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An Insight of D-Ribose Metabolic Imbalance in Type 2 Diabetes Mellitus*

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Diabetes mellitus (DM) is considered as a group of metabolic diseases characterized by hyperglycemia (high concentration of blood glucose) resulting from defects in insulin secretion, insulin action, or both. Many years ago, Marks [1] emphasized that pentose phosphate pathway is one of important pathways for glucose metabolism in diabetes. One year later, Segal and coworkers [2] observed the decrease in blood glucose levels when administrated intravenously with 20 g ribose to three diabetic subjects. Bierman and colleagues [3] used larger doses of ribose giving to patients with both mild and severe diabetes, and found that several aspects of the metabolism of the pentose (ribose) remain unaltered in the diabetic state similar to Segal's finding. Accordingly, ribose as an energetic enhancer was found to decrease the concentration of blood glucose, and thus "oral administration of ribose in diabetes mellitus" was ever described by Steinberg and colleagues[4]. In order to decrease blood glucose, Hammer and collaborators used benfotiamine to block three major pathways (hexosamine pathway, advanced glycation end product (AGE) formation pathway and diacylglycerol (DAG)-protein kinase C pathway) of hyperglycemic damage and prevented experimentally diabetic retinopathy[5]. However, a significant increase of AGE was observed although administration of ribose was used to lower the blood glucose[6]. Ribose is an efficient glycator [7~9], and is much more active in protein glycation than glucose under identical conditions [10]. Su and colleagues [11] first demonstrated that ribose is significantly increased in the urine of type 2 diabetic patients accompanying with higher level of glucose compared with those of age-matched control group, suggesting that T2DM is not only related with a dysfunction in glucose metabolism, but also in ribose metabolism[12]. Thus we emphasize here that besides blood glucose, ribose should be adjusted for diabetic patients because ribosylated products and some ribose derivatives are highly cytotoxic[13].

Ribose, a naturally occurring pentose monosaccharide, comes from the food containing high amounts of nucleic acids (RNA, DNA) and riboflavin such as eggs, meats, yeast, animal innards and wheat bran [14–15]. Ribose is often marked as a supplement for bodybuilders with a common recommended daily dose of 5g or more and has also been used to reduce fatigue in fibromyalgia and chronic fatigue syndrome [2,16]. Ribose is ingested as a supplement for cardiac energetic metabolism [17–19]. Furthermore, ribose comes from pentose phosphate pathway (pentose shunt), in particular of high levels of blood glucose resulting in accumulation of ribose-5-phosphate[20].

To explain the aberrant high-level of ribose in diabetic patients, we postulate the imbalance of ribose metabolism resulted from dysfunction in relative pathways (Figure 1). First, chronic and excess intake of food rich in nucleic acids and riboflavin leads to yield of ribose and its derivatives [14]. Thus, diet should be

