



Expanding the role of mobile apps in preventing hyperphosphatemia in patients undergoing haemodialysis: A systematic review and meta-analysis

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ABSTRAK

Latar Belakang: Pola makan yang tidak sesuai pada pasien penyakit ginjal kronis yang menjalani hemodialisis kemungkinan besar akan menyebabkan hiperfosfatemia, yang juga dapat mengakibatkan komplikasi lain seperti kekurangan kalsium dan protein. Menanggapi hal tersebut, manajemen diet berbasis aplikasi seluler menawarkan program diet yang spesifik bagi setiap pasien untuk mengontrol nutrisi.

Tujuan: Tinjauan ini bertujuan untuk mengidentifikasi efektivitas program diet mandiri berbasis aplikasi seluler untuk mengontrol kadar fosfat, kalsium, dan albumin pada pasien hemodialisis.

Metode: Tinjauan sistematis dan meta-analisis ini mengikuti Pedoman PRISMA (Preferred Reporting Items for Systematic and Meta-Analysis). Pemilihan studi dilakukan dengan menggunakan beberapa database elektronik seperti PubMed, Cochrane Library, ScienceDirect, Springer, EBSCO, EMBASE, Google Scholar, Proquest, SAGE, Taylor & Francis, dan SCOPUS. Risiko bias dianalisis dengan Cochrane Risk of Bias 2.0 Tool, kemudian dilakukan meta-analisis dengan menggunakan Review Manager V5.4.

Hasil: Penelitian ini melibatkan 5 studi acak terkendali yang kemudian diinterpretasikan dengan meta-analisis. Berdasarkan hasil penelitian, terdapat efek yang signifikan untuk penurunan kadar fosfat (pooled MD -0,63, 95% CI [-1,18,-0,08], p=0,02, I² =82%) dan peningkatan kadar kalsium (pooled MD = -0,51, 95% CI [-0,77,-0,24], p=0,0002, I² =0%). Sedangkan kadar albumin tidak berubah secara signifikan (pooled MD=-0,09, 95% CI [-0,33,0,16], p=0,49, I² =0%).

Kesimpulan: Diet mandiri berbasis aplikasi seluler secara signifikan menurunkan kadar fosfat dan cenderung mempertahankan kadar albumin pasien hemodialisis. Intervensi ini juga berpotensi meningkatkan kadar kalsium untuk mencegah penyakit tulang.

KATA KUNCI: hemodialisis; hiperfosfatemia; aplikasi seluler; meta-analisis



ABSTRACT

Background: *Improper diets of patients with chronic kidney disease undergoing hemodialysis are likely to develop hyperphosphatemia, which can also result in other complications such as lacking of calcium and protein. Meanwhile, dietary management using Mobile Apps can provide specific diet programs for every patient to control nutrition.*

Objectives: *This review aims to identify the effectiveness of Mobile App based self-management dietary program to control phosphate, calcium, and albumin level for patients with hemodialysis.*

Methods: *This systematic review and meta-analysis follows PRISMA (Preferred Reporting Items for Systematic and Meta-Analysis) Guideline. Study selection was done using several electronic databases such as PubMed, Cochrane Library, ScienceDirect, Springer, EBSCO, EMBASE, Google Scholar, Proquest, SAGE, Taylor & Francis, and SCOPUS. Bias risk was analyzed with Cochrane Risk of Bias 2.0 Tool, then meta-analysis was made using Review Manager V5.4.*

Results: *This study included 5 randomized controlled studies that were later interpreted with meta-analysis. Based on the result, there are significant effect for phosphate level reduction (pooled MD -0.63, 95% CI [-1.18,-0.08], $p=0.02$, $I^2=82\%$) and calcium level increase (pooled MD=-0.51, 95% CI [-0.77,-0.24], $p=0.0002$, $I^2=0\%$). Meanwhile, there is no significant change in albumin level (pooled MD=-0.09, 95% CI [-0.33,0.16], $p=0.49$, $I^2=0\%$).*

Conclusions: *In conclusion, mobile App based self-management diet significantly reduces phosphate level and is likely to maintain albumin level for hemodialysis patients. This intervention also has the potential to increase calcium levels to prevent bone disease.*

