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Review

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Low Potassium Content Vegetables Research For Chronic Kidney Disease Patients in Japan

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ABSTRACT

Chronic Kidney Disease (CKD) is a common disorder to the elderly people, and its prevalence is increasing globally. We are turning into a super-aged society very rapidly and the number of CKD patients with dialysis treatment is now over 310,000 in Japan, which is the second largest population in the world. Japanese researchers have a pioneering status in addressing this issue through basic and clinical nephrology research. In addition, advanced research related to the dietary supplementation of CKD patients is essential for the management of this life threatening disease. This review aims to provide recent research advances of CKD on low-potassium vegetable production and dietary supplementation to dialysis patients in Japan.

KEYWORDS: Potassium; Vegetables; Hydroponics; Dietary supplementation; Dialysis patients.

INTRODUCTION

Potassium requirement is essential for normal function of the muscles, heart, and nerves in human body. It plays an important role in the contraction or relaxation of skeletal, smooth, and cardiac muscles, nerve impulse transmission, acid base equilibrium, enzymatic action, intracellular fluid tonicity, and renal function.[1,2] It is one of the most important electrolytes in the human body whose excess or deficiency may cause impairment of the body function and even result in death. It is also main electrolyte in the intracellular compartment, which accumulates more than 98% of total body potassium. The serum concentration of potassium is usually 3.5 to 5.0 mEq/L, while intracellular concentration is 115 to 150 mEq/L. Increase or decrease in these levels can negatively affect an individual's health. For example, high serum concentrations have adverse effect on heart muscle and may cause cardiac arrhythmias. Two-three times elevation of normal serum potassium level may result in cardiac arrest, which can be detected through the electrocardiogram.[3]

The kidneys normally excrete more than 90% of daily body potassium but patients with CKD can't completely excrete it, and thus, residual potassium accumulates in the body. In a study it is reported that a normal kidney has the capacity to excrete over 400 mmol potassium day[1,4] and it is unlikely that an individual will become chronically hyperkalemic without some degree of chronic renal impairment. The abnormally (2-3 times) elevated level of potassium in the blood may cause hyperkalemia, resulting in adverse effects on human body such as

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arrhythmias, muscle weakness, disturbed consciousness, heart failure, and even leading to sudden death.[5,6] The CKD population is increasing gradually and it is expected that the total number of patients will continue to increase progressively. According to Japanese Society of Nephrology, the number of CKD patients is estimated about 13.3 million (one in eight adults) in Japan.[7,8]

Dialysis, resin adsorbent, diuretic medication, intravenous Ca, glucose and insulin, and sodium bicarbonate are the common treatment methods for hyperkalemia but dietary intake most important. Therefore, CKD patients should pay attention to the diet. As a primary control measure, doctors restrict foods with high potassium content such as fresh vegetables, seaweed, beans and fruits including melon, strawberry, banana and kiwi.[9] Moreover, as potassium dissolves easily in water, CKD patients with dialysis are advised to cut these potassium-rich fruits and vegetables into small pieces and boil or soak them in a large volume of water prior to eating.[10] Although potassium content is partially reduced by these methods, the degree of reduction is limited through these food-preparation procedures.[11,12] In addition, these food preparation methods might result in wash out of other essential nutrients such as water-soluble vitamins and minerals and also the breakdown of desirable texture of raw lettuce.[11] In the above condition, to put it in an extreme way, dialysis patients do not eat the same dishes with other family members. For example, eating melon fruits is like a dream to them. As a result of such dietary restriction, their quality of life decreases greatly. Therefore, supplementation of vegetables containing less amount of potassium than usual would be a useful preventive method.

In Japan, researchers are giving effort to produce vegetables with low potassium content for example; low-potassium spinach, lettuce, melon, tomato, carrot, and strawberry.[13-19] Plants of these vegetables are grown in standard nutrient solution following quantitative management of solution KNO_3 or replacing it by a non-potassium fertilizer like HNO_3. Using this method, it is possible to reduce the potassium content of crops without inhibiting their normal growth. Recently, Aizu-fuji-kako Co., Ltd. (Tokyo, Japan) applied this cultivation method to produce low-potassium content leaf lettuce in larger scale. In the next section, we will describe the role of potassium in plants and humans, and recent advances in low-potassium vegetable production for dietary supplementation to dialysis patients.

