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CLINICAL NUTRITION RESEARCH

The Korean Society of Clinical Nutrition

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Aims and Scope

Clinical Nutrition Research (Clin Nutr Res or CNR), which was launched in 2012 as the official journal of the Korean Society of Clinical Nutrition (KSCN), strives for academic advancement by stimulating research activities in the clinical nutrition research field. The CNR is published quarterly on the last day of January, April, July, and October, one volume per year. The CNR aims to contribute to human health and nutrition by exerting education effect, which can be practically applied in clinical nutrition care. Total or a part of the articles in this journal are abstracted in Science Central, Directory of Open Access Journal, Google Scholar, and Crossref.

The journal features original research articles, reviews, case reports, and notes related to the field of clinical nutrition, human nutrition, and public health nutrition. It publishes manuscripts on nutrition interventions contributing to disease prevention and health promotion, nutrient physiology and metabolism, human nutrition related to growth and development, nutritional assessments, and quality management of clinical nutrition, community nutrition, dietary behavior, nutritional epidemiology, nutrition education, food culture and other studies related to the promotion of human health. It also publishes animal experiments of which findings are applicable to human nutrition or diseases.

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Dietary management of pediatric patients with kidney disease: recommendations by the Korean Society of Pediatric Nephrology and the Korean Society of Clinical Nutrition

Yo Han Ahn[1,2], Hee Gyung Kang[1,2], Jiyoung Song[3], Sangmi Han[4], Eujin Park[5], Jin-Soon Suh[6], Jeong Yeon Kim[7], Min Ji Park[8], Keum Hwa Lee[9], Seon Hee Lim[10], Kyeong Hun Shin[11], Hyunji Ko[12], Hyun Joo Lee[13], Eunyoung Jeong[14], Jinsu Kim[15], Sohyun Park[15], Eonju Choi[16], Yuri Seo[3], Kyooyung Oh[3], Jin Kyoung Kim[17], Hyun Kyung Lee[18]

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Pediatric kidney disease has a lower prevalence than other pediatric conditions and has a notably different etiology from kidney diseases occurring in adults. Furthermore, the pediatric population is unique in that they experience ongoing growth and development, distinguishing them from adult patients. Consequently, pediatric patients with kidney disease require a more specialized and meticulous nutritional management plan compared with adult patients. To address this need and promote optimal dietary practices for pediatric patients with kidney disease, pediatric nephrologists from the Korean Society of Pediatric Nephrology and nutritionists from the Korean Society of Clinical Nutrition have collaborated to formulate nutritional guidelines specifically tailored to Korean dietary patterns. These guidelines offer detailed, nutrient-specific recommendations regarding the consumption of energy, protein, calcium, phosphorus, and potassium while providing practical, culturally relevant guidance intended to support both pediatric patients and their caregivers.

Keywords: Child; Kidney diseases; Nutritional requirements; Republic of Korea

INTRODUCTION

Nutritional management of pediatric patients with kidney disease is particularly challenging because unlike adults, pediatric patients undergo continued growth and development. As a result, providing adequate nutrition for growth while minimizing disease progression and complications is the primary challenge. However, for mitigating kidney disease, several patients and caregivers obtain nutritional information from online sources, which are often inaccurate, leading to the practice of inappropriate dietary restrictions.

To address this issue, pediatric nephrologists from the Korean Society of Pediatric Nephrology and nutritionists from the Korean Society of Clinical Nutrition have collaborated to develop dietary recommendations tailored to the dietary habits of Koreans. These recommendations aim to serve as the standard for nutritional care and dietary management of pediatric patients with kidney disease

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in Korea and have been structured in a practical format that categorizes key nutrients to ensure comprehensibility for both patients and caregivers. This approach was also adopted to assist healthcare professionals in managing and educating pediatric patients with kidney disease by providing them with helpful guides for nutritional management.

ENERGY IN PEDIATRIC KIDNEY DISEASE

The primary dietary energy sources are carbohydrates, fats, and proteins. Carbohydrates and proteins each provide 4 kcal/g of energy, whereas fats supply 9 kcal/g of energy. The daily energy requirement for pediatric patients with chronic kidney disease (CKD) is the same as that for healthy children and adolescents of the same age (Table S1) [1]. Patients with kidney disease often have insufficient dietary intake due to dietary restrictions or reduced appetite, potentially causing protein depletion, weight loss, and delayed growth [1-3]. Therefore, adequate energy intake is crucial for maintaining optimal nutritional status and supporting proper growth. In recent years, however, obesity has become a growing concern among children and adolescents, often more so than energy insufficiency. Therefore, tailoring interventions to the individual patient's condition is essential.

Dietary alternatives for insufficient caloric intake

When eating regular meals proves difficult, alternative foods with equivalent calories (kcal) can be selected as substitutes (Fig. 1) [4,5]. To increase energy intake, jam can be added to bread or crackers, and honey or rice syrup can be added to rice cakes. Even with the same ingredients, energy intake can be enhanced by stir-frying, deep-frying, or making pancakes out of the ingredients. Additionally, using sesame oil or perilla oil in the preparation of porridges or side dishes and using olive oil or oriental dressing on salads can help boost energy intake.

Enteral formulas

Patients with kidney disease who are required to restrict their protein, potassium, and phosphorus intake can use a specialized enteral formula. For infants, increasing the infant formula concentration by reducing the amount of water added can increase the energy content of the formula; however, this method may also increase the protein, sodium, potassium, and phosphorus levels in the formula. Therefore, infant formula concentration should not be altered arbitrarily. Instead, energy modules specifically designed for caloric and nutritional supplementation, such as glucose polymers or fat emulsions, can be added to the formula [1-3]. For instance, infants fed formula eight times a day at 100 mL per feeding obtain approximately 560 kcal of energy. By supplementing each 100-mL formula feed with 3 g of an energy-dense additive (e.g., high-calorie powder), the total daily energy intake can be increased to approximately 650 to 700 kcal, representing a 15% to 20% increase in caloric density [4].

