Chapter 10

The SUBLIME Approach: Efficacy and Cost-Effectiveness of a Blended Care Self-Management Approach facilitated by E-health for Dietary Sodium Restriction in Patients with Chronic Kidney Disease

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Abstract

Objective: Assess a multidisciplinary blended care self-management approach aimed at sodium restriction for efficacy, cost-effectiveness and implementation analysis

Design: Randomised, unblinded trial in 100 participants. Intervention was designed in co-creation with and evaluated by patients, consisting of e-health embedded in clinical care. Control group received care as usual.

Setting: Nephrology outpatient clinics in four Dutch hospitals (two teaching hospitals).

Participants: Adults with chronic kidney disease or renal transplant recipients with eGFR >25 mL/min/1.73m², hypertension and sodium intake >130 mmol/day. 89/100 patients completed the maintenance phase.

Intervention: Dietary sodium restriction, supported by a web-based self-management system with individual e-coaching and two group meetings in the intervention phase of 3 months, followed by 6 months maintenance phase with continued access to the website but without group meetings.

Main outcome measure: 24-hour urinary sodium excretion, office blood pressure, cost-effectiveness after 3 months (intervention phase) and 9 months (maintenance phase).

Results: Patients (44% renal transplant recipients) were on average 56.6 ± 12.4 (SD) years old with eGFR 55.0 ± 22.0 mL/min/1.73m² at baseline. During the intervention phase, the intervention reduced 24h sodium excretion from 188 ± 63 to 147 ± 55 mmol/day (linear mixed effects model effect ‒24.8 mmol/day (95% CI, ‒49.6 to ‒0.1; P<0.05) compared with control). The intervention reduced systolic blood pressure (SBP) from estimated marginal mean 140 (SE, 3) mmHg to 132 (3) mmHg (P<0.001; effect ‒4.7 mmHg (95% CI, ‒10.7 to 1.3; P=0.12) compared with control). After the maintenance phase, sodium excretion remained lower than baseline in the intervention (159 (8) mmol/day; P=0.001), but also decreased in the control group (154 (9) mmol/day; P<0.001; P=0.6 between groups). SBP remained lower in the intervention group compared with baseline: 131 (3) mmHg (P<0.001), ‒4.3 mmHg (95% CI, ‒10.2 to 1.7; P=0.16) compared with control. The incremental cost-effectiveness ratio was €0.39 [95%CI: – €10 to €16] per 1 mmol Na and €4 [– €88 to €106] per 1 mmHg reduction in the intervention phase for the intervention versus control group, as evidenced by bootstrap analyses. We found no effect on quality of life. Participants (focus groups) appreciated the program.
**Conclusion:** The SUBLIME intervention reduced sodium intake and blood pressure, moreover this reduction was maintained. Data in the control group suggest a trial-effect during the maintenance phase.

**Trial registration:** ClinicalTrials.gov identifier NCT02132013

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Introduction

The worldwide average salt intake by far exceeds 5 grams (or ~2000 milligrams/ 90 mmol of sodium) per day, the recommended value by the World Health Organization (1). Patients with chronic kidney disease (CKD) are particularly sensitive to excess sodium as reviewed in (2), and are strongly advised to limit sodium intake in guidelines (3-5). Observational studies revealed the potential of moderately reduced sodium intake, suggesting that every 1 gram less sodium intake is associated with a 15% lower risk of cardiovascular complications, a 15% lower risk for end stage renal disease (ESRD) in diabetic CKD (6), and a 10% lower risk for ESRD in nondiabetic CKD (7). A cost-effectiveness simulation stated that 3 gram reduction of salt intake would yield $10‒24 billion worldwide annually (8); this figure would be enhanced when taking ESRD and the accompanying excessive costs for renal replacement therapy (RRT) into account. In the Netherlands, CKD prevalence is estimated between 7.6 and 10.4 patients per 100 persons (10, 11), about 750 000 suffer from CKD Stage 3 or higher (4) and in 2015 16 316 patients were on RRT, of whom 6461 on dialysis according to the Dutch registry RENINE (www.renine.nl). Healthcare expenditure for RRT totals 750 million euros in the Netherlands. This emphasizes that sodium restriction may be beneficial from both a medical and macroeconomical perspective.

