of treatment with all these drugs is to improve glycemic control by inhibiting absorption of carbohydrates from the small intestine, by inhibiting the release of glucose from the liver, and by converting blood glucose to lipids, etc. What leads to the unsatisfactory outcome of treatment for diabetes despite having these five classes of drugs?

Type II Diabetes and Metabolic Syndrome

In recent years, a series of disorders have been labelled as metabolic syndrome, including obesity, type II diabetes, hyperinsulinemia, hypertension, fatty liver, hyperuricemia, arteriosclerotic cardiovascular (cerebrovascular) disease,

and abnormal lipid metabolism. All of these conditions are pathologically characterized by insulin resistance. It has been reported that tumor necrosis factor- α (TNF- α) and free fatty acids released from adipocytes induce insulin resistance. Thus, there is a common underlying pathological mechanism for these disorders. This concept is similar to "the holistic pattern of pathology, function, and predispositions (zhang)" that operates in traditional Chinese medicine. If a physical condition that predisposes to metabolic dysfunction is established, symptoms such as hyperglycemia, hyperlipidemia, hyperuricemia, and hypertension may develop alone or in combination depending on the patient and the timing. If blood glucose levels become too high, diabetes can be diagnosed. Type II diabetes is a relatively severe manifestation of metabolic syndrome, and hyperglycemia is a symptom of type II diabetes. Therefore, drug therapy for hypoglycemia is only symptomatic treatment.

Complications of Type II Diabetes

Hyperglycemia is only one of the symptoms of diabetes. If metabolic/circulatory disorders are persistent retinopathy, nephropathy, neuropathy, myocardial infarction, and other systemic lesions may develop. The process of metabolism is essential for the survival of cells and it is defined as the (circulation-dependent) intake and elimination of substances.

Metabolism is also essential for vascular endothelial cells. If both metabolic and circulatory functions decrease, vascular endothelial cells may be damaged, and thrombosis, inflammation, and atherosclerosis may affect the vessel walls. Since diffuse systemic vascular dysfunction is induced, lesions may occur in various tissues, resulting in the onset of systemic complications. In particular, if there is progression to calcification of the arterial walls, tissue gangrene can develop, including "diabetic foot" and intractable skin ulcers. The cause of death from type II diabetes is not hyperglycemia itself, but complications of diabetes in most cases. Even when blood glucose levels are controlled satisfactorily by antidiabetic drugs, complications still progress and the incidence of complications is very high among diabetic patients. These complications cannot be controlled satisfactorily by symptomatic treatment, and adverse reactions to treatment with multiple drugs are not uncommon. Not only improved glycemic control, but also improvement of the physical state that predisposes to this disease, is essential for the treatment of complications.

Viewpoint of Traditional Chinese Medicine

The predisposition to type II diabetes, which is a typical part of the metabolic syndrome, is considered to be a metabolic/circulatory disorder that is called "deficiency of

digestive function/blood stasis (pixuxueyu)" in traditional Chinese medicine. The "spleen (pi)" means the systems involved in digestion/absorption/metabolism, including the pancreas, gastrointestinal tract, liver, nerves, and gut hormones. Overall digestive/absorptive/metabolic function is called the "spleen-vital energy (piqi)." The fundamental substances of life are considered to be vital energy (qi) and blood (xue). Vital energy is defined as an important, but invisible, substance that exists like air (nutrients and physiological substances) and the concept also includes its function. If the function of such a substance is observed, its status can be estimated. Vital energy functions when nutrients are digested, absorbed, and metabolized with the cooperation of the circulation. Therefore, if there is no circulation of the blood, vital energy cannot function. On the other hand, blood cannot circulate in the absence of vital energy, so the body's vital energy and blood are inseparable. If the vital energy is somehow separated from the blood, death will occur. Abnormalities of the vital energy and blood are considered to lead to various diseases.

If "deficiency of the digestive/absorptive/metabolic functions (pixu)" occurs, a circulatory disorder that is called blood stagnation (yuxue) or blood stasis (xueyu) will develop and will promote metabolic disorders, leading to the occurrence of a vicious circle. After the onset of blood stasis, heat

(inflammation) is produced by the accumulation of wastes. Since important physiological substances (yin) become deficient because of decreased production due to inflammation-induced exhaustion and metabolic disorders, "hepatic and renal yin-deficiency (ganshenyinxu)" may occur if digestive/absorptive/metabolic dysfunction and blood stasis progress sufficiently. Synthesis of various substances by the body, including those modulating blood pressure (which belong to yin) and are produced in the liver and kidneys, becomes insufficient. Poor lifestyle habits, excessive stress, insufficient exercise, and overeating have a much greater role in the occurrence of "deficiency of digestive function/blood stasis" than any hereditary predisposition. Type II diabetes does not develop in a short period of time. In general, there is already an underlying predisposition to diabetes before an abnormal increase of the blood glucose level occurs. Diabetes can be prevented, if such a predisposition is controlled at an early stage.