1/3 Bowl of rice, three pieces of injeolmi (rice cakes), 1 slice of bread, 1/2 bowl of boiled noodles, 1/2 of a medium-sized sweet potato (70 g), 1/2 an ear of corn (70 g), 2 chopsticks full of ramen, 2 tablespoons of sugar (25 g), 1.5 tablespoons of honey (30 g), 5 pieces of candy (25 g), 30 g of jelly, 1 piece of yakgwa (25 g), 1 cup of sweet rice drink

Fig. 1. Examples of foods with 100 kcal.

PROTEINS IN PEDIATRIC KIDNEY DISEASE

Proteins serve as critical components of various body tissues and structures, including muscles, skin, bones, nails, and hair. In the form of hormones, antibodies, and enzymes, proteins play essential roles in growth, physiological function, and life maintenance. Additionally, proteins constitute an important energy source. However, pediatric patients with kidney disease may be required to restrict their protein intake due to impaired renal waste excretion and metabolic acidosis, the extent of which varies with disease severity. Thus, the appropriate protein intake should be carefully determined by considering factors such as disease severity, age, growth velocity, and the necessity for promoting optimal growth and nutritional status.

Dietary sources of protein

Proteins can be sourced from both animals and plants [4]. Animal-based protein sources mainly include meat, fish, shellfish, eggs, and milk. Except milk, animal-derived foods typically contain 8 g of protein per food exchange unit (a standardized measurement system that allows for interchanging foods within the same food group while ensuring equivalent nutritional value). Plant-based protein sources include grains, vegetables, legumes and their processed products (e.g., tofu), and soy milk. Among these, legumes have the highest protein content, providing 8 g of protein per food exchange unit [5]. Grains and vegetables each provide approximately 2 g of protein per food exchange unit, whereas soy milk provides 6 g of protein per food exchange unit, which is equivalent to that provided by cow milk (Table 1) [5].

Table 1. Major dietary protein sources according to exchange unit [5]

Source	Weight	Estimated serving size	Protein content (g)
Animal-based foods			
Meat	40 g	Size of one ping-pong ball	8
Fish	50 g	Small piece	8
Shellfish	70 g	1/3 Cup	8
Egg	55 g	1 Medium-sized egg	8
Milk	200 mL	1 Cup (pack)	6
Plant-based foods			
Grains	70 g	1/3 Bowl of cooked rice	2
Vegetables	70 g	1/3 Cup cooked	2
Beans	20 g	2 Tablespoons	8
Tofu	80 g	1/4 Block	8
Soy milk	200 mL	1 Cup (pack)	6

Protein intake in pediatric patients with nephrotic syndrome

Pediatric patients with nephrotic syndrome are recommended to maintain a protein intake similar to that prescribed for healthy children of the same age, without increasing or restricting protein intake even during steroid treatment or proteinuria (Table 2) [6,7]. Historically, high-protein diets have been found to compensate for protein losses in nephrotic syndrome; however, instead of improving serum albumin levels, such diets were found to accelerate renal damage due to protein overload. Conversely, studies have demonstrated that low-protein diets slow renal function decline in patients with CKD but exacerbate nutritional deficiencies due to inadequate protein intake [8-11]. According to the 2021 Kidney Disease: Improving Global Outcomes guidelines, protein restriction is recommended for patients with decreased kidney function and proteinuria, although its safety has not been conclusively established in pediatric populations due to concerns about the risk of malnutrition [12]. An exception to this recommendation is patients with congenital nephrotic syndrome, who may benefit from high-calorie, high-protein diets.

Protein intake in pediatric patients with chronic kidney disease

The protein intake of pediatric patients with CKD should be carefully planned to ensure normal growth and adequate nutritional status. Given that strict restriction of protein intake does not necessarily improve the preservation of kidney function, guidelines recommend that pediatric patients with CKD consume the same amount of protein as their healthy peers (Table S2). However, healthy children and adolescents typically consume more than twice the recommended protein intake. Therefore, patients with CKD must strictly adhere to nutritional guidelines rather than trying to match the high protein consumption of their peers.

Restricting protein intake often inadvertently reduces overall caloric and nutrient consumption. Thus, substantial protein restriction is generally not recommended for patients with stage 1 to 2 CKD. For those with stage 3CKD or higher, guidelines recommend a protein intake that closely aligns with age-specific nutritional requirements (Table 3) [1,2,6,7,13].

Suggested daily meat consumption

A serving of meat weighing approximately 40 g, approximately the size of a ping-pong ball, contains approximately 8 g of protein [4,5]. For example, the daily recommended protein intake for a 10-year-old boy is approximately 50 g. If this daily requirement were to be met exclusively through meat, approximately 250 g of meat (approximately six ping-pong ball-sized portions) would be required (Table 1). However, actual meals typically include rice and vegetables alongside meat. Considering that one bowl of rice contains approximately 6 g of protein, along with vegetable side dishes, a total of 20 to 25 g of protein can be obtained daily through these foods. Therefore, an additional 3 to 4 ping-pong ball-sized meat servings would suffice to meet the protein requirement.