KEYWORD: *hemodialysis; hyperphosphatemia; mobile app; meta-analysis*

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INTRODUCTION

Chronic kidney disease is a progressive disease that has been a burden worldwide. The 2023 International Society of Nephrology Global Kidney Health Atlas shows there are approximately 850 million people with chronic kidney disease in the world (1). Patients with chronic kidney failure will undergo hemodialysis as part of their therapy. Hemodialysis is a replacement therapy for kidney function which is carried out by passing the patient's blood through a filter device (dialyzer) to remove waste from the body's metabolism and balance the body's electrolytes through a semipermeable membrane (2). In this process, several side effects were found such as anemia, bone disease, low calcium levels, hyperparathyroidism, and hyperphosphatemia (3).

Hyperphosphatemia in the body can result in calcium deficiency because phosphate retention causes a decrease in serum ionized calcium, so that bone calcium will be released to replace the lost serum calcium and trigger bone damage. In

addition, lack of ionized calcium also causes the release of parathyroid hormone which triggers hyperparathyroidism (4).

In hyperphosphatemia, there is an elevation of serum phosphorus that can increase calcification and worsen chronic kidney disease progression, leading to end stage renal disease (5). Increased calcification can also increase vascular calcification, resulting in cardiovascular disease such as left ventricular hypertrophy, that causes sudden death (6). Cardiovascular disease is actually very common as hemodialysis complication that highly contributes to death among people with chronic kidney disease. It is proven in large studies, that serum phosphorus concentrations ≥ 5 mg/dL have a greater risk of increasing mortality (7). Hyperphosphatemia is caused by retention of serum phosphorus in patients with chronic renal failure, because the removal of remaining phosphate through hemodialysis is less adequate than the amount of

phosphate the body receives through the patient's daily diet (8). This is because hemodialysis patients are advised to consume foods high in protein to replace lost amino acid levels, but this also results in increasing the patient's phosphate consumption (9). In this case, controlling the amount of phosphate in the body cannot be done solely using hemodialysis, but also needs to be done by limiting the amount of phosphate consumed in daily food and still maintaining protein consumption. Thus, nutritional education for hemodialysis patients is very necessary (10). However, the levels of phosphate and protein in food certainly vary greatly in various types of food, accompanied by varying levels of phosphate and protein in the patient's body, so it is quite difficult to control the amount and type of nutrition that patients need to consume by simply providing education (11). In this problem, specific assistance is needed for each patient on hemodialysis in managing their daily consumption (12).

In this modern era, various health applications are widely used and provide good results, including the use of smartphone/cell phone-based applications to assist patients with chronic diseases (13). This development can be used to develop mobile-based applications to monitor the daily consumption of patients on hemodialysis. With this mobile application as personal assistance, the patient's amount of phosphate and protein consumption can be adjusted according to each patient's specific body nutritional condition, as well as providing more accurate education according to each patient's body condition (14). Moreover, with self-management-based applications, patients can be more aware and motivated about their own body condition, so it is estimated that patient education and nutritional management can be more adhered to (15).

Many researches have investigated the effect of mobile phone application regarding the hemodialysis hyperphosphatemia issue, but there is still no study that assesses the overall result of those research. This study summarizes the overall results of mobile application intervention articles for hemodialysis hyperphosphatemia, in order to provide more supporting evidence for implementing mobile phone application

interventions to hemodialysis patients, as the mobile phone application intervention is predicted to support patient's recovery and ultimately reduces mortality risk due to hyperphosphatemia. Therefore, the aim of this study was to examine the effectiveness of using a self-management-based mobile phone application, to control the amount of body phosphate, albumin, and calcium in patients on hemodialysis..

MATERIALS AND METHODS

Study Methodology

This meta-analysis and systematic review were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and statements.

Eligibility Criteria: Inclusion and Exclusion Criteria

Before conducting the literature search, inclusion and exclusion criteria were established to determine the relevance of the data. Study inclusion criteria are: (1) Study type, randomized controlled trials study; (2) Study population, hemodialysis patient with hyperphosphatemia; (3) Intervention, Mobile application; (4) Studies outcome measured changes in phosphate, albumin, and calcium.