Current approaches to sustainably reduce sodium intake are largely unsuccessful: a recent review of observational and intervention studies performed in over 10,000 CKD patients revealed that the average sodium intake in CKD patients is 164 mmol/day, even in the dedicated setting of the nephrology outpatient clinic (12). Behavioral approaches, starting from the behavioral roots of dietary habits, may provide more fruitful strategies. Participants that received dietary and intensive behavioral counseling in the Trials of Hypertension Prevention I and II had a 25% lower risk of cardiovascular events after 10‒15 years follow-up, and this intervention group reported a higher incidence of dislike of salty foods, use of low sodium products, and monitoring of daily sodium intake in the follow-up questionnaire (13). A theoretical framework such as the self-regulation theory (SRT) can provide a sound theoretical basis and practical guidelines for development of a lifestyle intervention (14). In this SRT framework, a change in dietary intake is approached as a behavioral change. SRT distinguishes three phases of behavioral change: goal-selection or motivational phase, to develop the intention to change one’s behavior; active goal pursuit or action phase, where behavior is actually changed; and a maintenance phase where the new behavior is implemented (15). A qualitative focus group study in 25 patients with CKD identified facilitators and barriers for reduction of sodium intake in the perspective of SRT, yielded the following recommendations for successful interventions: provide information on sodium content, strengthen intrinsic motivation, provide self-monitoring, enforce refusal skills regarding adverse environmental triggers, stimulate social support by involving partners, and provide coaching and evaluation of goals in the maintenance phase (15). In support of a SRT-based approach, in the ESMO intervention study we achieved effective sodium restric-
tion in CKD patients, although the effect did not persist after the intervention (Meuleman et al., Am J Kidney Dis, in press). Taken together, behavioral intervention could be a successful approach to achieve sodium restriction. However, sustained efficacy requires specific efforts aimed at maintenance. Moreover, coaching approaches involving one-to-one counseling are costly and time-expensive. To be effectively implemented in healthcare, an intervention should be cost-effective. E-health may facilitate a self-regulation–based approach in a cost-effective way. To achieve these aims, we designed the Sodium Burden lowered by Lifestyle Intervention: self-Management and E-health technology (SUBLIME) study, that builds on SRT-experiences from ESMO. The intervention included group counseling and a web-based self-management system instead of intensive individual coaching, and was followed by a maintenance period to achieve sustained efficacy. Here we evaluate the SUBLIME intervention on efficacy and cost-effectiveness, and explore possibilities for implementation in clinical practice.

Methods

Participants
SUBLIME was a randomised, unblinded controlled trial that aimed to assess the efficacy, cost-effectiveness and barriers and facilitators for implementation of a novel self-management program for reduction of dietary sodium intake. We screened patients that visited the outpatient clinics of the participating centers. Main inclusion criteria were age ≥ 18 years; chronic kidney disease or kidney transplantation, with an eGFR ≥ 25 mL/min/1.73m²; urinary sodium excretion at the last two visits both > 130 mmol/day or > 150 mmol/day at the last visit; systolic blood pressure > 135 mmHg or diastolic blood pressure > 85 mmHg or well-controlled blood pressure with antihypertensive therapy; sufficient command of the Dutch language; access to and ability to use the internet; and provision of written informed consent. Main exclusion criteria were rapidly and persistently progressive renal function loss, not from acute, intermittent origin; blood pressures > 170 mmHg systolic, or > 95 mmHg diastolic, or < 95 mmHg systolic not responding to withdrawal of antihypertensive medications; a history of cardiovascular event (myocardial infarction, cerebrovascular incident) < 6 months ago; renal transplantation < 1 year ago; medical conditions likely to interfere with the completion of the study at discretion of the treating nephrologist; previous participation in the ESMO trial (Dutch trial registry NTR2917), as this trial relied on a similar behavioral approach (self-management enhanced by motivational interviewing, self-monitoring, strengthening self-efficacy) and may thus confound the current study. Participants were recruited from June 2014 to March 2015 at the nephrology outpatient clinics in the four participating centers: Leiden University Medical Center, Leiden; Sint Antonius Hospital, Nieuwegein; University Medical Center Groningen, Groningen; and ZGT Hospital, Almelo. The medical ethics board approved the study protocol (METc2014/075). The study has
been registered at ClinicalTrials.gov with identifier NCT02132013, and was performed in acc-
cordance to the Declaration of Helsinki.

**Intervention**

The SUBLIME intervention aimed at reducing dietary sodium intake. A program was developed based on self-regulation theory. Participants randomised to the SUBLIME intervention were allocated to a coach and received a home blood pressure monitoring device (Microlife Watch BP Home). The coaches were dietitians, lifestyle professionals or research nurses, all trained by certified lifestyle professionals in the use of the intervention. The intervention consisted of a 3-month intervention phase followed by a 6-month maintenance phase (Figure 1).

![Figure 1](image-url). Design of the SUBLIME trial. Arrows indicate study visits at baseline, after intervention (3 months) and maintenance phase (9 months), respectively.

At the start of the intervention phase, the coach gave the participants access to a web-based self-management system dedicated to sodium restriction. The coach also offered a detailed instruction on how to use the web-based self-management system. The web-based self-management system consisted of different modules that addressed components of self-regulation theory ([Supplement A](#)). These components included exercises to strengthen intrinsic motivation and self-monitoring with a diary coupled with a food databank where individual food products could be entered. Next, the program would display in bar graphs sodium intake in total and per product. The algorithm translating food intake to sodium intake was based on the NEVO tables (16). Options for change could be entered and the effect for e.g. reducing the amount of or replacing a product for a low sodium alternative was displayed in bar graphs; exercises to increase self-efficacy, goal-setting, social support, and dealing with relapse; and a summary page that summarized a ‘change plan’. Exercises addressed subcomponents, e.g. for self-efficacy the perceived barriers, solutions and current self-assessment of self-efficacy. Coaches could view the change plan and use this as input for e-coaching, coaches to support the patient in setting tailored goals, rather than a more directive coaching approach. Participants were invited to attend two 2-h group meetings led by the coach with 5–8 participants and their partners. Group meetings took place in a nonclinical part of the hospital and addressed self-regulation skills regarding reducing salt intake, i.e. goal setting; self-monitoring; refusal skills; and relapse prevention, and
knowledge about hidden salt in food. Participants received individual e-coaching by telephone or email in the intervention phase of 3 months with a minimum of two e-coaching sessions.