URIC ACID IN PEDIATRIC KIDNEY DISEASE

Uric acid is the final product of the breakdown of purines. It is primarily obtained via two means: (1) breakdown of the body's own cells and (2) dietary intake of purine-rich foods. Most uric acid in the body is eliminated by the kidneys through urine. Hyperuricemia can result from either excessive uric acid production or insufficient renal excretion. In adults, hyperuricemia is defined as uric acid levels exceeding 7 mg/dL, whereas in pediatric pa-

Table 2. Recommended protein intake for healthy children and pediatric patients with nephrotic syndrome [6,7]

Parameter	Age group							
	Infant		Toddler	Child	Adolescent			
	0–6 mo	7–12 mo	1–3 yr	4–8 yr	9–13 yr		14–18 yr	
Sex	Both	Both	Both	Both	Male	Female	Male	Female
Protein (g/kg/day)	1.5	1.2	1.1	0.95	0.95	0.85	0.95	0.85

Table 3. Recommended protein intake for pediatric patients with CKD [6,7]

Parameter	Age group					
	Infant		Toddler	Child	Adolescent	
	0–6 mo	7–12 mo	1–3 yr	4–8 yr	9–13 yr	14–18 yr
Protein (g/kg)						
CKD stage 3	1.50–2.10	1.20–1.70	1.05–1.50	0.95–1.35	0.95–1.35	0.85–1.20
CKD stage 4–5	1.50–1.80	1.20–1.50	1.05–1.25	0.95–1.15	0.95–1.15	0.85–1.02

CKD, chronic kidney disease.

tients, hyperuricemia is defined as uric acid levels exceeding the 90th percentile for age and sex [14]. Severe hyperuricemia can cause gout, a condition characterized by the deposition of uric acid crystals in the joints, and contribute to the development of hypertension and worsening kidney function. Thus, dietary management aimed at maintaining normal blood uric acid levels is crucial for pediatric patients with CKD.

Uric acid-containing foods

Fig. 2 presents a list of the dietary sources of uric acid classified according to purine content [4].

Factors elevating uric acid levels

Fat

Excessive fat intake stimulates fatty acid synthesis in the liver, which has been linked to increased purine synthesis, consequently accelerating uric acid production and impairing uric acid excretion [15]. Therefore, reducing fat intake is important for managing hyperuricemia. To achieve this, studies recommend using alternative cooking methods, such as steaming or grilling, instead of frying or sautéing [16-18].

Fructose

Fructose has been established as a prominent risk factor for hyperuricemia [15-19], considering that uric acid is produced during fructose metabolism in the liver. Additionally, fructose and its metabolite lactate interfere with uric acid excretion, which quickly raises blood uric acid levels. Therefore, patients with CKD and hyperuricemia should limit their consumption of fructose-rich foods and beverages, including soft drinks, fruit juices, and syrups.

Protein

Traditionally, a low-protein diet has been recommended for the management of hyperuricemia in adults. However, reducing dietary protein intake can inadvertently increase the consumption of refined carbohydrates and foods high in saturated or trans fats. Moreover, protein is essential for growth in pediatric patients. Hence, pediatric patients with CKD should aim to meet their protein requirements rather than excessively restricting their protein intake [16].

SODIUM IN PEDIATRIC KIDNEY DISEASE

Sodium, primarily obtained through salt, plays a crucial role in maintaining fluid balance, stable blood pressure, and acid-base balance in the body [20]. Studies have shown that the sodium intake of Korean children and adolescents exceeds more than twice the sodium intake recommended by the 2020 Korean Dietary Reference Intakes for maintaining good health [21-25]. Excessive sodium intake in pediatric patients with CKD can increase blood pressure and potentially exacerbate kidney disease progression. Therefore, reducing sodium intake by identifying high-sodium foods and carefully managing their consumption is vital.

Foods containing sodium

Sodium is abundantly present in condiments or seasonings, pickled foods, processed foods, instant foods, and fast foods. Table 4 lists the primary dietary sources of sodium for Koreans. Condi-

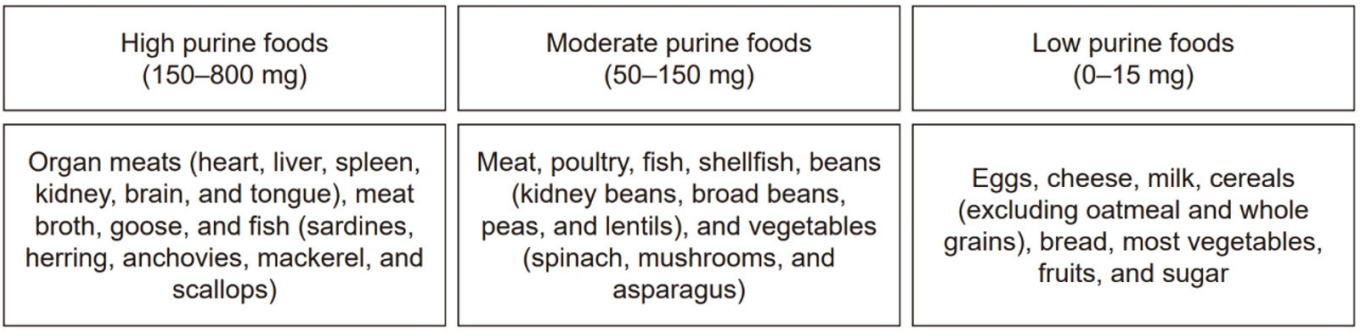

Fig. 2. Classification of foods according to purine content (per 100 g) [4].