Then, for exclusion criteria are: 1) Not using mobile apps or combined mobile apps with another intervention; 2) Study protocol and review articles; 3) Incompatible languages. The titles and abstracts of the included papers were selected by three independent reviewers (MFH, SAA, DEP).

References Standard

A randomized controlled trial demonstrating mobile apps' effect on hemodialysis patients was used as reference. The references were compiled using Mendeley desktop.

Data Sources and Search

The literature search was conducted using the following databases: PubMed, Cochrane CENTRAL, Embase, Taylor & Francis, ScienceDirect, Scopus, Sage, Proquest, EBSCO, and Google Scholar. The searches started from 20 October 2023. All terms were in accordance with the MeSH (Medical Subject Headings) browser. Keywords ("Mobile application" OR "application"

OR "mobile") AND ("Hyperphosphatemia") AND ("Hemodialysis" OR "Renal Dialysis") were used in the search field with the Boolean operator. The detail keyword for each database can be seen in supplementary file.

Selection of Studies

All studies from databases were collected in Rayyan.ai. The process of study search and selection is illustrated in the Appendix. All collected articles were screened for year, title, and abstract (MFH, SAA, DEP) by three independent reviewers after duplicates were removed. Full-text articles were then assessed for

eligibility. The final results were five randomized studies (randomized controlled trials and randomized clinical trials), which were included in the qualitative and quantitative synthesis. The PRISMA Flow Diagram is illustrated in **Figure 1**.

Data Extraction and Analysis

The data that were extracted from the selected studies were author, year, country, sample size, age, type of application, type of control, application content, intervention time, and assessment period. Review Manager 5.4 was used for all statistical tests and analyses for this review. The details can be seen in the **Table 1**.

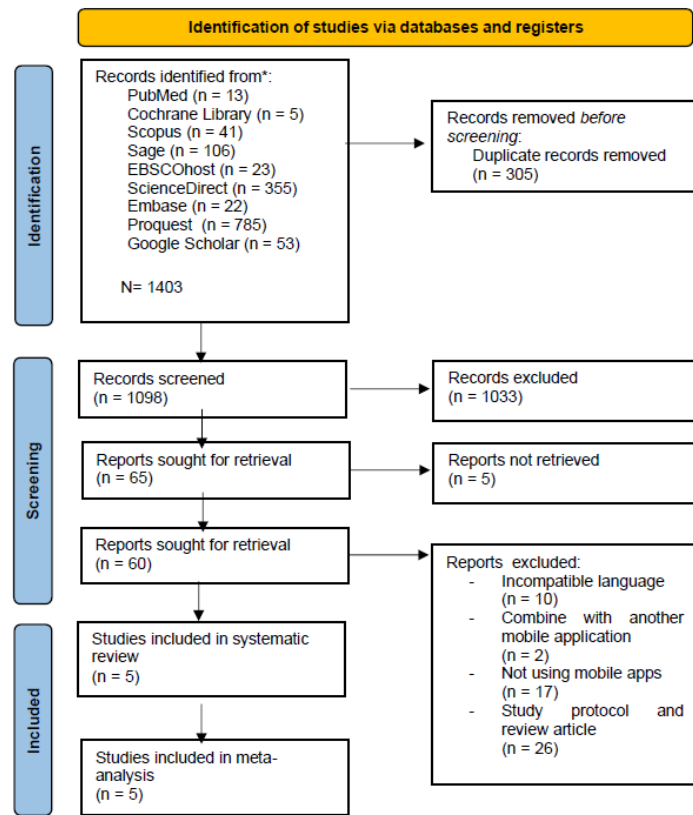


Figure 1. PRISMA flow chart diagram

Risk of Bias in Individual Studies (Qualitative Synthesis)

The quality of the selected studies was assessed using the Risk of Bias Tool for Randomized Trials version 2. The tool consists of five domains and 28 signaling questions to be assessed. These questions refer to the randomization process, the intervention, the outcome data and the reported results. The quality

assessment was analyzed by three independent reviewers (MFH, SAA, DEP). The domain file Bias (.xlsx) was used to record the results. The results were then posted on the ROBVIS website for summary and traffic light display. The score was presented based on algorithms for proposed judgment RoB 2, such as low risk, some concerns, and high risk. An indication of study quality is shown in **Figure 2**.