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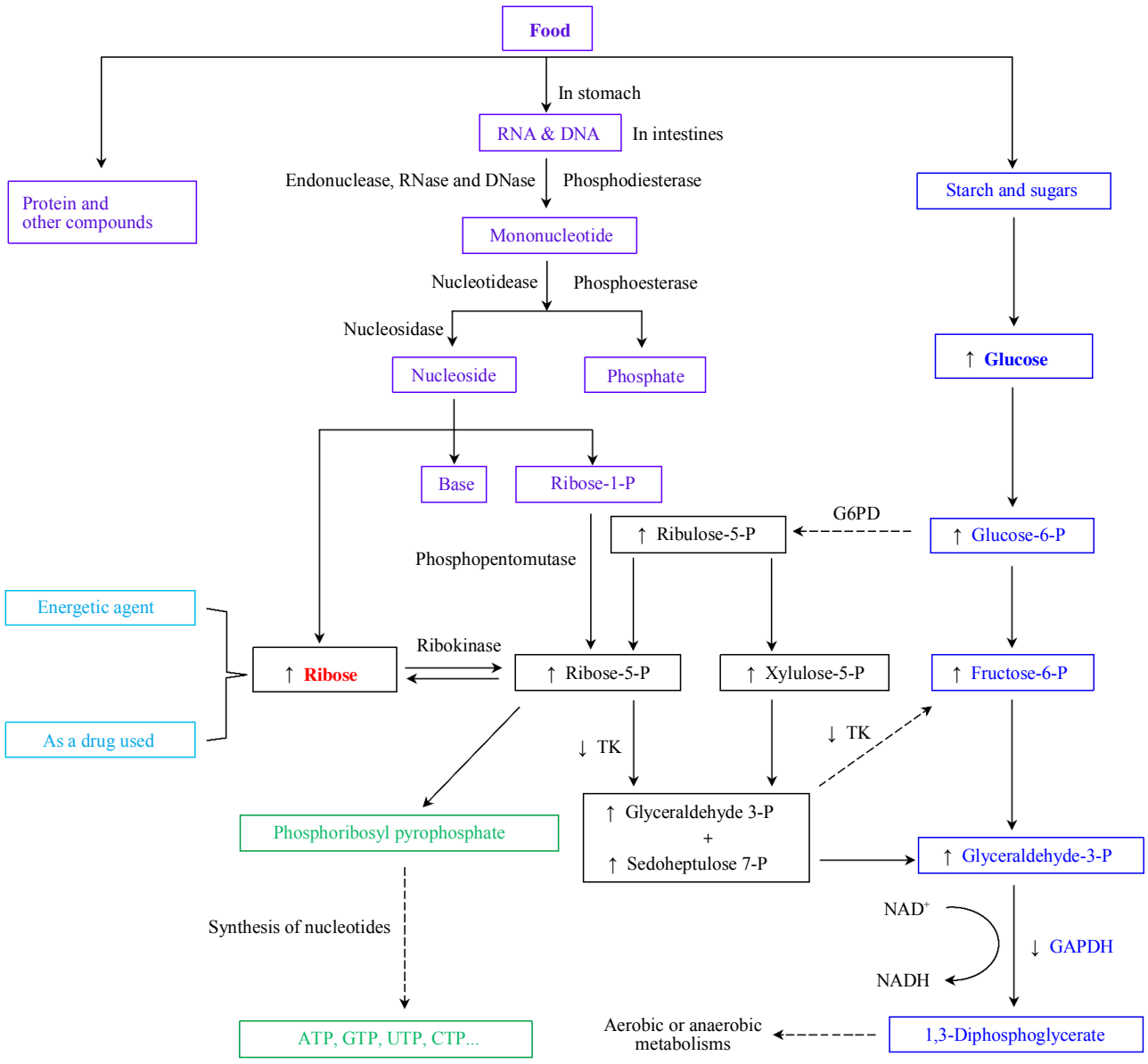

Fig. 1 A putative pathomechanism for ribose and its derivatives to be accumulated in diabetes mellitus

Increase in concentrations of ribose could be resulted from (1) food intake by degradation of nucleic acids or metabolism of the derivatives including uric acid (purple panels)[21-22], (2) administration of ribose as an energetic agent[23] or a drug (azure panels)[4], and (3) high activities of the enzymes for instance glucose-6-phosphatedehydrogenase (G6PD) which catalyzes the conversion of glucose into ribose (black panels)[24]. In contrast, ribose could be increased because of (4) low activities of the enzymes which catalyze the conversion of ribose or its derivates into fructose-6-P and glyceraldehyde-3-P, for instance transketolase (TK) (black panels)[5], and (5) low activities of synthesis of nucleotides to consume ribose (green panels)[25].

aware of not only adjusting starchy food for glucose but also the food for ribose. Second, our result demonstrated that overdose administration of ribose would impair mouse central nerve system [26] and kidney (data unpublished). That is to say, impairments of nerve system, blood vessels and other organs should be monitored during a long-term and overdose administration of ribose either as an energetic agent or a medical drug[13]. Third, low activities of the enzymes which will catalyze the conversion of ribose or its derivates into fructose-6-P and glyceraldehyde-3-P, for instance transketolase (TK), lead to an increase in ribose. These enzymes should be investigated as potential pharmaceutical targets. Benfotiamine was once considered to block hyperglycemia as described [5]. In fact, as an activator of TK,

benfotiamine could decrease ribose to prevent ribosylated damages, rather than blocking hyperglycemia. Decline of cell proliferation, differentiation, and apoptosis occur as aging [27], and also nucleic acid metabolism. Since diabetic patients commonly have low activities of synthesis of nucleotides decreasing the consumption of ribose and low efficacy of aerobic metabolism of glucose [28]. In/out exercise improves the synthesis of nucleotide *via de novo* pathway including ATP, glyceraldehyde-3-P and other compounds [29]. This consumes not only glucose but also ribose and its derivatives. Therefore, regular in/out-door exercise should be advised for diabetic patients in medical care.

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