PROCEEDING

Advantage of a low glycemic index and low phosphate diet on diabetic nephropathy and aging-related diseases

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Abstract : Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in Japan and other Westernized countries. Over 50% of the ESRD patients die from cardiovascular events. Cardiovascular disease (CVD) in ESRD patients with diabetes mellitus (DM) are implicated in the endothelial dysfunction caused by hyperglycemia, hyperlipidemia, and hypertension, and in the vascular calcification of intimal and medial arterial blood vessels caused by hyperphosphatemia. Therefore, dietary control of hyperglycemia and hyperphosphatemia should play an important role in the management of ESRD patients with DM. Furthermore, recent findings suggest that high concentrations of serum phosphate, even if within the normal range, may be a risk factor for CVD and mortality. An *in vivo* study using *klotho* knockout mice and fibroblast growth factor 23 (FGF-23) knockout mice has revealed that correction of hyperphosphatemia and hypervitaminosis D could ameliorate the premature aging-like phenotype. A low glycemic index and low phosphate diet may provide an advantage in the prevention of aging-related diseases in healthy individuals as well as in those with chronic kidney disease. J. Med. Invest. 54 : 359-365, August, 2007

CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASES

The number of individuals with chronic kidney disease (CKD) has dramatically increased in Japan as well as across the world. Patients with CKD, particularly those with end-stage renal disease (ESRD) on maintenance dialysis, have a high risk of cardiovascular disease (CVD) (1). CVD accounts for over 50% of annual mortality in individuals on hemodialysis (2). It is understood that both atherosclerosis and arteriosclerosis go hand-in-hand with vascular calcification, which is frequently observed in ESRD patients (3-5). Endothelial dysfunction, which is generally implicated in hyperglycemia, hyperlipidemia and hypertension, is a major pathomechanism in the process of atherosclerosis in both ESRD patients and non-CKD patients (6).

Diabetes mellitus (DM) is the leading cause of ESRD in Japan and the Western world. In Japan, about 40% of new hemodialysis patients (about 10,000 peoples per year) are diagnosed as having ESRD with DM (7). Hyperglycemia is also an important risk factor for CVD (8). The mechanism underlying the

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progression to CVD in ESRD patients with DM is very complicated, but chronic hyperglycemia and advanced glycation end products increase oxidative stress in the endothelial cells, resulting in lower NO availability, DNA damage and lipid oxidation, and eventually cause endothelial dysfunction (9). Improvement of hyperglycemia can slow the micro- and macro-vasculopathy that may play a central role in the development of CVD (10, 11).

Recent reports have demonstrated that the presence of vascular calcification is closely correlated not only with CVD but also with all-cause mortality (4, 12). Intimal calcification of the atherosclerotic plaques and medial calcification of both large and small arteries are frequently observed in ESRD patients (13). Both types of vascular calcification are associated with cardiovascular mortality (14). Jono, *et al.* have demonstrated that hyperphosphatemia and increased Ca×P not only accelerate intimal calcification, but also stimulate the differentiation of vascular smooth muscle cells to osteoblastic cells, resulting in medial calcification (15). Thus, hyperphosphatemia is also a risk factor for CVD in ESRD patients (16, 17).

From these observations, control of hyperglycemia and hyperphosphatemia might be important way to prevent CVD in ESRD patients with DM. Currently, many drugs are available for controlling hyperglycemia and hyperphosphatemia. However, nutritional treatment occupies a critical role in reducing CVD risk and preventing progressive damage to the kidneys and cardiovascular system.

CONTROL OF POSTPRANDIAL HYPERGLYCEMIA BY PALATINOSE-BASED FUNCTIONAL FOOD

Palatinose (isomaltulose) has been shown to be an insulin-sparing caloric sweetener with a lower glycemic index than that of either sucrose or a non-cariogenic caloric sweetener (18, 19). This difference may be due to variation in digestibility because the hydrolysis of palatinose by homogenates of human intestinal mucosa is one-quarter of that of sucrose (20). However, palatinose is completely cleaved and absorbed (21). We previously designed a novel enteral liquid formula, Inslow® (MHN-01), by replacing dextrin in the standard balanced formula (SBF) with palatinose at 55.7% of the carbohydrate content (Table 1) (22).