Potassium as a Dietary Component

Potassium is necessary for the normal water balance between the cells and body fluids. Studies indicate that the average daily potassium intake is 2000-3900 mg,[4,20,21] which is too high for patients with kidney dysfunction to excrete. Thus, CKD patients with hyperkalemia are recommended to limit potassium intake to <1500 mg/day (Stage 5 patients) or 2000-2500 mg/day (Stage 3 and stage 4 patients).[21] Among all the vegetables, potato is the highest source of potassium and it is often suggested to adopt special preparation for making potato dishes. Moreover, potassium in foods is present with phosphate, sulfate, citrate, and many organic anions including proteins. Therefore, it is essential to bring some change in the general food habit of CKD patients. Potassium intake may be decreased with the agricultural revolution, when energy intake is shifted from a variety of plants including potassium-rich tubers to cereals and animal products with lower potassium content, and further decreased with a shift to highly refined processed foods.[22] At present, however, because dietary management is an important factor to improve outcomes in dialysis patients, clinical guidelines provide a recommended intake of micronutrients[23] to prevent hyperphosphatemia, hyperkalemia, hypertension, and water retention; and also reduced intake of protein, raw vegetables, and salt is recommended.[24-30]

Chronic Kidney Disease in Japan

CKD is defined by progressive decline in kidney function, documented by serum creatinine and the rate of creatinine clearance as measured by the rate of glomerular filtration.[31] It is a relatively common disorder with an increasing prevalence worldwide, and especially in Japan, where the prevalence of CKD has increased significantly over time.[32,33] Patients with chronic kidney disease suffer from a common life-threatening complication called hyperkalemia, abnormal increase in serum potassium.[34] Severe hyperkalemia may cause cardiac arrythmia and cardiac arrest.[29] Patients with diabetes, hypertension, and cardiovascular disease are of high risk for CKD.[35,36] Additional risk for development and progression of CKD may be conferred through lifestyle factors such as smoking and obesity.[37] Five stages of CKD are defined by reduced glomerular filtration rate and ranged from stage 1 to stage 5. Damage to the kidney may ultimately progress to stage 5 kidney failure, necessitating dialysis or kidney transplantation.[35] It also presents an economic burden, with the medical cost of end-stage renal disease representing approximately 4% of the total health care budget in Japan.[38]

In Japan, more than 300,000 CKD patients are treated with maintenance dialysis, and the number is gradually increasing. It is easily supposed that the number of CKD patients will grow even larger than ever and their health problems will become more complex as their age. Therefore, taking countermeasure against future pandemic of CKD is the most important task for the Japanese Nephrologists. It is estimated that the prevalence of CKD in Japan was 13.3 million and of CKD stages 1, 2, 3 and 4 + 5 were 0.6, 1.7, 10.7, and 0.2 million, respectively.[39] In this regards, the Japanese Society of Nephrology published guidelines for standardize treatment of CKD in 2007 and 2009.[40,41]

Potassium as Major Plant Nutrition

Potassium is one of the major nutrients, essential for normal growth and development of plants.[42] Plants absorb more

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potassium than any other mineral element with the exception of nitrogen.[43-46] It is the only monovalent cation that is essential for all higher plants, and is involved in three major functions such as enzyme activation, charge balance and osmoregulation.[46,47] Voogt and Sonneveld[48] found that with increases in tomato plant growth, potassium absorption increases to a relatively greater extent than that of other nutrients. In other studies, it was found that potassium requirement of greenhouse tomatoes is high for vegetative growth,[49,50] fruit production,[51] and fruit quality.[52,53]