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and high risk. An indication of study quality is shown in **Figure 2**.

Quantitative Data Synthesis (Meta-Analysis)

Review Manager 5.4.1. (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) was used for the quantitative analysis of the data. The Mean Differences (MD) and Standard Deviations (SD) for both the intervention and the control groups before and after the treatment were extracted from the included studies beforehand. The pooled effect will be analyzed with a Fixed Effect Model (FEM) if the level of heterogeneity (I^2) is less than 50% and with a Random Effect Model (REM) if the level of heterogeneity (I^2) is greater than 50%.

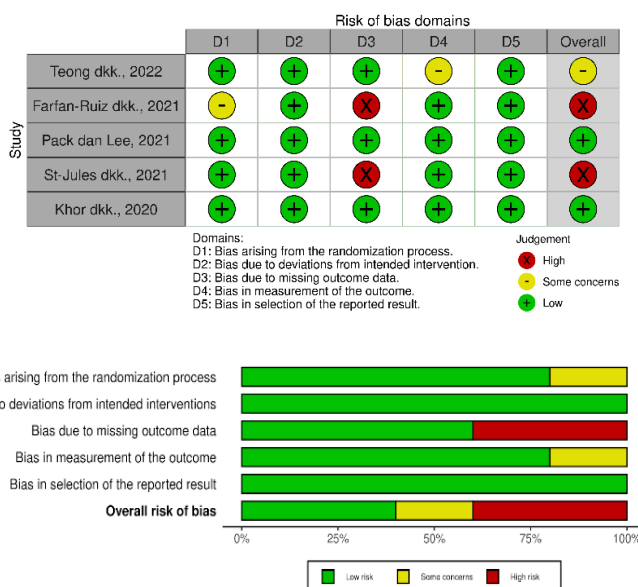


Figure 2. Risk of bias assessment using RoB 2.0

MD and SD for change from baseline using mobile application for hemodialysis patients were assessed as the main outcome guiding statistical analysis, as indicated by significant effects in phosphate, albumin, and calcium within each tool's range. Standardized mean difference (SMD) with 95% confidence interval (CI) was used to measure effect.

RESULTS AND DISCUSSIONS

Table 1 showed that almost half participants were 17 years old (41.1%). Over half of the

participants (67.1%) had normal nutritional status (BMI/A) and 79.5% of the participants had age of menarche in the normal category.

The mean of percentage body fat in this study was 26.79 ± 8.74 (normal body fat). Based on the participants' body fat percentage data, 28.8% participants had under fat, 43.9% had normal fat, and 27.3% had overfat-obesity category (**Table 2**). Half of participants were at risk of chronic energy deficiency that indicated by MUAC <23.5 cm (50%). **Table 2** also described that 75.8% participants had normal menstrual cycles, while

24.2% experienced irregular menstrual cycle, include polymenorrhea, oligomenorrhea, and amenorrhea.

Based on **Table 3**, it could be seen that participants who experienced polymenorrhea had obese body fat percentage. It also showed that oligomenorrhea and amenorrhea occurred in participants with underfat percentage. Spearman Rank test showed that there was a significant correlation between the percentage of body fat and the menstrual cycle with p-value 0.000 and r-value -0.865. r-value indicated that higher percentage of body fat affect shorter menstrual cycle.

From **Table 4**, it described that participants who experienced polymenorrhea were not at risk of developing chronic energy deficiency, while participants with oligomenorrhea and amenorrhea were at risk of developing chronic energy deficiency. Based on data analysis using the Spearman Rank test, p-value 0.000 (<0.05) with r-value -0.916 indicated that there was correlation between upper arm circumference and menstrual cycle in female students significantly.

RESULTS AND DISCUSSIONS

Result of Study Selection

After the search process in 10 databases, 1403 articles were collected. Then, 305 duplicate articles were removed leaving 1098 articles for screening. The screening process based on title and abstract was conducted by the three authors (MFH, SAA, DEP) and left 60 articles to be read in full text. Of the 60 articles, 55 were excluded because they did not meet the inclusion criteria, leaving five articles for full analysis. Details of the study selection process are provided in **Figure 1**.