The effects of Inslow® on carbohydrate metabolism in Sprague-Dawley rats have been compared with those of SBF (22). After a bolus ingestion of each formula, the peak levels of plasma glucose (PG) in the femoral vein of the Inslow® group were found to be significantly smaller than those of the SBF group (Fig. 1). Thus, because postprandial hyperglycemia leads to increased oxidative stress in blood vessels and other organs, Inslow® is likely to be beneficial for controlling the progression of both DM and CVD.

Table 1 Composition of Inslow® and standard balanced formula (SBF).

	Inslow®	SBF
Energy	1 kcal/ml	1 kcal/ml
Protein	20.0 %	16.0 %
Fat	29.7 %	25.0 %
Saturated fatty acid	10.9 %	9.0 %
Monounsaturated fatty acid	72.3 %	45.0 %
Polyunsaturated fatty acid	15.1 %	40.0 %
Carbohydrate	50.3 %	59.0 %
Branched dextrin	23.9 %	0 %
Dextrin	0 %	97.2 %
Sucrose	0 %	2.8 %
Xylitol	5.3 %	0 %
Palatinose	55.7 %	0 %
Other carbohydrate*	15.1 %	0 %

*Other carbohydrate : mixed carbohydrate from raw material and dietary fiber

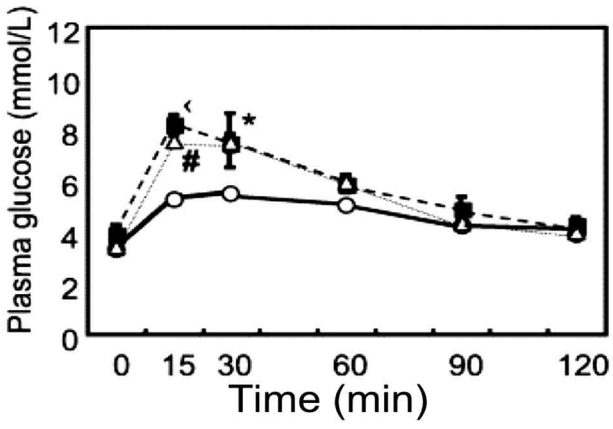

Fig. 1 Changes in plasma glucose in the femoral vein after oral administration of Inslow® (MHN-01) (open circle), standard balanced formula (SBF) (closed square), or glucose (open triangle) in Sprague-Dawley rats. The rats received 7.16 mL/kg BW of Inslow® (energy 30.0 KJ/kg, carbohydrates 0.90 g/kg BW, fat 0.24 g/kg, protein 0.36 g/kg), 6.11 mL/kg BW of SBF (energy 25.6 KJ/kg, carbohydrates 0.90 g/kg, fat 0.17 g/kg, protein 0.24 g/kg), and 6 mL/kg BW of 15% D-glucose solution (energy 15.1 KJ/kg, carbohydrates 0.90 g/kg). Data are mean ±SEM #P<0.05 vs MHN-01, *P<0.01 vs MHN-01.

CONTROL OF HYPERPHOSPHATEMIA IN ESRD PATIENTS BY A LOW PHOSPHATE DIET

Dietary control of hyperphosphatemia is another important way in which to prevent CVD in ESRD patients. Ganesh, *et al.* demonstrated that ESRD patients with elevated serum phosphate (>6.5mg/dL) show high cardiovascular mortality, as compared with those with low serum phosphate (≤6.5 mg/dL), in a 2-year follow-up study of two large random samples of patients on hemodialysis (n=12,833) in the United States (23). Another study has also reported that dialysis patients show increased risk of mortality and secondary hyperparathyroidism when their serum phosphorus levels exceed 6.5 mg/dL (24). By contrast, serum Ca showed no correlation with the relative risk of mortality in these studies (23, 24). These observations suggest that control of serum phosphate levels below 6.5 mg/dL could be needed to decrease the risk of CVD and mortality in ESRD patients.

Control of dietary phosphorus intake is the most effective way to manage hyperphosphatemia. In general, the average daily consumption of phosphorus in the Japanese population is approximately 1,200 mg. Cupisti, *et al.* recommended that a dietary intake of around 750-800 mg/day of phosphate can be planned for a large percentage of patients, although the acceptable amount of phosphate intake may vary with the frequency of dialysis, type and dose of phosphate binders, and nutritional status (25). In the past decades, several types of phosphate binder such as sevelamer hydrochloride, calcium acetate and lanthanum carbonate, among others, have become available for the treatment of hyperphosphatemia in hemodialysis patients (26) ; however, restriction of dietary phosphorus intake is likely to be needed to achieve optimal effects with these drugs. For dietary protein and phosphate restriction in CKD and ESRD patients, Renalen® Pro has been widely used as an enteral liquid formula in a low protein and low phosphate diet for the nutritional treatment of CKD and ESRD patients.