Lower potassium levels in the culture solution may limit its assimilation into plant parts and retard plant growth, flower development, and fruit set.[51] It has direct effects on the partitioning of dry matter to the fruits and roots, and the growth of these organs is inhibited at lower potassium[54] and also fruit quality.[52,55] During the reproductive growth periods, fruits are the strongest sink for both carbon assimilates and potassium, therefore, quantitative management potassium in the culture solution is important option for producing low potassium fruits. In some determinate tomatoes, the demand for potassium during rapid fruit growth is above the uptake capacity such that leaf potassium is remobilized, resulting in foliar deficiency of the element.[56] Because of remobilization and recycling from old parts to new organs,[57,58] visible symptoms of injury do not appear on the growing sinks immediately in potassium deficient nutrient medium.[59] Thus, it is inevitable that reduced potassium supply will inhibit plant growth and yield. Therefore, investigation on minimal requirements of potassium in plants required for maintaining their normal growth and development is important. Additionally, production of melon fruits with low potassium content will also provide supplemental diet to the dialysis patients and may be of great interest for the patients, their family, hospitals, as well as the research community.

PRODUCTION OF LOW POTASSIUM CONTENT VEGETABLES IN JAPAN

Melon

Generally greenhouse cultured raw melon has higher potassium content of 340 mg/100 g fresh weight.[60] Significant decreases in potassium content in melon fruits would improve the diet of dialysis patients. Therefore, our research group used quantitative management of hydroponic culture solution for producing low potassium content melon and it was found that a reduction in KNO_3 in hydroponic solution could reduce the potassium concentration in melon fruit.[16] As hydroponic culture provides more precise control of growth conditions, it is easier to study various factors or parameters. Since a regular nutritional testing is conducted in the hydroponic growing system, so it can be easily defined whether the desired amount of nutritional content is present in the plants or not. It has also the precise control over concentration and composition of culture solution, which can be used for the production of both mineral enriched or deficient fruits and vegetables. Considering the above advantage of hydroponics, simple management of culture solution used for melon by reducing the potassium at lowest possible level would decrease fruit potassium content. Therefore, melon (*Cucumis melo* L. cv. Panna) were grown in nutrient solution with reduced KNO_3 concentrations from anthesis till harvest to investigate its impact on the fruit potassium content while maintaining normal growth, yield and other fruit qualities.

Three independent melon cultures were verified during the spring seasons from 2009 to 2011. In spring 2009, melon plants were grown in nutrient solution with 1/4th KNO_3 decreased fruits potassium by 39% compared to fruits potassium in standard nutrient solution, whereas it was decreased by about 35% and 43% when melon plants were grown in nutrient solution with 1/16th and O levels of KNO_3 in the spring 2010 and 2011, respectively. Compared to Standard Tables of Food Composition in Japan,[60] about 39% (207 mg/100 g FW) decreased potassium was found in melon fruits grown in nutrient solution without KNO_3 from fruit formation to final harvest during spring 2011. Fruit potassium content was not decreased expectedly even after limiting the potassium level to zero. The possible reason behind was the excessive absorption into the plant foliage during vegetative growth and storage before the start of potassium restriction, which in turn translocated into the melon fruits. Therefore, consideration of potassium translocation from leaves and stems to fruits during fruit developmental stage is an important issue for this study. Quantitative supply of KNO_3 to culture solutions of melon during vegetative growth would lower the fruit potassium level considerably. We have tried to serve low-potassium melon for lunch or dinner in CKD patients to verify the safety (Table 1) and evaluate the effectiveness (Figure 1). So far, we have a good response and need further investigation.

Strawberry

Hydroponic culture of strawberries has gained popularity for the commercial production of strawberries.[61] Generally, greenhouse-cultured fresh strawberries have a high K content of 170 mg/100 g FW of fruit.[60] Reducing this level in strawberry fruit would provide a good option in the diet for CKD patients. Therefore, our

Eating low-potassium melon	Serum K (mEq/L)	Serum Na (mEq/L)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse (/min)
Before	4.6±0.4	136.6±3.1	118.7±11.8	70.1±11.4	71.6±13.5
After	4.6±0.3	137.7±1.9	119.4±14.8	67.8±9.6	71.7±15.1
p-value	0.5	0.67	0.58	0.92	0.39

Table 1: Serum K and Na levels, blood pressure, and pulse before and after eating low-potassium melon. We served 100 g of low-potassium melon for dinner and measured serum K and Na levels, blood pressure, and pulse in 9 CKD patients (estimated GFR<45 ml/min/1.73 m^2) with mean age of 69 in a hospital. No significant change was determined before and 1 day after eating low-potassium melon in addition to their usual diet.

