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# The 452nd International Symposium on Therapy

The 452nd International Symposium on Therapy was held by the Zoom Webinar on January 20, 2022. Dr. Ryozo Nagai, Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

## Effects of phosphate intake on health and CKD

### Introductory Message from the Chair

Ryozo Nagai, MD, PhD
Director, IMSJ

As the theme of the 452nd session, "Effects of phosphate intake on health and CKD" has been covered. Phosphorus metabolism is finely controlled in the body, and it is said that in renal failure, phosphorus concentration in blood increases, which poses a risk of developing cardiovascular disease. More recently, it has been suggested that phosphorus accelerates aging. How to use the achievements of such phosphorus metabolism research in clinical medicine and health management is a major issue. For example, phosphorus is abundant in soft drinks and processed foods, but the proper intake of phosphorus for healthy individuals and the difference between organic and inorganic phosphorus are not specified on the labels of the products. It may also be possible to reduce cardiovascular complications by reducing phosphorus levels in patients with renal failure. So this time, we receive a lecture about phosphorus and renal failure from Makoto Kuro-o, MD, PhD (Professor, Jichi Medical University), who discovered the klotho gene that regulates aging and phosphorus metabolism, and is promoting translational research, and Daisuke Nagata MD, PhD (Professor, Jichi Medical University), who has abundant clinical experience in kidney disease.

### Lecture I

## Chronic kidney disease and cardiovascular complications

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Chronic kidney disease (CKD) is defined as a renal disorder such as proteinuria or a condition in which GFR <60 mL/min / 1.73 m2 continues for three months or longer and is a critical disease category associated with end-stage renal failure and cardiovascular complications. As a concept, it was proposed by the National Kidney Foundation (NKF) in the United States in 2002. It has been exactly 20 years since then, and it is still hard to say that the concept is well-known to the public. Hypertension and diabetes mellitus (DM) is the majority of the causative diseases of CKD, and both of them account for about 60%. Therefore, therapeutic interventions for hypertension and DM are essential in controlling the progression of CKD.

Renin-angiotensin (RA) inhibitors, ACE inhibitors (ACEI) / ARBs reduce the risk of progression to end-stage renal disease and death, with or without DM complications and at the CKD stage. It is reported in CKD clinical guidelines (GL) 2018 ACEI and ARB are recommended as first-line drugs for DM and non-DM / proteinuria A2 or higher and for urinary protein (-) of CKD stage G1-3 without DM. On the

other hand, in ACC-AHA GL in 2017 and KDIGO CKD blood pressure treatment (BP) GL revised in the spring of 2021, RA inhibitors are not the first-line drug for proteinuria A1 even in CKD with DM. Regarding the blood pressure reduction target, since the SPRINT study in 2015, there is a strong tendency to aim for strict blood pressure reduction even in CKD. In CKD GL2018, the blood pressure reduction target is <140/90 mmHg for CKD without DM of proteinuria A1, <130/80 mmHg for DM, and proteinuria A2, A3, but <130/80 mmHg for CKD in ACC-AHA GL. In KDIGO BPGL, systolic pressure <120 mmHg and severe blood pressure reduction are recommended under the condition of standardized examination room blood pressure.

The EMPA-REG outcome trial reported that SGLT2 inhibitors improved the cardiac and renal prognosis in a population of patients with a background of arteriosclerosis. SGLT2 inhibitors have sodium excretion promoting action and antihypertensive action in addition to glucose by inhibiting SGLT2, a cotransporter of sodium and glucose expressed at the origin of the proximal tubule. SGLT2 inhibitors also increase the concentration of NaCl reach to the macula densa of the distal tubule and have a corrective effect on glomerular overfiltration due to afferent arteriole contraction via the TGF mechanism. It is believed that there are other mechanisms by which SGLT2 inhibitors have protective effects in cardiorenal therapy besides the optimization of TGF. Among them, the mechanism by glucagon and ketone bodies is considered the most promising. SGLT2 inhibitors release glucagon from a cells of the pancreas, and glucagon exerts a positive inotropic effect on the myocardium and works effectively to improve heart failure. Furthermore, due to a decrease in the insulin / glucagon ratio, the liver increases the production of 3-β hydroxybutyrate (β-HB), a type of ketone body. It is known that β-HB serves as a substrate for supplementing Acetyl-CoA via a pathway different from that of glucose or fatty acid.

Risk factors for cardiovascular complications in CKD can be divided into classical risk factors and non-classical risk factors. Classic factors are so-called risk factors for arteriosclerosis, such as diabetes, hypertension, high LDL cholesterol. Non-classical factors include albuminuria, abnormal Ca-P metabolism. In 2019, Sarnak et al. reported that cardiovascular disease associated with CKD mainly depends on classical risk factors while the CKD stage is low, but as the stage progresses, the proportion of non-classical one's increases. In CKD, the function of the cholesterol reverse transfer system from the vasculatures to the liver is reduced because of decreased LCAT activity, so if cholesterol is controlled with statins, atherosclerosis is expected to be prevented. The SHARP trial showed that simvastatin plus ezetimibe reduced initial atherosclerotic events by 17% in patients with advanced CKD.