Table 4. Ranking foods according to sodium content [21]

Rank	Food item	Sodium (mg/100 g)
1	Salt	33,417
2	Soy sauce	5,476
3	Kimchi (Napa cabbage)	548
4	Ramen (dried noodles and soup)	1,338
5	Soybean paste	4,339
6	Red pepper paste	2,486
7	Bread	516
8	Salted seafood	11,826
9	Anchovies	2,377
10	Noodles	395
11	Dried seaweed	7,535
12	Ham/sausage/bacon	759
13	Ssamjang	2,619
14	Powdered seasoning	15,836
15	Rice cake	261
16	Snacks	577
17	Cubed radish kimchi	501
18	Bulgogi marinade	1,964
19	Young radish kimchi	510
20	Fish cakes	699
21	Egg	131
22	Radish kimchi	692
23	Buckwheat noodles	455
24	Sandwich/hamburger/pizza	378
25	Milk	36
26	Pork (lean meat)	49
27	Cheonggukjang	3,083
28	Black bean sauce	3,227
29	Cheese	928
30	Dongchimi	533

ments account for nearly 46% of the daily sodium intake [20]. Therefore, pediatric and adolescent patients with CKD should make concerted efforts to reduce their consumption of sodium-rich condiments and processed foods and limit the frequency of dining out.

Recommended daily sodium intake for a 7-year-old child

The recommended daily sodium intake for a 7-year-old child is 1,900 mg (Table S3). Given that 1 g of salt contains approximately 400 mg of sodium, a 7-year-old child can safely consume approximately 5 g of salt per day. Typically, 1 to 2 g of salt is consumed naturally through unprocessed foods, allowing an additional 3 to 4 g of salt to be consumed through condiments or seasonings, which equates to approximately 1 g of salt per meal coming from condiments. A list indicating the amount of various condiments containing 1 g of salt is presented in Fig. 3 [26].

Methods for reducing sodium intake when cooking at home

Patients with CKD should avoid salted foods, processed foods, fast foods, dried fish, and chemically enhanced seasonings, all of which have a high-sodium content [26]. Clear soups or rice-water soups (Nurungji-guk) are preferable, given their lower sodium content. Vinegar, lemon juice, wasabi, chili powder, pepper, green onions, onions, garlic, ginger, herbs, perilla oil, and sesame oil can be used to enhance flavor while reducing sodium content. Additional measures for reducing sodium intake include serving sauces as separate dips rather than seasoning soups and side dishes directly, preparing only one side dish with adequate seasoning while leaving the others unseasoned, and using low-sodium condiments [27,28].

Methods for reducing sodium intake when dining out

Processed foods often contain high amounts of sodium for the purpose of preservation. Therefore, caution should be exercised when consuming bread, snacks, convenience store meals, frozen foods, and instant foods [26]. When eating school meals or dining out, only consume half portions of high-sodium foods, such as

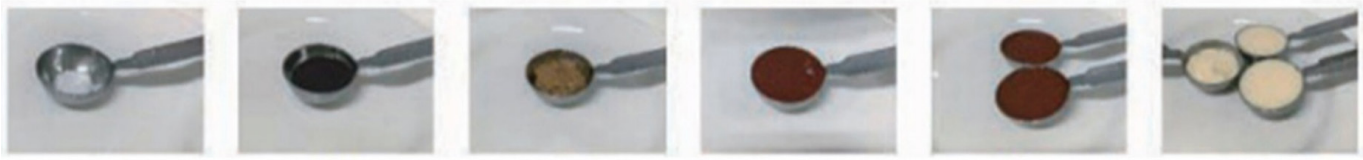

Fig. 3. Amount of condiments containing 1 g of salt (400 mg of sodium) [26]. Spoon used is 1 tablespoon.

braised or pickled dishes and soups. Moreover, individuals can request that the sauce be served separately and use minimal amounts for dipping. Consumption of pickles, ketchup, cheese, bacon, and processed meats should also be minimized [26-28].

CALCIUM AND PHOSPHORUS IN PEDIATRIC KIDNEY DISEASE

Calcium, the most abundant mineral in the body, plays a crucial role in bone health, blood coagulation, nerve conduction, muscle contraction, and hormone secretion. Similarly, phosphorus, the second most abundant mineral, contributes prominently to skeletal structure, regulation of acid-base balance, activation of vitamins and enzymes, and energy metabolism. Calcium and phosphorus concentrations in the body are maintained through integrated regulation involving intestinal absorption, renal reabsorption, and bone exchange. Imbalances that decrease calcium and phosphorus levels can cause bone disorders, such as rickets, osteomalacia, and osteoporosis, whereas high levels of calcium and phosphorus may cause cardiovascular diseases and calcification of blood vessels and kidneys. Thus, appropriate regulation of calcium and phosphorus is crucial in pediatric patients with CKD.

Dietary sources of calcium and phosphorus

Calcium-rich foods include milk, dairy products, anchovies, oysters, dried seaweed, cheese, and tofu. According to the 2018 Korean National Health and Nutrition Examination Survey [29], Koreans consume an average of 128.1 mg of calcium per day through milk and dairy, accounting for 29.4% of the daily calcium intake. Milk and dairy products, including manufactured infant formulas, are key calcium sources for infants and children.

Phosphorus is found in almost all animal- and plant-based foods, but it is particularly abundant in protein-rich foods, such as fish, meat, eggs, dairy products, grains, and nuts. The major dietary phosphorus sources for Koreans [29,30] include rice and animal-based foods, such as pork (lean meat), chicken, anchovies, milk, and eggs. For infants and children, milk and dairy products serve as more prominent sources of phosphorus than rice and meat.