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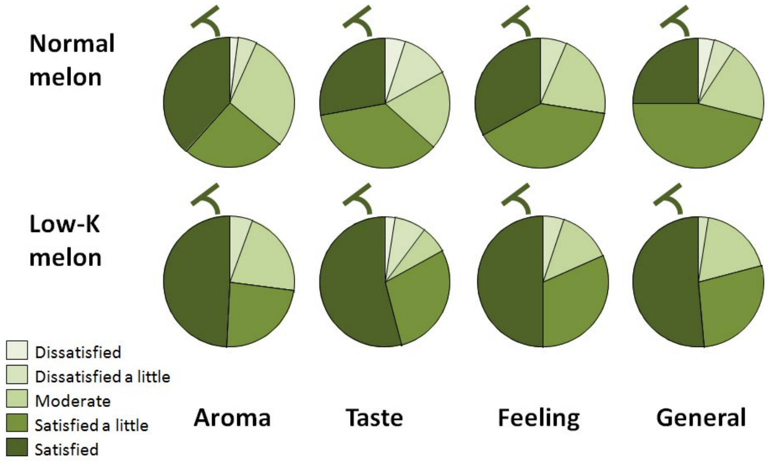

Figure 1: Results from a questionnaire regarding low-potassium melon in 76 dialysis patients. We served 50 g of low-potassium melon and 50 g of normal melon blindly in 76 maintenance dialysis patients in their lunch box. After eating melon, they answered some questions regarding the aroma, taste, and feeling without any information about melon. Interestingly, they satisfied with low-potassium melon at least as same as normal melon. Results were similar to those of healthy subjects (not shown).

research group attempted to produce low-potassium strawberry fruits through management of a KNO_3 fertilizer in nutrient solution from anthesis to the harvest period.[18] A general trend of decreasing potassium content in fruit was observed with the decrease of KNO_3 concentration in the nutrient solution. Among four strawberry cultivars, the fruit of the 'Toyonoka' exhibited a potassium reduction of about 64% when plants were grown in nutrient solution with KNO_3 at $1/16^{th}$ of the normal level. However, citric acid and ascorbic acid contents of 'Toyonoka' fruits were also reduced with decreasing KNO_3 concentrations in the nutrient solution. The use of $Ca(NO_3)_2$ in the nutrient solution to compensate the reduction in NO_3^- levels because of the use of low KNO_3 nutrient solution did not significantly affect the growth, yield and quality of these low-potassium strawberries. Compared with the standard potassium content in strawberry fruit, a 23.5% decrease (130 mg/100 g FW) in potassium was found in cultivars with $1/32^{nd}$ level of KNO_3. The potassium contents of plant parts suggested that the low KNO_3 level was responsible for the low potassium absorption, which may have affected the translocation and accumulation of potassium into fruit. Therefore, $1/32^{nd}$ of KNO_3 in nutrient solution lowers the fruit potassium content considerably.

Tomato

If low-potassium tomato fruit can be produced, it can improve the dietary options of dialysis patients. Effects of the amounts of potassium supply on the potassium content in fruits of cherry tomato and middy tomato were investigated in hydroponics for producing low-potassium content tomatoes.[62] A specific method of producing low-potassium content tomato (*Solanum lycopersicum* L.) fruit was investigated.[19] Several medium-sized tomato cultivars were tested, and the potassium supply was restricted using hydroponic production. Some plants were maintained through setting of a single fruit truss, and fresh fruit weight was not affected by potassium restriction. Total potassium uptake per plant decreased by 92% with lower potassium compared to conventional cultivation in which potassium content in fruit decreased by only 25%. Other plants were maintained until three trusses per plant were set, and fruit potassium content decreased 40% to 60% depending on cultivar because of potassium restriction. The variety "Aichan" was the most sensitive and variety "Frutica" was the least sensitive to potassium restriction. Total soluble solids content decreased slightly. Titratable acid content was affected by potassium restriction and decreased 20% to 40% depending on cultivar. In either case, potassium withdrawal in hydroponic culture following anthesis of the third truss was effective in producing low-potassium tomato fruit and could decrease fruit potassium content to at least 50% of expected tomato fruit potassium content.

