Dietary salt intake and diabetes complications in patients with diabetes: An overview

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Abstract
Dietary salt restriction is an essential constituent of diabetes care in preventing or slowing the development of diabetes complications, and many diabetes management guidelines include recommendations for dietary salt intake. However, descriptions of guidelines for salt intake are sometimes confined to studies of participants without diabetes or small short-term studies of patients with diabetes. However, in response to such situations, recent longitudinal studies of patients with diabetes have reported an association between dietary salt intake and diabetes complications. Thus, this review summarizes important points in the current situation regarding guidelines on salt intake and the latest findings and future issues on dietary salt intake for diabetes care focusing on (i) the current status and issues regarding the leading guidelines for dietary salt intake for diabetes care in various regions worldwide, and (ii) findings on salt intake from recent longitudinal studies of patients with diabetes whose dietary salt intake was restricted.

Keywords
diabetes complications, salt intake, type 1 diabetes, type 2 diabetes

1 INTRODUCTION
Reduction in dietary salt intake is encouraged throughout the world for reducing blood pressure, which is the major cause of cardiovascular disease (CVD).1 Particularly, consistent dietary salt restriction is emphasized for patients at high risk for arteriosclerosis such as those with diabetes, dyslipidemia, or renal disease.2-4 Guidelines for the treatment of diabetes throughout the world include recommendations for restriction of dietary salt intake4-7 to prevent or at least slow the development of diabetes complications related to macroangiopathy such as CVD and microangiopathy such as nephropathy, retinopathy, and neuropathy.

However, reports of studies of salt reduction in patients with diabetes have been limited, and guidelines for salt intake were sometimes based on epidemiological studies of participants without diabetes. It is also an issue that there are few studies of dietary interventions that do not focus on only dietary sodium intake but also include sodium reduction as a part of the protocol, although there have been several small short-term studies that targeted patients with diabetes. Additionally, longitudinal studies regarding the relationship between dietary salt intake and the prognosis of diabetes have been particularly sparse. In response to this situation, some follow-up studies were recently reported on the association between dietary salt intake and diabetes complications in patients with type 1 and 2 diabetes.8-10

Thus, this review summarizes important points in the current situation and the latest findings about dietary salt intake for diabetes care focusing on the following: (i) What are the current status and issues of leading guidelines for diabetes care in various regions in the world with regard to dietary salt intake? and (ii) What are the findings obtained from recent longitudinal studies with regard to salt intake in patients with type 1 diabetes and type 2 diabetes?
It is well known that medical nutritional therapy is positioned as an essential constituent in managing glycemic control and controlling the development of diabetes complications. In guidelines for the treatment for diabetes in various countries, medical nutritional therapy is described with an individual chapter, explaining recommendations for macronutrient intake including carbohydrate, protein, and fat and micronutrient intake as typified by salt. Table 1 summarizes recommendations for dietary salt intake by the American Diabetes Association (ADA)\(^4\) and European Association for the Study of Diabetes (EASD),\(^5\) which lead in the treatment of diabetes in the United States and Europe, and that of the Japan Diabetes Society (JDS).\(^6\) The current goals for daily intake of dietary salt in ADA guidelines are below 5.84 g/d\(^6\) and 6 g/d in EASD guidelines.\(^5\) Further reductions in sodium intake are recommended by these associations for patients with both diabetes and high blood pressure. Guidelines of the JDS\(^6\) provided a clearly numerical target only for patients with both diabetes and hypertension and for those with overt nephropathy or more severe disease (<6 g/d), although restriction of dietary salt intake is recommended for patients with diabetes regardless of the absence or presence of a diabetic complication.

As a reason for the strict dietary salt restrictions in ADA and EASD guidelines compared with those of the JDS, differences in the interpretation of previous studies among these associations and differences in dietary intake of salt among these countries have been considered. The ADA recommended a dietary salt intake of 5.84 g/d based on a systematic review of short-term randomized controlled trials (RCTs) that showed that decreases in sodium intake reduced blood pressure in patients with diabetes\(^1\) and an 8 week RCT of patients with type 2 diabetes that reported that the Dietary Approaches to Stop Hypertension (DASH) diet, in which salt intake is restricted to about 5.84 g/d and consumption of fruits, vegetables, and low-fat dairy products is increased, improved blood pressure values.\(^2\) The statement of EASD\(^5\) also cited studies of the DASH diet in which participants were nondiabetic individuals\(^3\) as well as an RCT focused on the association between moderate dietary sodium restriction and blood pressure in mildly hypertensive patients with type 2 diabetes.\(^4\)