In the maintenance phase of 6 months e-coaching was limited to 1–2 moments without group meetings or other counseling.

The control group received care-as-usual, which in the Netherlands consists of annually to up to three-monthly outpatient clinic visits. All participants visited the outpatient clinics at baseline, 3 months and 9 months for anthropomorphic and blood pressure measurements; blood sampling by venipuncture; 24-hour urine collection; assessment of medication use; and they also filled out a questionnaire at each time point. The baseline questionnaire was distributed after randomization.

**Objectives and Outcomes**

The main objective of this study was to assess the efficacy and cost-effectiveness of a web-based self-management approach on reducing dietary sodium intake, defined as urinary sodium excretion. The primary outcome sodium excretion was measured by a 24-hour urine collection. Blood and urinary electrolytes were measured with routine laboratory procedures (Roche Modular). The secondary outcomes were blood pressure; proteinuria; cost-effectiveness; physical and mental health-related quality of life, and self-management skills; and evaluation of barriers and facilitators for implementation of the SUBLIME approach. eGFR was calculated with the CKD Epidemiology Collaboration formula (17). Blood pressure was measured in a standardized fashion at the outpatient clinic, in upright sitting position, after 5 minutes of rest with an automated oscillometric device (WatchBP Home, Microlife), three times with a 1-minute interval in accordance with European Society of Hypertension guidelines (18), we took the mean of the second and third reading for analysis. Proteinuria was measured in 24-hour urinary collection. Changes in medication were explicitly asked at each control visit.

The questionnaires included sociodemographic factors, Short Form-12 (19), EuroQol-5D (20), and Partners In Health scale (21). Physical and mental health-related quality of life was measured using the Short Form (SF)-12. The scoring of SF-12 ranged from 0 to 100. Physical health summary scores (PHS) and mental health summary scores (MHS) were calculated for each item by converting the Likert scale used in the questionnaire to a score from 0 to 100, where higher scores indicate a better health-related quality of life. The SF-12 demonstrated good reliability with Cronbach alpha values of 0.86 for mental health and 0.89 for physical health, respectively (22). Self-management skills were assessed using the Partners In Health (PIH) scale, which showed a good reliability (Cronbach alpha = 0.82) (21).
Healthcare expenditure costs were calculated based on health care consumption data and productivity losses measured on a patient level with a CRF and patient questionnaire, and valued according to the Dutch guideline for costs studies (23). Incremental Cost-Effectiveness Ratios were computed for each of the major outcome measures separately. Displaying the additional cost per unit of improvement of health with the SUBLIME approach, compared to standard care. In addition, Cost Utility ratios were computed, based on EQ-5D defined utilities, displaying the additional costs of SUBLIME per Quality Adjusted Life Year (QALY) compared to standard care.

For future implementation, the identification of facilitators and barriers started with meetings with end users including representatives of the Dutch Kidney Patients Association to discuss design of the study and the prototype of the web-based self-management system. Thus, users could indicate points for improvement which led to including the interactive submodule for visualizing the effect of changing food products for low sodium alternatives on sodium intake. After completion of the study we organized focus groups to evaluate the intervention and identify barriers and facilitators. Every center organized a focus group for participants whom completed the intervention, aiming at 6 participants per group. Each focus group followed an interview protocol covering the three aspects of the intervention: web-based self-management system, group meetings, and individual coaching. The focus group was led by a representative of the Dutch Kidney Patients Association who had experience with focus groups, and the session was observed by two note-takers from TNO. The sessions were also audiotaped after permission was granted by the participants. One note-taker attended all four focus groups (WO), and was checked by the second observer and the discussion leader. These registrations were qualitatively analyzed to identify barriers and facilitators for implementation.

Sample Size
The sample size calculation was based on a target difference of 2 grams of salt (corresponding to 34 mmol sodium/day) between the control and intervention group. Based on data from previous studies (24-26) we assumed a standard deviation of 40 mmol/day. To obtain a power of 80% to demonstrate a 34 mmol difference, 42 patients per group are needed. Accounting for possible drop-out, and 10% loss of data due to inaccurate urine collections, we targeted a size of 49 patients per group.

Randomisation
A randomisation list was generated automatically, stratified per participating center. The randomisation list was concealed from (a) local coordinators until all interventions had been allocated; (b) personnel involved in selection, recruitment and outpatient management of participants; and (c) from the principal investigators throughout the whole study. Upon receipt of a signed informed consent form, the local coordinator allocated a study number, contacted
the list coordinator and received the randomisation result. Due to the design of the intervention with active behavioral counseling, blinding was not feasible.