Calciminetics used in the treatment of secondary hyperparathyroidism can be expected to suppress Monckeberg's medial sclerosis by optimizing Ca-P metabolism. In the EVOLVE trial, cinacalcet did not significantly suppress cardiovascular complications in dialysis patients. However, non-classical risk factors cannot be underestimated, and we should find appropriate intervention methods by changing the population and timing of administration.

## Lecture II

# Phosphate accelerates kidney aging

Makoto Kuro-o, MD, PhD
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Division of Anti-aging Medicine, Center for Molecular Medicine
Jichi Medical University

Chronic kidney disease (CKD) is defined as any abnormality of kidney structure and/or function lasting 3 months or longer. CKD progression can be viewed as a process of a decrease in the functional nephron number that occurs during the natural course of kidney aging and that is accelerated by specific renal diseases and systemic disorders causing renal complications such as diabetes and hypertension. Despite the recent development of new drugs for diabetes and hypertension, the number of CKD patients is increasing in the aging society. It is of urgent medical need to establish effective therapeutic strategy for age-related nephron loss. We have identified phosphate as a universal factor that accelerates nephron loss and kidney aging.

Phosphate is toxic to the kidney. Excess phosphate intake induces renal tubular damage and interstitial fibrosis in rodents and humans. The renal toxicity of phosphate correlates with phosphate excretion per nephron, which is primarily regulated by fibroblast growth factor-23 (FG23). FGF23 is a bone-derived phosphaturic hormone secreted in response to dietary phosphate intake. FGF23 increases phosphate excretion per nephron through suppressing phosphate reabsorption at renal tubules. FGF23 plays a critical role in the maintenance of phosphate homeostasis by balancing between dietary intake and urinary excretion of phosphate.

An FGF23-induced increase in phosphate excretion per nephron raises phosphate concentration in the renal tubular fluid. We hypothesized that renal tubular cells might be damaged when

exposed to high extracellular phosphate. To test this hypothesis, we cultured renal tubular cells and added phosphate to the medium. As expected, phosphate induced renal tubular cell damage in a dose-dependent manner. During this experiment, we noticed that the medium became slightly cloudy when the phosphate concentration exceeded a certain threshold. Electron microscopic observation revealed that numerous electron-dense nanoparticles were dispersed in the cloudy medium, which turned out to be calciprotein particles (CPPs). CPPs were colloidal particles composed of solid-phase calcium-phosphate and serum protein fetuin-A. Importantly, the phosphate-induced cell damage was completely blocked in the presence of bisphosphonate that inhibited formation of calcium-phosphate crystals. These findings indicated that it was not phosphate per se but CPPs that were toxic to renal tubular cells.

We demonstrated that dietary phosphate load increased serum FGF23 levels and induced CPP formation in the renal tubular fluid in mice. Once the nephron number was decreased due to CPP-induced renal tubular damage, serum FGF23 levels were required to rise further to maintain the phosphate homeostasis, thereby triggering a deterioration spiral leading to progressive nephron loss.

We also demonstrated that the phosphate concentration in the proximal tubular fluid (PTFp) could be estimated by the following equation:

$$estimated\ PTFp\ (ePTFp) \equiv \frac{Up}{Ucr} \times Scr \times 3.33$$

Up, Ucr, and Scr represent concentration of urinary phosphate, urinary creatinine, and serum creatinine, respectively. We placed mice on diet containing different amounts of phosphate, measured their FGF23, ePTFp, and renal tubular damage markers, and found that progressive renal tubular damage and nephron loss ensued when the FGF23 and ePTFp levels exceeded certain thresholds. In humans, the thresholds of FGF23 and ePTFp were 53 pg/mL and 2.3 mg/dL, respectively. Individuals whose FGF23 and ePTFp levels are higher than these thresholds represent approximately one-quarter of adults over the age of 45 years and two-thirds of early to mid-stage CKD patients, indicating that the amount of phosphate consumed daily can be a universal factor that accelerates the onset and progression of CKD.

Phosphate restriction (control of dietary phosphate intake and administration of phosphate binders) is currently applied for CKD patients with hyperphosphatemia to lower serum phosphate levels for prevention of vascular calcification and cardiovascular events. However, its application is limited to advanced CKD patients, because hyperphosphatemia is a terminal symptom observed only in end-stage renal disease (ESRD). On the other hand, our findings suggest that phosphate restriction may be beneficial not only to ESRD patients but also to the aged and early-stage CKD patients with normal serum phosphate levels. Clinical trials targeting these populations are awaited to determine whether phosphate restriction to lower FGF23 and ePTFp levels below the thresholds may prevent the onset and progression of CKD.

## Discourse

### Introduction of the speaker of discourse

Ryozo Nagai, MD, PhD
Director, IMSJ

Hiroki Shimazu (Fellow/Unit Leader, Center for Research and Development Strategy, Japan Science and Technology Agency) provides a topic on the issues of Japan's innovation system.

