Are the polyol pathway and hyperuricemia partners in the development of non-alcoholic fatty liver disease in diabetes?

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver disorders worldwide. NAFLD is considered to be the hepatic component of metabolic syndrome, because its features are very similar to those of metabolic disorders, such as obesity, inflammation, insulin resistance and type 2 diabetes. It is clear that NAFLD and type 2 diabetes have a close relationship. However, the exact mechanisms underlying the pathogenesis and progression of NAFLD are still incompletely understood.

It is well known that hyperglycemia-induced polyol pathway hyperactivity can lead to the development of diabetic complications, such as microangiopathies, macroangiopathies and others. Furthermore, it has been thoroughly confirmed by many studies that the inhibition of aldose reductase (AR), a key enzyme in this pathway, is useful to prevent these complications. The polyol pathway consists of just two steps: glucose is first reduced to sorbitol by AR, and the resulting sorbitol is then changed to fructose by sorbitol dehydrogenase (Figure 1). During normoglycemia, the use of glucose through the polyol pathway accounts for <3% of glucose consumption in cells. However, during hyperglycemia, the utilization of glucose through this pathway represents up to 30%, resulting in the progress of diabetic complications in target tissues. The mechanisms of diabetic complications induced by hyperglycemia-activated polyol pathway hyperactivity are not as simple as we expect. Generally, metabolic factors, such as protein kinase C, glycated, oxidative stress and others, are involved in the lower reaches of this pathway and contribute to the progress of diabetic complications with complex issues. Furthermore, the following factors in relation to polyol pathway hyperactivity might also be partially involved, depending on the types of diabetic complications: inflammation, endothelial nitric oxide synthase, thromboxane, matrix metalloproteinases, nicotinamide phosphoribosyl transferase, nitric oxide, tissue factor, vascular cell adhesion molecule and the expression of multiple genes of the transforming growth factor-β pathway.

Recently, Sanchez-Lozada et al. proposed a very interesting and attractive hypothesis of the pathogenesis of the development of NAFLD through uric acid-induced polyol pathway hyperactivity. The concept of that study is based on the fact that the two primary sweeteners, sugar (sucrose) and high fructose corn syrup, induce fatty liver in animals. Furthermore, previous studies by this group have shown that the pathogenesis of inducing fatty liver using fructose is due to the generation of uric acid in the course of fructose metabolism, resulting in mitochondrial oxidative stress and an impairment of adenosine triphosphate production. They also confirm that hyperuricemia itself is not only strongly related with hypertriglyceridermia and NAFLD, but also predicts the progression of NAFLD. Furthermore, they found that uric acid upregulated fructokinase/keto-hexokinase (KHK) and fructose metabolism through the activation of the transcription factor, carbohydrate response element-binding protein. Their recent study based on these facts evaluates whether uric acid regulates AR expression both in cultured hepatocytes (HepG2 cells) and in the liver of hyperuricemic rats, and also whether this stimulation is associated with endogenous fructose production and fat (triglyceride) accumulation.

Their latest results are summarized as follows. In human HepG2 cells exposed to uric acid of 4 mg/dL (normouricemia), 8 mg/dL and 12 mg/dL (hyperuricemia) for 72 h, AR expression was upregulated by uric acid in a dose-dependent manner.
and significant upregulation of sorbitol dehydrogenase and fructokinase/KHK was also observed. Interestingly, coexistence of uric acid and probenecid, a uric acid transporter inhibitor, prevented AR upregulation, signifying the regulation of AR expression by intracellular uric acid. However, as sorbitol and fructose did not increase in AR-deficient cells, it is clear that these products in the polyol pathway were mediated through the upregulation of AR. In the next step, they observed that uric acid-dependent AR expression was mediated by increased transcriptional activity. Namely, they found a significant enrichment of the transcription factor, nuclear factor of activated T cells 5 (NFAT5) in pure nuclear fractions of HepG2 cells exposed to uric acid. Furthermore, AR upregulation by uric acid decreased remarkably in NFAT5-deficient cells. It is interesting to note that the luciferase signal system (obtained by cloning the human AR promoter upstream) activated by uric acid was strongly prevented by the anti-oxidant molecule, apocynin, suggesting that NFAT5-dependent activation of AR is induced by oxidative stress. Finally, they attempted to confirm whether the activation of AR can shift glucose into the polyol pathway for endogenous fructose production and metabolism, and then fat accumulation in human hepatocytes and in rats. They observed that AR upregulation induced from high glucose (25 mmol/L) led to a marked increase in both sorbitol and fructose in hepatocytes, resulting in the elevation of intracellular triglycerides. However, none of these increments was found in AR-deficient cells. Intracellular oxidative stress, as well as sorbitol, fructose and triglycerides, were markedly greater in HepG2 cells exposed to both high glucose (12.5 and 25 mmol/L) and high uric acid.
(12 mg/dL), as compared with the control