Food additives and supplements

Phosphorus can be consumed in various forms through natural foods, food additives, and supplements. Food additives are widely used in food processing; thus, frequent consumption of processed foods increases the intake of food additives [31]. These additives, which are mostly inorganic phosphates, are more readily absorbed than naturally occurring phosphorus in foods. Additionally, phosphates are added to various medications (e.g., antacids and antihypertensive drugs) to aid dispersion and absorption [32,33]. Therefore, the assessment of phosphorus intake should consider the consumption of carbonated beverages, processed foods, and medications containing inorganic phosphates.

In Korea, 27 types of phosphates, including potassium phosphate, calcium phosphate, and sodium phosphate, have been approved for use as food additives in food production [34]. Phosphates function as acidity regulators, emulsifiers, nutrient enhancers, leavening agents, and preservatives. In Korea, phosphates are most commonly used in bakery products, processed foods, and complex seasonings. Although Koreans primarily consume phosphorus through natural agricultural and animal products [21], the growing trend of processed food consumption among adolescents may increase phosphate intake from food additives.

Calcium and phosphorus intake in pediatric patients with chronic kidney disease

Pediatric patients with CKD must regularly monitor their calcium and phosphorus intake, including intake from food additives, processed foods, and calcium-containing medications (e.g., calcium-based phosphate binders). Calcium intake should be aligned with the recommended daily allowance for that age (Table S4) and should ideally not exceed twice this amount. Phosphorus intake should also adhere to age-specific recommendations (Table S5)

while still ensuring adequate nutritional intake. However, given the high phosphorus content in dairy products, fish, and meat, strict adherence to the recommended levels can be challenging, often necessitating the use of phosphate binders to manage phosphorus effectively.

Meal planning for phosphorus control

Meal planning should prioritize foods low in phosphorus (Table 5) [4]. Given that phosphorus from animal-based foods is absorbed more efficiently than that from plant-based foods, animal proteins should be evenly distributed across meals rather than consumed excessively at one time [32]. Considering that phosphorus is water-soluble, the phosphorus content of foods can be reduced by boiling them in plenty of water [31,35,36]. After boiling, the cooking water is discarded as it contains high levels of phosphorus. Boiling reduces phosphorus content in vegetables, legumes, and meats by approximately 51%, 48%, and 38%, respectively [4]. Boiling food for over 30 minutes using a pressure cooker is more effective than using a regular pot. If processed foods are desired, they should be cut into small pieces, boiled, and drained before consumption. Always check the labels on processed foods to identify phosphorus additives (e.g., phosphate compounds) and manage intake carefully.

Calcium-rich beverages as alternatives to milk

Breastfeeding is recommended even for infants with CKD [35]. However, if breastfeeding is not possible and manufactured infant formulas are chosen instead, studies have recommend the use of standard formulas suitable for the infant's age and weight. As infant formulas advance in stages, their protein and mineral contents increase slightly despite similar caloric contents. Thus, if an infant consumes adequate amounts of formula, maintaining a lower-stage formula might be beneficial to prevent excessive intake of proteins and minerals [4]. Specifically, infants older than 6 months who primarily rely on formula due to difficulties transitioning to complementary foods may consume excessive amounts of minerals when consuming large amounts of advanced-stage formula. The use of formulas low in phosphorus can be considered after consulting with healthcare providers. Table 6 compares the nutritional contents of breast milk and infant formulas [37].

POTASSIUM IN PEDIATRIC KIDNEY DISEASE

Potassium is an essential mineral necessary for maintaining muscle, nerve, and heart function. In patients with decreased kidney function, impaired potassium excretion can cause potassium imbalances and related complications. Therefore, identifying potassium-rich foods and managing their intake as needed is imperative. Pediatric patients with CKD whose potassium levels remain normal can follow the potassium intake recommendations for healthy children (Table S6). However, patients with hyperkalemia should avoid foods high in potassium and employ cooking methods that lower the potassium content in food (Table 7) [37]. Conversely, patients with hypokalemia should prioritize the consumption of potassium-rich foods.

Table 5. Foods rich in phosphorus [4]

Food group	Food item
Grain	Potatoes, taro, black rice, barley, mung beans, Job's tears, sorghum, millet, chestnuts, bread, breadcrumbs, oatmeal, corn, and ginkgo nuts
Animal protein	Dried fish (anchovies and whitebait), fish roe (pollock/cod eggs), liver, ham, beef bone broth, and egg yolks
Dairy product	Milk, cheese, yogurt, ice cream, and custard cream
Nut	Peanuts, walnuts, and almonds
Other	Chocolate, brown sugar, raw sugar, royal jelly, and coke

Table 6. Nutritional contents of breast milk and infant formulas [37]

Type	Energy (kcal/100 mL)	Protein (g/100 mL)	Calcium (mg/100 mL)	Phosphorus (mg/100 mL)	Potassium (mg/100 mL)	Sodium (mg/100 mL)
Breast milk	61	1.1	27	14	48	15
Infant formula, step 1 (up to 6 mo)	71	1.7	77	45	98	23
Infant formula, step 2 (6–12 mo)	71	1.8	89	52	103	24
Infant formula, step 3 (after 12 mo)	67	2.4	119	73	130	26
Infant formula, low-phosphate	70	2.0	52	12	63	20

Table 7. Dietary sources of potassium (mg/serving) [37]