**Statistical analysis**

Data are reported as mean ± standard deviation (SD) for continuous variables that follow the normal distribution, or median (first to third quartile) for skewed continuous variables. Categorical variables are reported as frequency (percentage). We performed an intention-to-treat analysis on the primary and secondary outcomes using a linear mixed-effects model with restricted maximum likelihood approach and scaled identity (ID) covariance structure for the outcomes sodium excretion, systolic and diastolic blood pressure. Fixed effects were treatment group, time and time × treatment group, random effect was participant number. We report estimated marginal means and standard errors for continuous variables in our linear mixed-effects models. PIH and SF-12 data were non-normally distributed. Therefore, within-group differences over time were tested using Wilcoxon Signed Rank test. PIH and SF-12 delta scores were normally distributed, hence the between-groups differences at the three time points were tested using independent samples t-test. Occurrence of antihypertensive dose reduction between control and intervention was compared with Fisher’s exact test, similarly for dose increase. We conducted two sensitivity analyses. First, we performed a sensitivity analysis for completion of 24-hour urine collection, by calculating the estimated creatinine excretion rate (eCER) according to Ix’ Equation D (27). We repeated the mixed model analysis for sodium excretion in patients whose 24-hour creatinine excretion fell within 30% and 35% eCER, respectively. Second, although 24-hour urine collection is the gold standard, it may vary between outpatient clinic visits. Because one inclusion criterion was sodium excretion >130 mmol/d, this study is vulnerable for regression to the mean (inclusion bias). We therefore conducted a subgroup analysis in 34 patients to compare baseline sodium excretion with average sodium excretion at the outpatient clinic during two years before baseline. P-values smaller than 0.05 were considered to represent statistical significance. Analyses were performed with PASW Statistics, version 22.0 (SPSS Inc.); STATA Statistical Software: Release 13 (StataCorp.); and Graphpad Prism, version 5.01 (GraphPad Software Inc.). For the cost effectiveness analysis, composite outcomes were calculated by dividing the difference in mean costs between the two treatment alternatives by the difference in effect. In addition, bootstrapping (5000 replications) was performed to estimate 95% confidence intervals. Furthermore, a cost effectiveness plane was made. The south east quadrant shows the replications in which the new intervention is less costly and more effective, the south west quadrant shows less costly and less effective replications, north west is less effective and more costly, and the north east quadrant shows the more costly and more effective replications.
Results

Participants Flow

We randomised 99 patients: 52 patients to the intervention group and 47 patients to the control group. Five patients did not attend the baseline visit for various reasons, as depicted in Figure 2. The group size was 50 and 44 for intervention and control group, respectively. 89 patients completed the study, there were 5 drop-outs in the intervention group: three participants had no time for further participation, one patient deceased, and one was lost to follow-up.

Enrollment: Participants

- Received informed consent, n=100

Allocation: Participants

- Allocated to intervention, n=52
  - Received allocated intervention, n=50
  - Did not receive, n=2 (2 withdrawal informed consent)

- Allocated to control, n=47
  - Received allocated control, n=44
  - Did not receive, n=3 (2 no shows, 1 violated inclusion criteria)

Allocation: Care Providers

- Care providers: 4 teams in 4 centers performed the intervention. Each center treated median 13 (min 6, max 19) participants

- Care providers: 4 teams in 4 centers observed controls. Each center observed median 11 (min 4, max 18) participants

Follow-up: Participants

- Received Intervention, n=45
  - Drop-out: 5 (3 too busy, 1 lost to follow-up, 1 deceased)

- Received Control, n=44
  - Drop-out: 0

Figure 2. Flow diagram of the SUBLIME trial.
**Baseline Characteristics**

Participants were 56.6 ± 12.4 (mean ± SD) years old, 15/94 were female, and patients had a mean eGFR of 55.0 ± 22.0 mL/min/1.73m². Forty-four percent of the participants were renal transplant recipients. Baseline characteristics were similar between control and intervention groups (Table 1). At baseline, participants had a mean sodium excretion of 188 ± 63 mmol/day and a systolic blood pressure of 139 ± 17 mmHg.