group. They also found that elevated hep-
amic uric acid induced upregulation of AR

and KHK in rats, as well as an increase in

intrahepatic sorbitol and fructose levels,

and an increase of NFAT5 expression

appeared in the nucleus of hyperuricemic

rats as compared with the control or allo-

urinol, xanthine oxidase inhibitor-treated

animals. In Figure 1, their new results are

summarized, along with their previous

data that uric acid also upregulated KHK

and fructose metabolism through the acti-

vation of the transcription factor, carbohy-
drate response element-binding protein.

This observation by Sanchez-Lozada

et al. is very important, because it means

that hyperglycemia-induced polyol path-

way hyperactivity in diabetes might cause

further activation with uric acid, con-

tributing not only to the development of

NAFLD, but also the progress of diabetic

complications in related tissues. Inciden-
tally, the relationship between uric acid

and diabetes is still inconclusive. However,
a recent study of non-diabetic individuals

showed that uric acid levels in plasma

increase with 2-h plasma glucose, but not

showed that uric acid levels in plasma

correlate well with clinical and electrophysiological

levels in diabetic and non-diabetic

populations. Differences in the association

between glycemia and uric acid levels in diabetic and non-diabetic populations. J Diabetes Complications 2019; 35: 511–515.

2. Sanchez-Lozada LG, Andres-Hernando A, Garcia-Arroyo FE, et al. Uric acid activates aldose reductase and the polyol pathway for endogenous fructose and fat production causing development of fatty liver in rats. J Biol Chem 2019; 294: 4272–4281.

3. Miyamoto T, Matsuoka T, Shimano H. Rho-associated, coiled-coil-containing protein kinase 1 as a new player in the regulation of hepatic lipogenesis. J Diabetes Investig 2019; 10: 1165–1167.

4. Hotta N, Akanuma Y, Kawamori R, et al. Long-term clinical effects of epalrestat, an aldose reductase

inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. Diabetes Care 2006; 29: 1538–1544.

5. Hotta N, Kawamori R, Fukuda M, et al. Long-term clinical effects of epalrestat, an aldose reductase

inhibitor, on progression of diabetic

neuropathy and other microvascular complications: multivariate epidemiological analysis based on patient background factors and severity of diabetic neuropathy. Diabet Med 2012; 29: 1529–1533.

6. Hotta N. Is there a place for inhibition of transforming growth factor-β and the polyol pathway in therapy for diabetic retinopathy? J Diabetes Investig 2010; 1: 134–136.

7. Umemura T, Kawamura T, Hotta N. Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: A possible link between cerebral and retinal microvascular abnormalities. J Diabetes Investig 2017; 8: 134–147.

8. Kun K-T, Chang Y-F, Wu I-H, et al. Differences in the association between glycemia and uric acid levels in diabetic and non-diabetic populations. J Diabetes Complications 2019; 35: 511–515.

9. Abraham A, Breiner A, Barnett C, et al. Uric acid levels correlate with the severity of diabetic sensorimotor polyneuropathy. J Neurol Sci 2017; 379: 94–98.

10. Ahmadi, H, Azar, S. Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus. Diabetes Technol Ther 2017; 19: 507–512.

11. Inoue M, Hayashi A, Taguchi T, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease. J Diabetes Investig 2019; 10: 1004–1011.

Doi: 10.1111/jdi.13190