On the other hand, JDS guidelines do not describe references regarding dietary salt intake although it is explained that excessive salt intake may lead to the onset of vascular diseases through elevation of blood pressure as well as to an increase in appetite.\(^6\) Guidelines of JDS for the treatment of diabetes are based on a comparative review of diabetes treatment guidelines from overseas and management of high blood pressure from home and abroad; therefore, it can be considered that previous studies described in the ADA and EASD guidelines similarly became the basis of the recommendation of dietary salt intake by the JDS, that is, <6 g/d. However, all of these previous studies were reported from Western countries. Additionally, Asian people are more susceptible to pancreatic β-cell secretory defects and pronounced dysfunction in early insulin secretion than Caucasian people,\(^6\) body mass index and body weight are markedly different between Japanese and Caucasian patients,\(^7\) and Asian patients have a much lower risk of CVD compared with Caucasian patients and higher risk of end-stage renal disease (ESRD).\(^8\) For the above reasons, because of the lack of evidence from Asian patients, it can be said that JDS guidelines for dietary salt reduction were not based on specific published recommendations but rather by consensus.

In addition, dietary sodium consumption is different in each country, especially between Asian and Western countries. For example, according to the distribution of mean dietary sodium intake, the mean dietary salt intake by Japanese patients with type 2 diabetes was 10.7 g/d,\(^8\) and their intake was lower than that in the general Japanese population (11.7 g/d)\(^1\) and higher than that in the US and UK general populations (9.1 and 8.6 g/d, respectively),\(^2\) as well as a diabetic population in the United States (6.4–8.6 g/d).\(^2\) Therefore, based on the current situation of dietary salt intake by countries, it is reasonable that the goals for daily intake of dietary salt in guidelines are below 6 g/d for Western diabetic patients regardless of the presence or absence of hypertension and/or diabetic complications although a clearly numerical target (<6 g/d) was set only for patients with diabetes having hypertension and/or diabetic complications in Japan.

In summary, recommendations for dietary salt intake for diabetes care in each country are defined considering the latest evidence, the actual situation of salt intake according to the dietary habits of each country, and the biological aspects of ethnic differences. As for future issues, further discussions are needed that involve recent longitudinal

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**Table 1** Goals for daily sodium intake according to leading guidelines for diabetes care in the United States, Europe and Japan

| Name of association                      | Year | Dietary salt intake (g/d)                                                                 |
|------------------------------------------|------|------------------------------------------------------------------------------------------|
| American Diabetes Association\(^4\)      | 2014 | >5.84 mg/d\(^6\) For individuals with both diabetes and hypertension, further reduction in sodium intake should be individualized |
| European Association for the Study of Diabetes\(^5\) | 2004 | <6 g/d Further restriction may be appropriate for those with elevated blood pressure |
| Japan Diabetes Society\(^6\)             | 2013 | Salt intake should generally be limited Salt should be restricted to <6 g/d in patients with diabetes and hypertension and in those with overt nephropathy or more severe disease |

\(^{a}\)Dietary salt was calculated by following formula: dietary salt (g/d)=sodium (mg/d)/1000×2.5.
studies to develop guidelines. These should include not only existing short-term studies that report the association between dietary salt intake and blood pressure but also follow-up studies that will investigate dietary sodium intake and the incidence of diabetes complications.

3 | WHAT ARE THE FINDINGS OBTAINED FROM RECENT LONGITUDINAL STUDIES WITH REGARD TO SALT INTAKE IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES?

3.1 | Type 1 diabetes

The epidemiological associations between sodium intake and long-term outcomes in patients with type 1 diabetes were firstly reported in 2011 in Finland. That study investigated whether dietary salt intake is associated with mortality and ESRD in a nationwide setting. Participants were 2807 adults with type 1 diabetes, and type 1 diabetes was defined as an onset of diabetes before the age of 35 years. Baseline dietary salt intake was measured by a 1-day urine collection as urinary sodium excretion per day. All participants were followed up from 8 to 12 years, and all-cause mortality was confirmed with death certificate data. ESRD was defined as the requirement for dialysis or kidney transplantation and data were collected from a search of renal registries or medical records.