Food group	Food item (serving size, g)	Potassium (mg)
Vegetable	Dried seaweed (2)	8.6
	Bean sprouts (70)	58.8
	Seaweed sheets (2)	70.1
	Onion (70)	101.5
	Cucumber (70)	112.7
	Soybean sprouts (70)	152.6
	Zucchini (70)	156.8
	Cabbage (70)	168.7
	Kimchi (50)	177.5
	Radish (70)	182.7
	Lotus root (40)	191.2
	Carrot (70)	209.3
	Bok choy (70)	255.2
	Broccoli (70)	255.5
	Chard (70)	393.4
	Spinach (70)	483.7
	Chamnamul (70)	538.0
Grain	Rice (70)	14.0
	Boiled noodles (90)	6.3
	Spaghetti (boiled, 90)	26.1
	Potato (140)	522.9
	Sweet potato (70)	262.5
	Corn (70)	212.1
Fat	Almonds (8)	60.7
	Sesame oil (5)	2.8
Dairy	Soy milk (200)	304.0
	Milk (200)	284.0
Fruit	Blueberry (80)	56.0
	Persimmon (50)	66.0
	Apple (80)	88.2
	Mango (70)	99.4
	Lychee (70)	119.0
	Mandarin (120)	121.2
	Grapes (80)	133.0
	Pear (110)	136.4
	Orange (100)	158.5
	Watermelon (150)	163.5
	Banana (50)	177.5
	Pineapple (200)	194.0
	Kiwi (80)	218.4
	Strawberry (150)	229.5
	Plum (150)	246.0
	Peach (150)	324.0
	Nectarine (150)	346.5
	Melon (120)	448.8
	Avocado (100)	485.0
	Korean melon (150)	675.0
	Cherry tomato (300)	731.5
	Tomato (350)	1,006.3
Animal protein	Chicken (40)	130.8
	Pork (40)	127.2
	Beef (40)	132.3
	Anchovy (15)	79.65
	Egg (55)	69.9
	Quail egg (40)	67.8
	Tofu (80)	105.6

Dietary sources of potassium and food additives

Table 7 lists the dietary sources of potassium in Korean cuisine. Additionally, potassium intake can be influenced by potassium salts used as food additives in various processed foods. Thus, individuals who are prescribed a potassium-restricted diet should carefully check the food ingredient label on processed foods for the content of potassium additives. In Korea, potassium salts approved for use as food additives [34] have been primarily used as acidity regulators, flavor enhancers, nutrient enhancers, coloring agents, sweeteners, emulsifiers, thickeners, stabilizers, flour treatment agents, bleaching agents, preservatives, and leavening agents. Potassium intake can be increased by consuming more amounts of processed or instant foods instead of fresh foods. Patients with hyperkalemia should therefore evaluate nondietary factors causing potassium imbalance (e.g., adjustments to dialysis prescriptions, medication review) before modifying their dietary intake.

Meal planning for hyperkalemia management

When consuming a regular diet, processed foods containing potassium additives should be avoided. If hyperkalemia persists, the intake of high-potassium foods should be reduced, and cooking methods that lower the potassium content of food should be adopted [4]. If dietary adjustments fail to control potassium levels, oral potassium binders may be necessary [38].

Regarding vegetable intake, not all raw vegetables must be blanched. Instead, select low-potassium options and avoid high-potassium varieties. Vegetables can be peeled, and their stems can be removed. Then, they can be sliced thinly or diced and soaked in water (10 times the volume of the vegetables) for at least 2 hours before being rinsed and cooked [4,38]. If blanching is preferred, vegetables can be blanched in water five times their volume, boiled thoroughly, and rinsed [4,38].

When consuming fruits, the skin should be peeled off before eating. Dried fruits must be consumed with caution because they typically have at least twice the potassium content of fresh fruits [4]. Canned fruits generally have a lower potassium content and can be consumed safely in moderation, but excessive syrup intake should be avoided [4].

CONCLUSIONS

Following the dietary recommendations developed jointly by the Korean Society of Pediatric Nephrology and the Korean Society for Clinical Nutrition, pediatric patients with kidney disease in

Korea can better establish optimized dietary regimens and nutritional management plans. These recommendations, which reflect essential nutrient-specific recommendations tailored to the Korean dietary context, are expected to serve as a valuable resource not only for patients and caregivers but also for healthcare professionals involved in the management and education of pediatric kidney disease.

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Conflicts of interest

None.

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Data availability

The data presented in this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary materials are available from https://doi.org/10.7762/cnr.2025.0033.

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CLINICAL NUTRITION RESEARCH

Clinical field survey and multidisciplinary expert in-depth interview study on food for special medical purpose products for patients

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Objective: Food for special medical purpose (FSMP) has become essential in clinical nutrition care. However, comprehensive data on FSMP utilization practices among healthcare professionals in South Korea are limited. This study aimed to investigate perceptions, current practices, and needs regarding FSMP among healthcare professionals.

Methods: A mixed-methods approach was employed, combining a cross-sectional survey of 417 healthcare professionals (47 physicians, 219 nurses, and 151 dietitians) from 90 institutions with focus group interviews of 24 Nutrition Support Team members from six institutions. Data were collected from May to October 2025.

Results: Substantial interphysician variability was observed in documentation for enteral formula prescriptions. Infusion rates were documented in 9.2% of the physician orders; feeding method was recorded in 14.1%. Across all professional groups, diarrhea was the most common reason for changing enteral formulas (36%–39%). In education related enteral formulas, 59.6% of the physicians expected dietitians to educate patients; however, this role was most commonly performed by nurses (59.8%). Dietitians prioritized hygiene (66.9%) and safety (64.2%) when selecting products, and 84.1% of the institutions were providing oral nutritional supplements.

Conclusion: These findings highlight the need for standardized prescription documentation, evidence-based feeding protocols, and clearly defined professional roles in multidisciplinary frameworks, to optimize FSMP utilization.