Table 1. Baseline Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>94</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>Age, years</td>
<td>56.6 ± 12.4</td>
<td>58.2 ± 13.2</td>
<td>55.1 ± 11.5</td>
</tr>
<tr>
<td>Female gender, n</td>
<td>15 (16%)</td>
<td>8 (18%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>eGFR (CKD-EPI), mL/min/1.73m²</td>
<td>55.0 ± 22.0</td>
<td>54.3 ± 21.6</td>
<td>55.6 ± 22.6</td>
</tr>
<tr>
<td>History of DM, none</td>
<td>65 (69%)</td>
<td>30 (68%)</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>DM I</td>
<td>7 (7%)</td>
<td>3 (7%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>DM II</td>
<td>22 (23%)</td>
<td>11 (25%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>History of Dialysis, n</td>
<td>27 (29%)</td>
<td>12 (27%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Renal Transplant Recipient, n</td>
<td>41 (44%)</td>
<td>19 (43%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Antihypertensive drug use, n</td>
<td>90 (96%)</td>
<td>41 (93%)</td>
<td>49 (98%)</td>
</tr>
<tr>
<td>Number of classes</td>
<td>2.0±1.0</td>
<td>2.0 ± 1.1</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>RAAS blockade, n</td>
<td>70 (74%)</td>
<td>32 (73%)</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>Beta-blocker, n</td>
<td>41 (44%)</td>
<td>15 (34%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Calcium channel antagonist, n</td>
<td>33 (35%)</td>
<td>16 (36%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Diuretic, n</td>
<td>40 (43%)</td>
<td>22 (50%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Calcineurin-inhibitor use</td>
<td>27 (29%)</td>
<td>12 (27%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Possession HBPM</td>
<td>64 (68%)</td>
<td>35 (80%)</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>Uses never</td>
<td>11 (17%)</td>
<td>6 (17%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Uses daily</td>
<td>5 (8%)</td>
<td>2 (6%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Uses weekly</td>
<td>19 (30%)</td>
<td>10 (9%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Uses monthly</td>
<td>29 (45%)</td>
<td>17 (49%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6 ± 5.3</td>
<td>28.4 ± 5.0</td>
<td>28.7 ± 5.6</td>
</tr>
<tr>
<td>Caucasian, n</td>
<td>89 (95%)</td>
<td>40 (91)</td>
<td>49 (98)</td>
</tr>
<tr>
<td>Higher educated, n</td>
<td>39 (41%)</td>
<td>19 (43)</td>
<td>20 (40)</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; DM, diabetes mellitus; RAAS, renin–angiotensin–aldosterone system; HBPM, home blood pressure monitor.

**Primary and Secondary Clinical Outcomes after Intervention Phase**

In the intervention group sodium excretion was reduced from 188 ± 63 mmol/day to 147 ± 55 mmol/day (Figure 3). Compared with the control group, this reflected an additional effect of the
intervention of ‒24.8 (95% confidence interval, ‒49.6 to ‒0.1; \( P < 0.05 \)) mmol/day. The control group demonstrated a nominally but not significant reduction in sodium excretion (Table 2). There was a concomitant drop in systolic blood pressure from 140 ± 16 to 131 ± 14 mmHg; and in diastolic blood pressure from 84 ± 9 to 80 ± 9 mmHg in the intervention group (Figure 4). Linear mixed-effects model analysis confirmed that this was a significant reduction compared to baseline with estimated marginal mean, 140 (standard error, 3) to 132 (3) mmHg, \( P = 0.001 \) (table 2). In the control group systolic blood pressure did not significantly change 139 (3) to 136 (3) \( P = 0.08 \). Only 14 patients had proteinuria ≥ 1.0 g/d (8 intervention, 6 control patients). Antihypertensive drug use in the control group was reduced in 1 and increased in 3 patients whereas it was reduced in 5 and increased in 3 patients in the intervention group (Fisher’s exact test, \( P = 0.2 \) for dose reduction, \( P = 0.99 \) for dose increase). The intervention group received 2.8 ± 1.2 times e-coaching, 4 patients had only one e-coaching moment and 8 did not receive e-coaching (2 due to drop-out) according to logs of the coaches.

Table 2. Baseline Values and Effects on Sodium Excretion and Blood Pressure after Intervention and Maintenance Phase

<table>
<thead>
<tr>
<th>Months</th>
<th>Na, mmol/24h</th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean* (SE) Intervention</td>
<td>Mean* (SE) Control</td>
<td>Δ Intervention</td>
</tr>
<tr>
<td>0</td>
<td>187.6 (7.9)</td>
<td>139.6 (2.5)</td>
<td>83.9 (1.4)</td>
</tr>
<tr>
<td>3</td>
<td>147.5†† (8.2)</td>
<td>131.8†† (2.5)</td>
<td>80.5† (1.4)</td>
</tr>
<tr>
<td>9</td>
<td>159.3† (8.4)</td>
<td>131.5†† (2.5)</td>
<td>79.2†† (1.5)</td>
</tr>
<tr>
<td>0</td>
<td>188.8 (8.5)</td>
<td>139.2 (2.6)</td>
<td>83.3 (1.5)</td>
</tr>
<tr>
<td>3</td>
<td>173.5 (8.8)</td>
<td>136.1 (2.7)</td>
<td>81.7 (1.5)</td>
</tr>
<tr>
<td>9</td>
<td>153.6†† (8.6)</td>
<td>135.3 (2.6)</td>
<td>80.1† (1.5)</td>
</tr>
</tbody>
</table>

Linear mixed-effects model for change after intervention phase (3 months) and maintenance phase (9 months) compared with baseline (0). * Estimated marginal means and standard error (SE). †† Effect of interaction term time × treatment with 95% confidence interval (CI). * \( P < 0.05 \) versus control group; † \( P < 0.05 \) versus baseline within group (intervention or control); †† \( P < 0.001 \) versus baseline within group (intervention or control). Abbreviations: SE, standard error; CI, confidence interval; BP, blood pressure.