At baseline, the mean age of participants was 39 years, and the percentage of men was 51%. Mean urinary sodium excretion of participants was 150 mmol/d, and their mean estimated dietary salt intake was 8.8 g/d. More than half of the participants had retinopathy and 30% had micro- or macroalbuminuria. During the follow-up, there were 126 (4.5%) incidents of ESRD and all-cause mortality was 217 patients (7.7%). The hazard ratio (HR) of all-cause mortality per 100 mmol/d increment in urinary sodium excretion was 2.09 (95% confidence interval [95% CI] 1.50–2.92) (P <.01) when urinary sodium excretion was ≥104.6 mmol/d after adjustment for confounders including age, gender, duration of diabetes, eGFR, and urinary albumin excretion. The incidence of ESRD was also significantly associated with high urinary sodium excretion, and the risk of ESRD was ≥2.15-fold higher for every 100 mmol/d increment in urinary sodium excretion (urinary sodium excretion ≤104.6 mmol/d: 2.69 [1.30–5.55], P <.01, and urinary sodium excretion ≥104.6 mmol/d: 2.15 [1.49–3.11], P <.01), respectively (Table 2).

Results of that study suggested that dietary salt restriction as part of medical nutritional therapy would be useful to reduce the progression of ESRD and risk of mortality in patients with type 1 diabetes. On the other hand, several points remain to be resolved. First, dietary salt intake was surveyed by urinary sodium excretion calculated based on a 1-day 24-hour urinary sodium collection. Data from dietary assessments across multiple days as well as urinary sodium excretion over several days would be useful to clarify habitual dietary sodium intake because medical nutritional therapy consists of day-to-day dietary intake. Second, participants were included for analyses regardless of the presence or absence of diabetic complications and the study focused only on ESRD and mortality. Further detailed analyses are needed to clarify whether the prognosis of type 1 diabetes differs depending on the presence or absence of a diabetic complication.

### TABLE 2
Summary of previous studies of diabetes complications and all-cause mortality according to dietary salt intake

| Study name or author | Method for measurement of dietary intake | Study population | Type of diabetes | Follow-up period (y) | No. of participants (No. of men) | Outcome | HR | 95% CI | P-value |
|----------------------|----------------------------------------|-----------------|-----------------|---------------------|------------------------------|---------|----|-------|---------|
| FinnDiane (2011)     | 1-d 24-h sodium collection             | Finnish Type 1 diabetes | 8-10            | 2807 (51%)          | Included                      | All-cause mortality: HR=2.09 (per 100 mmol/d, when urinary sodium excretion ≥104.6 mmol/d)
Cardiovascular disease: HR=2.07 (vs lowest quartile)
Overt nephropathy: nonsignificant
Diabetic retinopathy: nonsignificant |
| JDCS (2015)          | Food Frequency Questionnaire            | Japanese Type 2 diabetes | 8               | 1598 (48%)          | Not included                  | All-cause mortality: HR=0.47 (per 100 mmol/d)
Cardiovascular mortality: HR=0.51 (per 100 mmol/d) |
| Ekinci EI et al. (2011) | 1-d 24-h sodium collection | Australian Type 2 diabetes | 10.5            | 638 (56%)           | Included                      | Non-significant                        |

HR = hazard ratio, CI = confidence interval
3.2 | Type 2 diabetes

Type 2 diabetes comprises 90% of patients with diabetes worldwide.22 Type 2 diabetes is one of the major lifestyle-related diseases, and its onset and progression are highly correlated with genetic and behavioral/environmental factors.23,24 Treatment of diabetes should be consistently practiced by the patients themselves in daily life such as by nutritional therapy. However, there are a few longitudinal studies of medical nutritional therapy in patients with diabetes.8,10 and a longitudinal study on dietary salt intake and the incidence of diabetes complications in patients with type 2 diabetes were published from Japan in 2014.8

The latter study was of a nationwide cohort consisting of 1588 patients with type 2 diabetes aged 40–70 years with hemoglobin A1c (HbA1c) ≥6.5% without any diabetic complications at baseline who enrolled in the Japan Diabetes Complications Study. Dietary salt intake was assessed as part of a dietary assessment using the Food Frequency Questionnaire, which is based on food groups (FFQg), at baseline and 5 years after registration. In brief, the FFQg elicited information on the average intake per week of 29 food groups and 10 kinds of cookery in commonly used units or portion sizes and was externally validated by comparison with 7 day dietary records.25 Cardiovascular disease included the incidence of definite coronary heart disease (angina pectoris or myocardial infarction) or stroke, and cardiovascular events were adjudicated by an independent central committee. The nephropathy end point was defined as the development of overt nephropathy. Diabetic retinopathy end points were development of retinopathy and progression of one stage to the next stage.