As noted above, dietary control of both hyperglycemia and hyperphosphatemia should be considered to be the basic treatment in patients with diabetic nephropathy. Recently, Renalen® LoGIC, in which the carbohydrate content in Renalen® Pro has been partially replaced with palatinose, similar to Inslow®, has become available. Administration of Renalen® LoGIC in GK rats results in a lower peak value of serum glucose as compared with Renalen® Pro (Fig. 2). Thus, Renalen® LoGIC is designed for use as a low phosphate and low glycemic index diet, and can be useful for the prevention of postprandial hyperglycemia as well as hyperphosphatemia. The beneficial effects of Renalen® LoGIC are likely to be helpful in the treatment of diabetic nephropathy to decrease the risk of CVD.

HYPERPHOSPHATEMIA IS NOT ONLY A PROBLEM IN ESRD PATIENTS

Hyperphosphatemia is not a problem limited to ESRD patients. Tonelli, *et al.* reported a graded independent relation between higher levels of serum phosphate and risk of death or cardiovascular events in people with prior myocardial infarction, most of whom had serum phosphate levels within the normal range (27). In addition, Nishida, *et al.* demonstrated that after ingestion of a meal containing 400 mg of phosphate and 200 mg of calcium, designated as the average mineral consumption in Japan, serum Pi levels increased at 2 h and were sustained until 6 h after the meal in eight healthy young males (28). Furthermore, a meal containing 1200 mg of phosphate and 200 mg of calcium increased serum Pi levels at 2 h after ingestion (Fig. 3). The peak values exceeded the normal range (between 2.5 and 4.5 mg/dL) in seven of the eight subjects. These results suggest that over-intake of phosphorus from diet can cause postprandial hyperphosphatemia, even

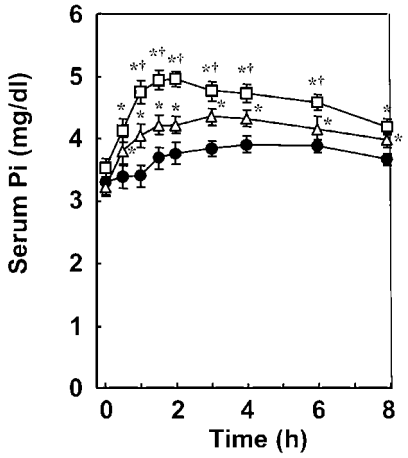

Fig. 2 Changes in serum phosphate levels in the femoral vein after oral administration of meals with different amounts of phosphate in humans. P400 (closed circle) contained 200 mg of calcium and 400 mg of phosphate, P800 (open triangle) contained 200 mg of calcium and 800 mg of phosphate, and P1200 (open square) contained 200 mg of calcium and 1,200 mg of phosphate. Data are mean±SEM for eight subjects. *P<0.05 vs P400, † P<0.05 vs P800.

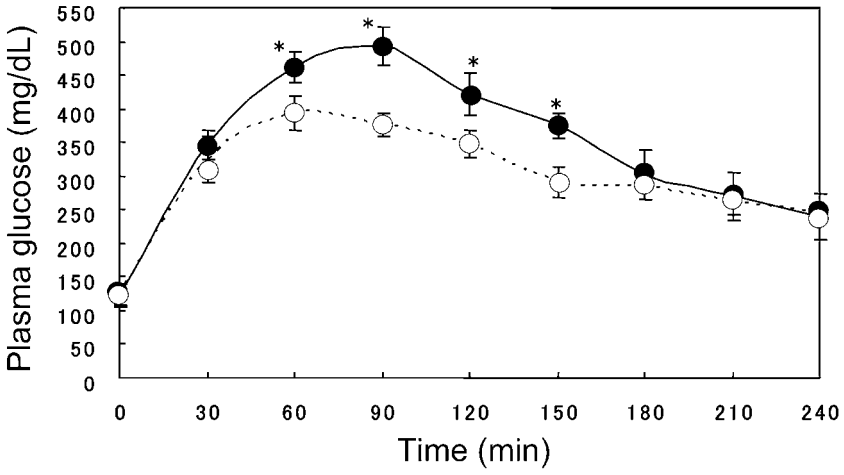

Fig. 3 Changes in plasma glucose levels in the femoral vein after oral administration of Renalen® Pro 1.0 (closed circle) or Renalen® LoGIC (open circle) in GK rats. The rats received 12 kcal/kg of Renalen® Pro1.0 or Renalen LoGIC®1.0 orally. Data are mean±SEM for five rats. *P<0.05 vs Renalen® Pro 1.0