Keywords: Enteral nutrition; Health care surveys; Focus groups; Surveys and questionnaires

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INTRODUCTION

In the evolving landscape of clinical medicine, the paradigm of patient care has been profoundly transformed. Although diagnostic accuracy and pharmacological treatment have advanced remarkably, the nutritional status of patients continues to determine recovery and clinical outcome. Food for special medical purpose (FSMP) or enteral nutrition (EN) is not merely considered a supportive adjunct to medical therapy, rather it has emerged as a core therapeutic modality that modulates disease pathophysiology and metabolic responses; ultimately improving prognosis [1]. The transition from passive "nutrition support" to active "nutrition therapy" represents a critical recognition that targeted nutrition is essential to mitigate the detrimental effects of disease-related malnutrition (DRM). DRM results from inadequate intake or impaired absorption of nutrients, leading to alterations in body composition, specifically reduction in fat-free mass and body cell mass, ultimately decreasing physical and cognitive function and worsening clinical outcomes [2].

The clinical efficacy of FSMP is most pronounced in patients with severe catabolic stress, such as those admitted to the intensive care unit (ICU) or undergoing major surgical procedures. In clinical situations where oral intake is either impossible or inadequate, disease-specific or high-protein formulations serve as crucial immunometabolic support, functioning as both an immune defense and a metabolic stabilizer [3]. Early EN, initiated within 24 to 48 hours of injury or surgery, attenuated the catabolic response, preserved intestinal mucosal integrity to prevent bacterial translocation, and reduced mortality significantly [4]. Meta-analytic evidence indicates that critically ill pediatric patients who received early EN had an up to 64% lower risk of mortality than those who received delayed nutritional intervention [5]. Collectively, these findings underscore the role of FSMP not merely as a nutritional option but as an essential therapeutic component integral to survival and recovery.

FSMP plays a vital role in managing chronic conditions such as cancer, diabetes, and chronic obstructive pulmonary disease. These diseases induce chronic inflammation that dramatically alters patients' nutritional requirements in addition to what a normal diet can provide [6]. Specialized formulations of FSMP designed for specific disease states help minimize metabolic stress while optimizing nutrient utilization, leading to shorter hospital stays and lower readmission rates. From a health economics perspective, the systematic management of DRM through targeted FSMP interventions represents a key strategy for achieving healthcare sustainability. In Europe, DRM imposes an annual economic burden of more than €10 billion, primarily due to extended hospitalization and associated complications. Conversely, proactive nutritional therapy reduced acute care costs by approximately $2,818 per patient within the model timeframe of 6 months ($63,228 in the intervention group vs. $66,045 in the control group) through reduced infection rate and shorter length of stay, which decreased resource utilization [7].

Consistent with global trends, South Korea faces a similar urgency due to its rapidly aging population and the increasing burden of chronic disease. This escalating clinical demand has catalyzed a significant expansion in the domestic FSMP sector. According to the Food and Drug R&D Issue Report published by the National Institute of Food and Drug Safety Evaluation, the production value of FSMP in South Korea reached 98.2 billion Korean won in 2021, demonstrating a compound annual growth rate of 30.4% from 2019 to 2021 [8]. This market expansion was further accelerated by a strategic decision made by the Ministry of Food and Drug Safety in 2020 to reclassify FSMP as an independent food category and establish disease-specific standards. Such growth indicates a rising dependency on specialized nutritional management in hospitals and long-term care facilities.

Providing optimal nutrition to patients unable to meet their nutritional needs represents a practical application of the ethical principles of beneficence and non-maleficence [9]. As utilization patterns of FSMP continue to evolve among healthcare professionals and patients, it has become increasingly important to understand how FSMPs are utilized in clinical practice. Therefore, this study conducted a field survey to investigate the actual use of FSMP products in hospitals and long-term care facilities, followed by in-depth interviews with three key professional groups—physicians, nurses, and dietitians—to examine their perceptions and needs regarding patient-tailored nutritional formulas. The findings are expected to provide foundational evidence for developing strategies that enhance the clinical application of FSMP and inform the design of products that meet clinical demands better.

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Hanyang Women's University (No. AN01-202505-HR-001-01). Data collection was conducted from May to October 2025. All participants were provided with a written study information sheet containing the research purpose, procedures, voluntary participation,

confidentiality measures, and research team contact information. Written informed consent was obtained from all participants before they completed the questionnaires and participated in focus group interview (FGI). Participants were informed that they could withdraw from the study at any time without penalty. For the survey, consent was confirmed through signed consent forms; for FGI, written consent was obtained before each interview session.

Study design

This study employed a mixed-methods approach, combining a cross-sectional survey with FGI, to investigate healthcare professionals' perceptions, utilization practices, and needs regarding FSMP in South Korea. The quantitative survey was conducted to assess the perceptions of healthcare professionals who prescribe or administer FSMP in clinical settings. Qualitative FGI was to evaluate factors influencing FSMP utilization in clinical practice. This study was conducted by the Korean Society of Clinical Nutrition from February to November 2025. Funding support was provided by the Ministry of Food and Drug Safety.

Study participants

Survey participants were recruited using convenience sampling. The target was to collect 520 questionnaires from ≥130 healthcare institutions nationwide, including at least 20 tertiary hospitals, 30 general hospitals, 50 long-term care hospitals, and 30 long-term care facilities. Hospital lists categorized by grade were obtained from the Ministry of Health and Welfare and Health Insurance Review and Assessment Service. Cooperation was requested through the research team's network from professional associations (e.g., Korean Dietetic Association). Long-term care hospitals and facilities were recruited through contact with regional public health centers and welfare organizations. The survey targeted healthcare professionals including physicians who prescribe FSMP and nurses and dietitians who directly provide prescribed FSMP to patients. To enable comparison of perceptions across all professional groups, recruitment efforts ensured that all professional groups responded from each participating institution.