Figure 3. Sodium excretion as assessed by 24-h urine collection at baseline, after intervention (3 months) and maintenance phase (9 months). * denotes \( P < 0.05 \) versus control group. \( P \)-values represent change within group compared with baseline.
Primary and Secondary Clinical Outcomes after Maintenance Phase

In the intervention group the effect on sodium excretion persisted throughout the maintenance phase at 157 ± 64 mmol/day (Table 2 and Figure 3). In the control group a reduction of sodium excretion was found after the maintenance phase to 154 ± 40 mmol per day. Accordingly, there was no significant difference in sodium excretion between intervention and control group after the maintenance phase. Also the intervention effect on blood pressure was maintained, without however, significant differences from control. Antihypertensive drug use was reduced during the maintenance phase in 5 patients and increased in 3 patients, in both control and intervention group (Fisher’s exact test, both $P=0.99$). 11 patients had proteinuria ≥ 1.0 g/d (5 intervention, 6 control patients). In the intervention group 33 patients received 2.1 ± 0.6 times e-coaching, 17 patients did not receive e-coaching (5 due to drop-out) according to logs of the coaches.

Sensitivity Analyses

To account for possible confounding by urine collection errors, we repeated the analysis for patients with a creatinine excretion in all three 24-hour urinary collections within 30% of the estimate creatinine excretion rate. This yielded similar results: a −26.1 mmol/day (95%CI, −58.6 to 6.4; $P=0.11$) reduction in sodium excretion in 21 control vs. 23 intervention patients. Within 35% limit, the effect was −22.7 mmol/day (95%CI, −51.3 to 6.0; $P=0.12$) for 30 intervention patients compared with 29 control patients. Under-collection thus did not materially influenced our results.

To account for possible regression to the mean, we tested in a subset of patients (n=34) whether sodium excretion before the study was different from baseline. We compared mean sodium excretion during all subsequent visits from 2 years before baseline to baseline with baseline values. This was not significantly different (182.7 ± 47 mmol/day before; 192.8 ± 55.3 mmol/day
at baseline, \( P=0.3 \)) and markedly higher than sodium excretion at the end of the maintenance phase. There was no difference between patients allocated to intervention or control group (intervention 185.9 ± 54.5 versus control 178.7 ± 37.2 mmol/day before, \( P=0.7 \); 198.8 ± 52.8 versus 185.2 ± 59.2 mmol/day at baseline, \( P=0.5 \)).

**Effects on Quality of Life and Self-Management Skills**

Quality of life and self-management skills were not significantly different between the groups at baseline. No within-group differences over time were observed in self-management skills and quality of life (Table 3). After the maintenance phase however, a significantly higher change in PHS score was observed in the intervention group compared to the change in the control group.

<table>
<thead>
<tr>
<th>Months</th>
<th>PIH-score</th>
<th>SF-12, physical health summary score</th>
<th>SF-12, mental health summary score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median [IQR] Intervention</td>
<td>Median [IQR] Control</td>
<td>Mean difference intervention group</td>
</tr>
<tr>
<td>0</td>
<td>86 [72-102]</td>
<td>97 [82-105]</td>
<td>96 [84-104]</td>
</tr>
<tr>
<td>9</td>
<td>91 [76-104]</td>
<td>97 [82-105]</td>
<td>96 [84-104]</td>
</tr>
<tr>
<td>∆ 3</td>
<td>4.46</td>
<td>2.33</td>
<td>-2.09</td>
</tr>
<tr>
<td>∆ 9</td>
<td>-1.94</td>
<td>4.07*</td>
<td>-9.44</td>
</tr>
<tr>
<td>∆ 3</td>
<td>0.87</td>
<td>0.08</td>
<td>-4.62</td>
</tr>
<tr>
<td>∆ 9</td>
<td>-0.87</td>
<td>0.08</td>
<td>-4.62</td>
</tr>
</tbody>
</table>

Mean differences for change after intervention phase (3 months) and maintenance phase (9 months) compared with baseline (0). Data are non-normally distributed and shown as median [IQR]. Differences within-groups over time were tested with Wilcoxon sign test. Differences over time between groups were tested with Independent Samples T-test. *denotes a significant change over time in intervention group versus control group (\( P < 0.05 \)).

Abbreviations: PIH, Partners in Health scale; SF, Short Form.

**Cost-Effectiveness**

The intervention group gained 0.02 QALYs, the control group 0.05 QALYs as assessed by EQ-5D. Quality of life and self-management skills were not significantly different between groups at baseline (Table 2). The incremental cost-effectiveness ratio (ICER) was €0.39 [95%CI: −10 to 16€] per 1 mmol Na\(^+\) reduction and €4 [−88 to 106€] per 1 mmHg systolic blood pressure reduction in the intervention phase (intervention versus control). This means that, compared to the control group, for every 4 euro invested, blood pressure is reduced by 1 mmHg. The cost-effectiveness plane in Figure 5 demonstrates this effect and the strong efficacy of the intervention on blood pressure at acceptable costs. The results were similar for blood pressure after 9 months with €7 [−98 to 123€] per mmHg, as evidenced by bootstrap analyses. For sodium restriction, the
ICER became negative with €–7 [–68 to 85€] per 1 mmol Na⁺ reduction. This follows from the nominally lower sodium excretion in the control group compared to the intervention group. The cost-utility analysis for QALY at 9 months is similarly inconclusive with a negative ICER of –€1422 (95% CI, –€22.685 to €25.055).