At baseline, mean age, percentage of men, mean BMI, and mean HbA1c were 59 years, 48%, 23 kg/m², and 7.9%, respectively. Blood pressure level and serum lipid level were well controlled, and mean daily dietary salt intake was 10.7 g/d. During the 8 year follow-up, the incidence rates per 1000 patient-years of CVD, nephropathy, and retinopathy were 13.6, 8.7, and 42.5, respectively, and the mortality rate was 6.7. After adjustment for confounders, dietary salt intake was associated with an increment of incident CVD (trend \( P=0.03 \)). The HR for CVD in the fourth quartile compared with the first quartile was 2.07 [1.16–3.71] (\( P=0.01 \)). Meanwhile, overt nephropathy, diabetic retinopathy, and all-cause mortality were not significantly associated with dietary salt intake. In addition, among patients who had HbA1c ≥9.0%, dietary salt intake was associated with a dramatically increased HR for CVD compared with the first quartile (Q2: 3.52 [0.95–13.09], Q3: 3.75 [0.95–14.83], and Q4: 9.91 [2.66–36.87], respectively, trend \( P<0.01 \)). However, no significant difference was observed when analysis was restricted to patients who had HbA1c levels <9.0% (Table 2).

According to previous studies, it is reported that the risk of CVD in patients with type 2 diabetes was associated with an 18% increase for each 1% point increase in HbA1c26 and that a higher sodium intake tended to be associated with a high incidence of CVD in nondiabetic individuals (HR [95%CI]=1.14 [0.99–1.32], \( P=0.07 \));27 suggesting a synergistic effect between the HbA1c level and dietary sodium intake for the development of CVD. It can be speculated that dietary salt restriction as part of medical nutritional treatment would be particularly important in those with poorly controlled blood glucose.

Regarding the association between dietary salt intake and mortality in patients with type 2 diabetes, a prospective cohort study was also reported from Australia in 20118,9 in addition to that from Japan as described above.8 Included in the Australian study were 638 patients who attended a single diabetes clinic; they were registered regardless of the presence of preexisting CVD. Baseline dietary salt intake was measured as urinary sodium excretion per day from a 1-day urine collection. Participants were followed up for 10.5 years, and all-cause mortality was identified from medical records and death certificate data. Mean age at baseline was 64 years and 56% were men. Their clinical condition was poorly controlled, as the mean HbA1c level was 7.8%, 47% were obese, and 85% had hypertension. Regarding diabetic complications, 45% had previously experienced a cardiovascular event, 33% had diabetic retinopathy, and 45% had micro- or macroalbuminuria. Mean urinary sodium excretion was 184 mmol/d, and the mean estimated dietary salt intake was 10.7 g/d. There were 175 fatalities from all causes, and 43% of all deaths were caused by CVD during the median follow-up of 9.9 years. After adjusting for confounders, all-cause mortality was inversely associated with urinary sodium excretion, and for every 100 mmol/d increment in urinary sodium excretion, there was a 28% reduced risk of all-cause mortality (HR [95%CI]=0.72 [0.55–0.94], \( P=0.02 \)). Cardiovascular mortality also had a significant inverse association with urinary sodium excretion, and a 35% risk reduction was estimated for every 100 mmol/d increment of urinary sodium excretion (HR [95%CI]=0.65 [0.44–0.95], \( P=0.03 \)) (Table 2).

Based on the findings described above on the relationship between dietary salt intake and mortality in patients with type 2 diabetes,8,10 results of the association between dietary salt intake and mortality were confusing. A possible reason for such inconsistent results might be large differences in the background of patients in each study such as HbA1c, BMI, blood pressure control, and presence or absence of diabetic complications. For instance, in the Australian study,10 half of the patients had a history of a cardiovascular event and/or albuminuria. In contrast, participants in the study in Japan10 had good control of diabetes and none had diabetic complications. Another possible reason is the difference in education for salt reduction between Australia and Japan. In Australia, progressive salt reduction policy has been implemented in cooperation with government, nongovernmental organizations, medical institutions, and food industries.28 Further studies are needed to clarify the association between daily salt intake and mortality risk based on a careful consideration of the characteristics of patients and situation of education for salt reduction.

4 | CONCLUSION

Dietary salt restriction has been noted as an essential constituent of diabetes care in many guidelines,4–7 although supportive evidence is apt to depend on studies of participants without diabetes or small short-term studies of patients with diabetes. On the other hand, some longitudinal studies were recently reported regarding the association between dietary salt intake and diabetes complications in patients...
with diabetes. Based on such situations, this review summarized important points on the current status and issues related to leading guidelines for diabetes care from various countries and findings from recent longitudinal studies for patients with diabetes. Most of the recent longitudinal studies supported current guidelines for diabetes care; yet an inconsistent result was obtained for the association between dietary salt intake and mortality. Further research that considers ethnic-specific characteristics, intercultural differences, and patients’ clinical condition is important in exploring effective medical nutritional therapy and developing guidelines based on firm evidence.

CONFLICT OF INTEREST
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