Spinach

Hydroponic culture methods for spinach have been investigated with lower levels of potassium in the culture solution.[13] Spinach plants were grown hydroponically either with reduced potassium application throughout the growth period or without potassium applications during the last half of the growth period. There were no significant differences in fresh weight were observed in plants cultured with either of the solution. However, the potassium content in plants was reduced as much as 32% by reduced potassium application throughout growth period and 79% by without potassium application during the later half of growth period compared to control. These results suggest that it is possible to produce low-potassium spinach maintaining the normal plant growth. Other minerals like sodium and magnesium content increased with the decrease of potassium content, showing antagonistic role in osmotic pressure balance.

Lettuce

Lettuce is a popular potassium rich vegetable usually eaten raw in salad. CKD patients with hyperkalemia can't intake large

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quantities of raw vegetables like lettuce, tomato, strawberry etc. To help these patients offset deficiencies in their vegetable intake, Fujitsu has started growing low-potassium lettuce. Capitalizing on know-how accumulated by manufacturing semiconductors to grow vegetables, Fujitsu has been carrying out agricultural management using ICT to optimize cultivation efficiency through developing infrastructure and performing data analysis. A patent has been given by Aizufujikako Co. Ltd. (Japan) for "Vegetable Having Low Potassium Content and Method for Culturing Said Vegetable". They reported that compared to normal leaf lettuce, low-potassium content lettuce has 100 mg or less of K/100 g fresh weights, while leaf lettuce contain 490 mg of potassium/ 100 g of fresh weight.[63] Fujitsu grows low potassium content lettuce at the Aizu-Wakamatsu Akisai Vegetable Plant located in Aizu-Wakamatsu City in Fukushima Prefecture. In this plant, the meticulous sanitary control and development management using ICT and Utilizing semiconductor fabrication technology allows production of lettuce that has approximately 80% less potassium. Vegetables are grown in an area of 2,000 square meters, which is the largest scale of plant factory growing low-potassium vegetables in Japan, where up to 3,500 heads of low-potassium lettuce per day. Therefore, it is possible to support dialysis patients under circumstances like that of the Great East Japan Earthquake in March 2011, where dialysis treatment is not available, by preparing a system to distribute low-potassium lettuce as an emergency relief supply across Japan. In this connection, agriculture, industry and medical fields work together at the cultivation and provision of low-potassium vegetables, with the Fujitsu Akisai agricultural cloud contributing to great food from Fukushima and Tohoku Region recovery.

In recent studies, it was found the low potassium lettuce contains a lower amount of potassium (-87%) than the normal leaf lettuce, while there was no significant difference in other nutritional contents, except for higher sodium and lower nitrate contents. Taste evaluation revealed that low potassium lettuce had lower bitterness and higher saltiness than the normal leaf lettuce. Soaking in water decreased the potassium content to 82% of that in the raw normal leaf lettuce. The overall preference score was significantly higher in low potassium lettuce, compared to that of the normal leaf lettuce.[14]

CONCLUSION

Currently there are 0.3 million dialysis patients, 2 million potential dialysis patients and 1.5 million of patients with kidney disease in Japan. This means 1 in 10 Japanese are suffering from renal disease, and most of them are following dietary restrictions of salt, protein, phosphate, and potassium. In addition, it is estimated that there are 2.0 million dialysis patients and 0.6 billion kidney disease patients around the world who need to follow dietary instructions. Therefore, our research and innovation on low potassium vegetable technology will change the boundaries of what is edible and what is not for such patients. Also, low potassium content vegetables are useful supplementation for increasing the variety of foods in diet of CKD patients who are apt to hyperkalemia. The studies highlighted in this article show that several Japanese researchers are successful in producing low-potassium melon, strawberry, tomatoes, spinach and lettuce. We hope that these products make dialysis patients happy, leading to an improvement of their quality of life. Indeed, many patients enjoyed these foods and gave us encouraging comments. Although our trial has just started, future work is necessary to provide these products to patients or hospitals with low cost and to produce other fruits and vegetables with low-potassium content.

CONFLICTS OF INTEREST: None.

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