Figure 5. Cost-effectiveness plane for systolic office blood pressure. Data points reflect bootstrap analyses (5000 replications). Incremental effect in mmHg and incremental costs in Euros are depicted compared to control group. The upper-right quadrant reflects non-dominance of the intervention: more effective but at higher costs. The lower-right quadrant reflects dominance of the intervention: more effective and less costly.

Barriers and Facilitators for Implementation: Focus Groups and Logging Data

Thirty-six out of fifty intervention participants were invited to attend a focus group, because at that moment in time they had completed the intervention. In total, 21 patients participated (response rate 56%) and in addition 5 partners and 1 daughter also took part in a focus group. The focus group consisted of 5–6 participants per center. Three participants indicated that they did not use the web-based self-management system (one insisted in reducing sodium intake at once without further help, two experienced difficulties in accessing the module). The 18 participants who used the system thought the exercises clearly formulated and easy to use, but questioned the necessity to complete exercises that addressed intrinsic motivation “because we are already motivated to reduce our salt-intake, otherwise we would not have participated.”. However, the user-friendliness of the intake monitoring module was the largest perceived barrier to implementation: filling out the diary was time-intensive; not all products were available in the database, or not retrievable when searched for by a synonym; and it is difficult to estimate salt content from food prepared in restaurants or combined products. Patients generally valued the ‘options for change’ menu. They used the ‘change options’ to reduce salt intake and to plan in a week how to compensate for excess salt intake. Most participants used the
system the first 2–4 months. According to logging data, 44/50 participants used the e-Health module. 1647 recordings of dietary intake were registered during the 9-month study period. Participants registered 4256 (55.4%) main meals (breakfast, lunch, dinner) and 3428 (44.6%) snacks. Participants registered on average 37.4 days. 6 participants registered less than 5 days, 21 participants registered between 5 and 31 days, 12 registered between 32 and 93 days, and 5 participants registered for more than 94 days. If they registered, they usually registered every other day. When asked to which extent the modules provided insight in actual salt consumption, participants strongly valued the monitoring module (average 8.3/10): “You think you know what you eat, until you write it down.”. Most participants valued the possibility for e-coaching. Some patients expressed the wish for a reminder after a longer period of non-use. Most participants would have appreciated “an unannounced reminder contact” in the maintenance phase, lest they would be triggered to adhere to the program. The group meetings were valued for practical advices, increased awareness, exchange of experiences and contact with fellow renal patients. An exercise where participants could write themselves a postcard was less appreciated. Participants stressed that support of the partner/family was important. Two partners of participants reported that their own antihypertensive medication was reduced, accordingly due to reduced sodium consumption and another partner suggested partners should have been allowed to hand-in a 24-hour urine collection as well to quantify their sodium reduction. Food intake and salt reduction impacts not only patients, but also their family. Most participants did not feel their relation with their treating nephrologist had changed due to SUBLIME. Overall, participants valued participation in SUBLIME with 7.8/10, and would recommend use of this web-based self-management system to other patients with renal disease, notwithstanding current sub-optimal user-friendliness.

Discussion

The multidisciplinary, self-management– and web-based SUBLIME intervention reduced sodium intake in patients with chronic kidney disease after the intervention phase, with a concomitant reduction in blood pressure compared to baseline. After a maintenance phase of 6 months the reduction in sodium excretion and blood pressure was maintained, whereas in the control group sodium excretion was also reduced compared to baseline. The intervention was cost-effective for sodium restriction and blood pressure reduction.

The SUBLIME study has several strengths. The intervention was designed from start in a multidisciplinary setting, with psychologists, nephrologists, a lifestyle professional and dietitians in co-creation with patients with CKD, represented by the Dutch Kidney Patients Association. We measured sodium intake with the gold standard method 24-hour urine excretion, checked for effects by collections errors and confirmed the representativeness of baseline sodium excre-
tion in a subgroup. Of note, patients valued the feedback by hard biomedical data. Our study population consists of a mixture of different CKD stages and renal transplant recipients, improving generalization of the results. Further, the intervention was thoroughly evaluated by focus groups and logging data, to identify barriers and possibilities for eventual wide implementation.

A potential weakness of this study is selection bias. By design the study population reflects a more motivated portion of the outpatient population, because patients were willing and able to co-create, and participate in a RCT. Further, our intervention relied heavily on access to internet and literacy. In the Netherlands internet penetration is 95.5% (as of November 15, 2015) (28), which is markedly higher than European average of 74.5%, which impairs generalization. Further, the intervention is not suitable for (digital) illiterates and thus results cannot be generalized to the whole patient population. It must also be mentioned that the feedback on sodium intake by the web-based system relies on availability of validated data on sodium content of food products, as provided for the current study by the NEVO tables (16), that cover most food products consumed in The Netherlands. As dietary habits and food products are substantially different in different countries, application in countries other than The Netherlands will require specific adaptation to local food habits.