Diabetes was called "emaciation-thirst (diaoke) disease" in ancient China. Since there is a clear difference in the mechanism of onset of diabetes between the olden days when there was a shortage of food and the present times (a period of satiation), satisfactory efficacy cannot be obtained without changing the ancient formulations. Thus, there has been a demand for the development of formulations that are more

appropriate for treating people today.

Wang's Ketumeisei

When blood glucose levels are too high, symptomatic treatment (such as decreasing the glucose level) is necessary, but it is more important to simultaneously improve the underlying predisposition. Just as the government cannot be managed entirely by the head of state alone, it is impossible to improve such a predisposition by using a single herb or chemical, although it is possible to improve symptoms with such agents. To improve the physical state predisposing a person to metabolic and circulatory disorders (pixuxueyu), it is necessary to blend multiple herbs that can act together. In Wang's Ketumeisei, the following edible herbs are blended together. Cassiae Semen, Gardeniae Fructus, and Glycyrrhizae Root are included to improve hepatic function and inflammation, while Astragali Radix, Dioscoreae Rhizoma, and Denshichi Ginseng Root supplement spleen-vital energy (promotion of metabolism, etc.). In addition, Safflower, Pueraria Root, and Denshichi Ginseng Root are included to activate the circulation and improve blood stasis (circulatory disorder). In particular, Denshichi Ginseng Root, which promotes metabolism, has both thrombolytic and hemostatic effects. Cassiae Semen is mentioned in the "Materia Medica of Shen Nong," which is the oldest currently available compendium of drugs in the world (written 2500 years

ago). It is used for the purpose of preventing hepatic disease, eye disease, and aging.

Wang's Ketumeisei is suitable for improving the physical state that predisposes to metabolic/circulatory disorders and the complications of diabetes. In patients with type II diabetes, when Wang's Ketumeisei was administered orally in combination with an antidiabetic drug for 1-2 months, various symptoms (including malaise) showed a marked improvement and the free fatty acid level was decreased. Numbness of the hands and feet, recurrent fundal hemorrhage, and skin ulcers were also improved. (Monotherapy is also effective for mild disease or for preventive purposes.)

A Substitute for Aspirin

Circulatory disorders are called blood stasis (blood stagnation) in traditional Chinese medicine, which means abnormalities of the circulation, blood properties, and vessels. Such disorders include hemorrhage, ischemia, stagnation of the blood (decreased flow rate), increased coagulability, increased blood viscosity, thrombosis, arteriosclerosis, and vascular pain. As a result of the accumulation of experience over thousands of years, a group of herbs that are effective for blood stasis have been found. The therapeutic concept of activating the circulation to eliminate blood stasis (huoxuehuayu) clearly surpasses that of antithrombotic

therapy.

At present, aspirin and other agents are widely used to prevent thrombosis. Aspirin inhibits prostaglandin (PG) production and thus has antipyretic and analgesic effects. It reduces platelet adhesion and aggregation by inhibiting the production of thromboxane A₂. PGs are substances that especially protect mucosal cells. It is known that prolonged use of aspirin causes adverse reactions due to a decrease of PGs, including gastric ulcer, small intestinal ulcer, aspirin asthma, and hemorrhage (including fatal cerebral hemorrhage). Since platelets produce growth factors, such as PDGF and IGF, they are not only involved in hemostasis but also in tissue repair. When vascular endothelial cells are damaged, collagen is exposed, and platelets are activated and form aggregates on the wound. As a result, a thrombus forms and it stops hemorrhage. This is the original function of platelets. The body also has a system that automatically dissolves thrombi. In diabetic patients, thrombi are continuously being formed on diffuse vascular lesions that are present because of the underlying predisposition to metabolic/circulatory disorders. Although aspirin inhibits thrombus formation, it cannot control atherosclerosis and vascular calcification. Wang's Ketsumeisei improves blood stasis, prevents and dissolves thrombi, and simultaneously improves vascular wall function by invigorating vital energy to activate the circulation

(promotion of metabolism and circulation: buqihuoxue).

References

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β 細胞 : β -cells

p. 5 の図と説明

細胞障害 : Damage to cells

血小板凝集 : Platelet aggregation

血栓・粥腫 : Thrombosis/atheroma

石灰化 : Calcification

Thrombus forms because of damage to a blood vessel. Aspirin prevents thrombosis by inhibiting platelet aggregation. Wang's Ketsumeisei improves the underlying systemic metabolic/circulatory disorder, normalizes thrombolytic activity, and reinforces the functions of vascular endothelial cells, thus improving vascular damage.