if the fasting serum phosphate level is in the normal range. We note that postprandial hyperphosphatemia might be a risk factor for CVD and mortality even in individuals without ESRD.

ADVANTAGE OF A LOW GLYCEMIC INDEX AND LOW PHOSPHATE DIET ON AGING-RELATED DISEASES-LESSONS FROM KNOCKOUT MICE

The mechanism underlying the association between serum phosphate levels and adverse clinical outcomes has not been clarified as yet. However, two experimental animals have provided us with interesting information : one is fibroblast growth factor 23 (FGF-23) knockout mice (*Fgf23*$^{-/-}$) (29), the other is *klotho* mutant mice (30). FGF 23 is a recently identified phosphaturic factor that is produced in bone and is a potent inhibitor of renal phosphate reabsorption activity (31, 32). Klotho has been identified as an anti-aging factor (29). *klotho* mutant mice, in which *klotho* gene expression is dramatically decreased by a mutation in the promoter region, show a premature aging-like phenotype and short lifespan (33, 34). Both *Fgf23*$^{-/-}$ and *klotho* mice exhibit short lifespan and various premature aging-like characteristics, such as arteriosclerosis, ectopic calcification in various soft tissues, osteopenia, emphysema, atrophy of the skin, and severe hyperphosphatemia with increased concentration of serum 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$). Surprisingly, depletion of dietary vitamin D intake can ameliorate the most of the phenotypic characteristics of these mice including hyperphosphatemia (34, 35). Furthermore, a vitamin-D-deficient diet decreased blood glucose and insulin concentrations in *klotho*-deficient mice (34). Therefore, Klotho protein plays a key role in the control of mineral and vitamin D metabolism.

How can *klotho* work as a regulator of vitamin D and mineral metabolism® Most recent reports have demonstrated that Klotho protein is necessary for binding of FGF23 to the FGF receptors (36, 37). The resulting signaling complex regulates both 1 α-hydroxylase, which is a rate-limiting enzyme in the production of 1,25-$(OH)_2D_3$, and the sodium-dependent phosphate transporters (NaPi-IIa and NaPi-IIc), which mediate the rate-limiting step in renal phosphate reabsorption (38). Thus, impairment of FGF23/Klotho signaling in *klotho* knockout mice and *Fgf23* knock out mice may cause disregulation of mineral metabolism, leading to the premature aging-like phenotype observed (39, 40).

One possible pathomechanism may be oxidative stress. Yamamoto, *et al.* have demonstrated that Klotho-induced inhibition of insulin/IGF-1 signaling is associated with increased resistance to oxidative stress (41). In addition, Morishita, *et al.* have reported that phosphate restriction can increase the expression of Klotho protein in normal and *klotho* mutant mice (36). Recently, we reported that an elevation of extracellular phosphate increased the production of reactive oxygen species in bovine aortic endothelial cells (42), suggesting that hyperphosphatemia may be involved in endothelial dysfunction and insulin resistance resulting from oxidative stress. Thus, impairment of the counter-regulation between phosphate metabolism and FGF23/Klotho signaling may play a part in various aging-related diseases and short lifespan. Controlling phosphate and vitamin D intake, coupled with a low glycemic index diet, may thus provide an advantage in both the prevention of aging-related diseases and increasing lifespan by reducing oxidative stress and other adverse effects.

CONCLUSION

A low glycemic index and low phosphate diet would be a useful treatment for CKD patients, especially those with DM, to reduce their risk of CVD and mortality. In addition, this diet may be beneficial in the prevention of several aging-related diseases such as CVD even in healthy individuals. Further studies are required to clarify the mechanism underlying the association between phosphate and adverse clinical outcomes in patients, and a large-scale trial of the prevention of aging-related diseases by phosphate restriction in the human population is warranted.

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