Result of Risk of Bias Assessment

Furthermore, for the risk of bias assessment using RoB 2.0, two studies were indicated with a high risk of bias because in domain 3 there was an imbalance in baseline and number of participants between the trial and control groups due to the participant's withdrawal in the middle of the study without a clear reason. One study and the two remaining studies showed low risk of bias. One study showed some concerns risk of bias in domain 4 because the assessor team was not blinded and there was no assurance or information from the authors whether it affected

the results provided. While, the rest studies showed low risk of bias. Details of the results of the risk of bias analysis can be seen in **Figure 2**.

Result of Meta-analysis

Our review summarizes information from five inclusion studies from different countries, such as, Malaysia, South Korea, Canada and USA. The total number of participants in these studies was 329, the majority of whom were adults and only the study by St-Jules et al., 2021 had a sample with majority of geriatric. The length of intervention also varied, ranging from 3 months to 9 months. All studies compared the use of mobile apps with general dietary consultation and education. Only the study by Khor et al., 2020 that specifically educated on dietary phosphate in the control group. Our outcomes included phosphate, albumin, and calcium values as seen in **Table 1**.

The results of our meta-analysis showed that the use of mobile apps significantly controlled phosphate levels as per the primary objective of this study (pooled MD = -0.63, 95% CI [-1.18, -0.08], p = 0.02, I²=82%) (Figure 3.). The first secondary outcome, calcium, was found to be significant in favor of the application group (pooled MD = -0.51, 95% CI [-0.77, -0.24], p = 0.0002, I²=0%). Unlike phosphate, the significance in calcium level refers to an increase in calcium level.

As for the second secondary outcome, there was a non-significant result in the app group on albumin levels (pooled MD = -0.09, 95% CI [-0.33, 0.16], p = 0.49, I²=0%). The non-significant effect of the mobile app on changes in albumin levels is good news, because it means that the mobile app is able to control phosphate levels without excessively reducing albumin levels so that there is no risk of hypoalbuminemia.

Hyperphosphatemia and its Correlation to Hypoalbuminemia

Hyperphosphatemia is one of the side effects of hemodialysis found in at least 40% of patients (16). Hyperphosphatemia needs to be prevented because in addition to disrupting bone function it also increases the risk of heart disease. Hence, it is necessary to have a phosphate diet to prevent this condition (17).

Table 1. Data Extraction Table

Author, Year	Country	Sample Size		Age (Mean ± SD)		Application Type	Control Type	Application Content	Intervention Time	Assessment Period
		Trial	Control	Trial	Control					
Teong <i>et al.</i> , 2022	Malaysia	33	33	47.5 ± 15.3	49.15 ± 13.63	Phosphate based mobile application MyKidneyDietPhosphate Tracker	One nutrition counseling session with a nutritionist	The app provides six interactive animated videos covering topics about hyperphosphatemia, dialysis, phosphate binders, phosphate diet, lifestyle, and the needs of dialysis patients.	3 months	Twelfth week
Pack and Lee, 2021	South Korea	37	38	52.00 ± 10.01	50.66 ± 9.15	Self-management diet based smartphone app	General diet education	Dialysis patient diet regulator application with diet diary features, food selection, favorite food adjustments and diet history, recommended foods, as well as diet therapy progress charts.	3 months	Eighth and twelfth week
Farfan-Ruiz <i>et al.</i> , 2021	Canada	27	36	55.2 ± 12.6	56.7 ± 15.3	OkKidney app that adjusts the phosphate binders to the phosphate content of foods	A multidisciplinary team education that includes kidney nutritionists	An application to calculate how many phosphate binding pills are recommended each meal.	3 months	Every month
St-Jules <i>et al.</i> , 2021	USA	13	14	62 ± 14	61 ± 17	Cellular App-Based Diet Program (MyNetDiary)	Multidisciplinary education on diet	A diet management application with personal diet monitoring features, records of phosphorus and protein intake, use of phosphate binding agents, as well as diet pattern advice.	6 months	Third and sixth month
Khor <i>et al.</i> , 2020	Malaysia	49	49	54.5 ± 13.3	50.3 ± 14.7	Apple iPod Mobile App	General dietary advice on low phosphate diets	A dedicated Apple iPod app to calculate the amount of phosphate binder needed at each meal in the patient's food intake.	9 months	Third, sixth, and ninth month