After graduating from the Graduate School of Science, Osaka University, Mr Shimazu has been involved in bird's-eye view and research strategy planning in fields such as information, nanotechnology/materials, and life sciences at JST after being in charge of industry-academia collaboration projects. He has written reports such as “Bird's eye view report”, “Materials informatics”, “Transformation of science and technology/ innovation with digital transformation”, “AI x Bio”, and “International benchmark of research system at universities and national research institutes for the purpose of strengthening research capabilities” in each field. He is also a qualified patent attorney.

We expect many people to attend his lecture.

# Discourse: Biotech Ventures and Innovation Ecosystem : from Case Studies of Recent S&T Innovation

Hiromoto Shimazu
Fellow/Unit Leader
Center for Research and Development Strategy
Japan Science and Technology Agency

Global venture capital (VC) investment continues to grow year by year, surpassing $621 billion and reaching more than double the previous year in 2021. More than 800 startups became unicorns which have a corporate valuation of over $1 billion within 10 years of establishment. This is because the progress of science and technology and the creation of startups in various fields are closely linked to radical innovation. In the 1970s, at the dawn of the PC, Microsoft and Apple were founded. With the birth of biotechnology, Genentech, Amgen and others were established and each of them now is one of the world's leading pharmaceutical companies. As a result of the spread of the Internet in the 1990s, NVIDIA, Amazon, and Google were established, Facebook was established when smartphones appeared in the 2000s, and Tesla was established when clean energy became an issue. Tesla is now leading the way in autonomous driving. Widely used vaccines were also realized by the science and technology of startups called BioNTech and Moderna. Global innovation and economic growth are supported by these startups. Currently, worldwide, investment in deep tech that has the potential to bring about radical innovations in the future such as AI, robots, VR/AR (augmented reality), quantum, space, energy, brain tech, precision medicine, and synthetic biology is increasing. Although the culture of Europe used to center around large companies like Japan, the European Innovation Council has been established and startup promotion measures related to deep tech are being promoted. As far as the biotechnology field is concerned, the investment level is comparable to that of the United States due to the success of BioNTech (Germany) and others.

Even if new science and technology emerges from universities, large companies are unlikely to undergo radical innovation due to the innovator's dilemma. It is also the existence of startups that makes up for that.
It is no exaggeration to say that even in Japan, currently, the second university-launched venture boom has arrived following the 2000s, but until now, startups with a strong presence in the world have not grown up. The following items were reported as global macro trends.

- In the biotechnology field, venture companies play a major role in radical innovation. In other words, large companies are entrusting new basic applied research to venture companies.
- The essence of the ecosystem in Boston is shared by each high-risk-high-return (capital gain) player (entrepreneur/venture, university, support organization such as VC, large company).
- A strong group of academia (research seeds) in the innovation ecosystem greatly increases the probability to innovate.
- Since pharmaceuticals and medical devices are fields where it is difficult to produce results (sales) within 10 years of VC investment-return deadline, not only IPO but also M & A culture is necessary.
- Ventures that are very active in the world are hybrid types that combine platform technology with pharmaceutical/healthcare services.
- An ecosystem based on the characteristics of the biotechnology field is required. High-risk-high-return biotechnology field is similar to the IT field in that it is suitable for venture companies, but its risk governance framework is different. New science and technology will be the core of the business for what it is. However, it is necessary to reconcile technologies from a wide range of different fields such as life science, chemistry, engineering (optics/microfluids, etc.), and informatics. There is also legal regulation that requires government authorities to scrutinize trials through preclinical and three phases of clinical (human) trials.

In addition, the following were extracted as micro trends.

- In the United States, an average of about 3 billion yen/year is collected within a year or two after the startup of a venture. In Japan, it is around 500 million yen/year.
- As the volume of VC funds continues to grow, it is easier for venture companies to raise large amounts of funds without listing their stocks early.
- Hybrid ventures such as gene therapy (genome editing) and cell therapy can be expected to have the highest returns, but they also require appropriate funds. The IPO has been carried out about three years after its establishment.
- For platform technology ventures such as AI and NGS, a process has been established to raise a large amount of necessary funds in an unlisted state and take a sufficiently long preparation period for growth to become a unicorn.

Research and innovation capabilities at universities are two sides of the same coin. Silicon Valley and Boston, the birthplaces of typical innovations, have built a startup ecosystem since the 1980s. Emerging forces such as Shenzhen, Israel, and Singapore have regional characteristics where ventures are made up of foreign capital, and there

are also field-specific characteristics. For example, while there are many student/faculty-launched ventures centered on business models in the IT field, there are many R & D-type ventures that use the results of universities in the biotechnology field. What is indispensable in all of these is not only the traditional industry-academia-government collaboration, but also the accumulation and circulation of entrepreneurial and commercialized human resources such as entrepreneurs, VCs, incubators, and accelerators. We need a culture and an environment that allow researchers to easily startup ventures and tolerate failure.

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