There was a clear difference in sodium excretion between intervention and control after the intervention phase, and moreover, the effects were maintained during a six month maintenance phase. However, in the control group a reduction in dietary sodium intake occurred during the maintenance phase as well. This suggests a trial-effect, supported by the observation that baseline values did not differ from pre-study outpatient clinic values. There are several possible explanations for this trial-effect. First, regression to the mean may have occurred, although this is not likely a problem according to our subgroup analysis on pre-study sodium excretion values. Second, patients that participate in a RCT are generally more motivated than those who decline participation. This was also literally expressed during the focus groups in intervention patients. Also, patients allocated to control group may be more willing to reduce sodium intake a priori and could have become more vigilant to their sodium intake, because they had to collect 24-hour urine collections. Three-monthly 24-hour urine collection may not fully reflect care as usual for some patients, and could not be performed in a blinded fashion. Some participants indeed expressed disappointment about being allocated to the control group at the baseline visit. This so-called contamination effect is a major bias of RCTs in behavioral interventions that by design cannot be performed in a blinded fashion (29). Our patients scored relatively high on physical and mental health scales as assessed by SF-12 compared to studies performed in similar populations (30, 31). The observed difference in change in SF-12 between intervention and control group suggests that patients feel better about their health after the maintenance phase. Notably, our participants had relatively high self-management skills, indicated by PIH-scores, at baseline which might explain why their score did not further improve during the study. This also
bolsters the notion that our population may be selected. Indeed, the majority of the patients already possessed a home blood pressure monitor at the start of the study.

The effect on sodium restriction observed here is comparable to other behavioral interventions that addressed sodium intake. The 18-month PREMIER study in untreated (pre)hypertensives consisted of biweekly behavioral counseling in the first half year that aimed at weight reduction alone, or combined with adherence to the DASH diet (32), or advise-only (33). Sodium excretion was reduced with 31.6, 32.6 and 20.6 mmol/day respectively, which is comparable to the 41 mmol/day change achieved in our intervention phase, and also in line with 44 and 33 mmol/day reductions achieved in the TOHP trials (13). There are very few studies that investigated behavioral interventions in CKD for sodium restriction. The MASTERPLAN study was performed in a setting similar to SUBLIME, namely a multicenter outpatient clinical study in the Netherlands. It investigated in 788 Dutch CKD patients a nurse-led intervention that targeted eleven treatment targets, including adherence to dietary sodium intake < 2000 mg (90 mmol) per day (34). MASTERPLAN did not address all components of self-regulation theory (34) and had a long intervention phase of two years, with on average 7.2 outpatient clinic visits yearly (35). The MASTERPLAN intervention had no effect on sodium excretion (150 vs 148 mmol/day). The authors contribute this to contamination bias and to the observation that multiple-target approaches tend to be ineffective. Of note, this study was effective in increasing compliance to several pharmacological interventions, but with none of the lifestyle factors. This reinforces the rationale of a specific behavioral approach for lifestyle related factors. In line with this assumption, the ESMO intervention in CKD based on SRT showed effective reduction of sodium excretion and blood pressure (Meuleman et al., Am J Kidney Dis, in press).

Cost-effectiveness of a sodium intervention program in CKD was previously assessed in the CanPREVENT study. The study addressed 8 surrogate targets in patients with CKD, and did not achieve better control of most risk factors e.g. blood pressure or cholesterol, notably sodium intake was not targeted (36). The CanPREVENT relied on nurse-led self-management based intervention. Notwithstanding, the cost-effectiveness analysis of CanPREVENT was deemed favorable in that the intervention reduced costs without reducing quality of life for patients (37). The reported, not significant difference of 0.046 QALYs gained in the intervention group (n= 238) reflect a similar effect size of the 0.02 and 0.05 QALYs gained in our analysis. We feel that these results are not significant nor representative due to the strong influence of individual events in such small populations and the limited sensitivity of the EQ-5D questionnaire for effects of the intervention on quality of life. Higher sodium intake correlates with higher antihypertensive drug use in 141 patients with CKD Stage 4 and 5 (38). In SUBLIME there was more dose reduction in the intervention group after the intervention phase, while after the maintenance phase both groups displayed a similar incidence of dose reduction, in line with the effects on sodium intake.
What are the implications of our study? It presents an effective, multidisciplinary integrated strategy of blended care for sodium management in CKD, developed in co-creation, and appreciated by patients, thus providing a basis for affordable programs for management of sodium intake in CKD. The evaluation by patients provided several options for further improvements, and suggestions for improved user-friendliness of the interface, that may prove useful during further implementation. By its affordability it fulfills a prerequisite for large scale application, be it in clinical practice, or in the context of prospective intervention studies.

Acknowledgements


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