Author, Year	Country	Phosphate (Mean ± SD)				Albumin (Mean ± SD)				Calcium (Mean ± SD)			
		Pre-app	Post-App	Pre-Placebo	Post-Placebo	Pre-app	Post-App	Pre-Placebo	Post-Placebo	Pre-app	Post-App	Pre-Placebo	Post-Placebo
Teong <i>et al.</i> , 2022	Malaysia	2.34 ± 0.34	2.08 ± 0.41	2.17 ± 0.34	1.95 ± 0.50	42.2 ± 3.3	41.1 ± 3.7	41.1 ± 3.6	40.5 ± 3.5	2.33 ± 0.23	2.30 ± 0.25	2.33 ± 0.28	2.33 ± 0.25
Pack and Lee, 2021	South Korea	6.34 ± 1.05	5.45 ± 0.97	6.28 ± 1.07	6.11 ± 1.01	3.74 ± 0.45	3.79 ± 0.44	3.72 ± 0.42	3.75 ± 0.37	-	-	-	-
Farfan-Ruiz <i>et al.</i> , 2021	Canada	1.94 ± 0.50	1.85 ± 0.44	2.04 ± 0.61	6.3 ± 2.0	32.1 ± 4.6	-	31.6 ± 5.5	-	2.28 ± 0.19	2.23 ± 0.48	2.16 ± 0.17	2.22 ± 0.16
St-Jules <i>et al.</i> , 2021	USA	6.1 ± 1.6	5.6 ± 1.5	6.3 ± 2.0	6.4 ± 1.8	4.0 ± 0.3	4.0 ± 0.3	3.8 ± 0.5	3.9 ± 0.4	-	-	-	-
Khor <i>et al.</i> , 2020	Malaysia	2.15 ± 0.22	1.68 ± 0.43	2.22 ± 0.27	2.10 ± 0.39	38.51 ± 3.10	37.18 ± 3.10	38.04 ± 3.92	36.80 ± 3.10	2.26 ± 0.19	2.32 ± 0.23	2.30 ± 0.24	2.32 ± 0.17

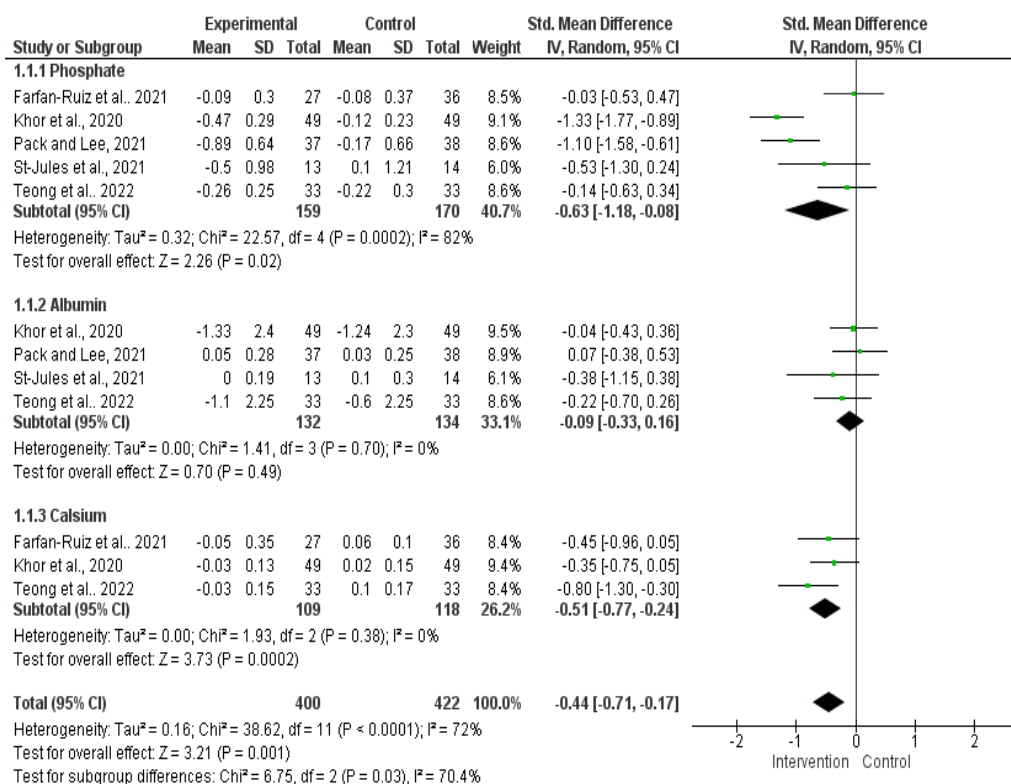


Figure 3. Result of Meta-analysis

High-protein foods are the main source of phosphate, so patients who are on a phosphate diet are very susceptible to hypoalbuminemia (16). A study showed that hemodialysis patients who experienced hypoalbuminemia had a higher mortality rate than patients who experienced hyperphosphatemia (18). Therefore, in a study that aims to control phosphate levels in the blood, it is also necessary to evaluate blood albumin levels.

Calcium as a Phosphate Binder

Chronic renal failure patients have a significantly reduced ability to perform excretory functions including a reduced capacity to remove phosphate in the body (19). This condition can lead to phosphate accumulation in the blood and tissues. Calcium is one of the nutritional components that can prevent phosphate from accumulating in the blood circulation by binding phosphate in the stomach (20). This results in phosphate not being absorbed in the jejunum and unable to enter the blood circulation. Therefore, one method to keep phosphate levels stable is to

also pay attention to the calcium levels in the food consumed (21).

Potential of Mobile Apps in Preventing Hyperphosphatemia in Hemodialysis Patients

The significant results obtained are inseparable from the potential of mobile apps from each inclusion study. All the inclusion studies we used utilized mobile apps to prevent hyperphosphatemia in hemodialysis patients by offering various features in one app. The first feature offered includes interactive animated videos covering topics on hyperphosphatemia, dialysis, phosphate binders, dietary phosphorus, lifestyle, and dialysis patient responsibilities (14). There is also a feature to calculate the approximate amount of phosphate that has been consumed in a single meal to be used as a reference to calculate the amount of phosphate-binding pills that should be taken. There is also a variety of information on the nutritional value of each food and cuisine often consumed by local resident, daily meal recommendations, consultation with a nutritionist, and a daily diet progress chart (22)(23)(24)(25).

From the many features offered by each inclusion study, we conclude that there are two purposes of these features, to increase the knowledge of app users to be more aware of their food and help to calculate the phosphate levels that have been or will be consumed at each meal. When viewed from the mean difference, the most significant change was found in the study conducted by Pack and Lee (22). This study offers more features than other studies and there is a unique difference that is not done by other studies in the form of a 30-minute exercise program directly at the hemodialysis center three times per week accompanied by routine blood checks. Participants will be given advice on dietary issues based on the blood test results.

Strengths and Weaknesses of This Review

This review is the first systematic review and meta-analysis to assess the effectiveness of mobile apps in preventing hyperphosphatemia in patients undergoing hemodialysis and its secondary outcomes of blood albumin and calcium levels. Our inclusion studies included studies from 4 different countries with clear administration of the intervention. All inclusion studies also provided results with mean and standard deviation with low overall heterogeneity. Unfortunately, there are still some studies with a risk of bias that may affect the conclusions. In addition, the level of heterogeneity in this study is still high and it is not possible to conduct sensitivity analysis due to the limited number of studies.

CONCLUSIONS AND RECOMMENDATIONS

Based on the results of our meta-analysis, the right dietary method can have a huge impact on a patient's recovery. The use of mobile apps has a significant effect on preventing hyperphosphatemia in patients undergoing hemodialysis therapy and preventing common side effects of phosphate diet patients due to nutrient imbalance. In this modern era, health education can be improved and disseminated more easily. Therefore, the use of mobile apps could be one of the promising interventions with great potential in the present and future to prevent various health problems. In the development of the application, the author suggests the food recommendation feature and daily diet as the

main feature to prevent hyperphosphatemia in hemodialysis patients so that other important nutrients are still fulfilled. Future studies are expected to pay more attention to the possible risk of bias that occurs. So, the results obtained are more accurate. There is also a need for more comprehensive inclusion studies to represent conditions from different continents.

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