For FGI, participants were recruited using purposive sampling to ensure diversity and maximize representativeness. Following the distribution of cooperation request letters, institutions that voluntarily agreed to participate were prioritized for selection. To ensure institutional quality and standardization of nutrition care practices, selection criteria required either Nutrition Support Team (NST) certification from the Korean Society for Parenteral and Enteral Nutrition or healthcare accreditation from Korea Institute for Healthcare Accreditation. A total of six institutions were selected based on hospital type and geographic region as follows: one tertiary hospital, one general hospital, and one long-term care hospital from the capital region and one each from noncapital regions. One physician, nurse, and dietitian each most closely involved in FSMP prescription and administration was selected to participate in the interviews. To prevent conflicts of interest, the researchers' affiliated institutions were excluded from the selection. The FGI participants consisted of NST members from multidisciplinary teams directly involved in FSMP prescription and administration. A total of 24 participants were selected from six institutions, with one expert from each of the four professional groups (physician, nurse, dietitian, and pharmacist) per institution.

Survey and interview instruments

A structured questionnaire was developed to assess healthcare professionals' perceptions and needs regarding FSMP. Three versions of the questionnaire were developed to reflect the roles and work characteristics of the three professional groups. Survey items were derived through literature review and expert consultation. Physician and nurse questionnaires comprised the following four domains: institutional characteristics and respondent demographics, perceptions, current FSMP utilization practices, and needs assessments. The dietitian questionnaire included an additional domain on oral nutrition supplements (ONS) utilization practices, totaling five domains.

The physician questionnaire consisted of 27 items covering institutional characteristics (5 items), FSMP classification and labeling (7 items), enteral formula utilization practices (13 items), and FSMP needs (2 items). The dietitian questionnaire consisted of 30 items covering institutional characteristics (8 items), FSMP classification and labeling (4 items), enteral formula utilization practices (11 items), ONS utilization practices (1 item), and FSMP needs (6 items). The nurse questionnaire consisted of 23 items covering institutional characteristics (6 items), FSMP classification and labeling (7 items), and enteral formula utilization practices (10 items).

Survey items were constructed using multiple-choice, 5-point Likert scale, and open-ended questions. Content validity was verified through consultation meetings with clinical nutrition experts and literature analysis. The final survey showed <5% nonresponse and inappropriate responses, indicating sufficient reliability of the survey responses. The FGI interview guide was designed

with reference to the Consolidated Criteria for Reporting Qualitative Research checklist [10]. The final FGI questionnaire was developed through three internal research team meetings, three review meetings, and expert consultation. Interview items were structured to include FSMP prescription, utilization practices, problems, and development needs.

Data collection

Survey data were collected in May–September 2025 using both online and offline methods. Information letters and questionnaires were sent to each healthcare institution by mail, and respondents could choose to submit surveys either online or offline. For offline submissions, completed questionnaires and consent forms were photographed and submitted. For online submissions, respondents completed a Google forms questionnaire and consent form using QR code. Questionnaires were requested to be submitted within 2 weeks of receipt when possible.

FGI sessions covered roles and experiences in NST, current status of FSMP prescription and utilization, FSMP needs, and utilization and management practices. Interviews were conducted for 60 to 90 minutes per institution with NST healthcare professionals. All interviews were audio-recorded with participant consent. The recordings were transcribed verbatim without omissions. Meaningful statements that aligned with the research objectives were extracted from the transcripts and categorized based on similar or common content.

Statistical analysis

Survey data were analyzed using IBM SPSS ver. 29.0 (IBM Corp.). Descriptive statistics were used to summarize participant characteristics, perception levels, utilization practices, and needs. Categorical variables were presented as frequencies and percentages.

RESULTS

Participant characteristics

A total of 417 questionnaires were collected from 210 healthcare institutions nationwide, including 26 tertiary hospitals, 56 general hospitals, 85 long-term care hospitals, and 43 long-term care facilities. The institutional response rate was 161.5% of the target 130 institutions (210 institutions), and the questionnaire response rate was 80.2% of the target 520 questionnaires (417 questionnaires).

Characteristics of study participants are presented in Table 1. A total of 417 healthcare professionals participated in the survey, comprising 47 physicians (11.3%), 219 nurses (52.5%), and 151 dietitians (36.2%). The most common age group was 40–49 years (35.2%), followed by 30–39 years (32.6%). The majority had 10–20 years of clinical experience (36.7%), with 18.9% having ≥20 years of experience. Notably, physicians had a higher proportion of those with ≥20 years of experience (27.7%) than nurses (21.0%) and dietitians (13.2%).

By hospital type, respondents were distributed as follows: general hospitals (37.6%), long-term care hospitals (30.7%), tertiary hospitals (21.6%), and long-term care facilities (10.1%). Distribution patterns varied by professional group. In tertiary hospitals, 36.2% physicians, 18.3% nurses, and 21.8% dietitians responded. In general hospitals, 51.1% physicians, 33.8% nurses, and 39.1% dietitians responded. In long-term care hospitals, 12.7% physicians, 39.7% nurses, and 23.2% dietitians responded. In long-term care facilities, 8.2% nurses and 15.9% dietitians responded. No physician responded from long-term care facilities.

To ensure nationwide representativeness, respondents were recruited from healthcare institutions located across all administrative regions. Seoul (28.3%) and Gyeonggi-do (25.2%) had the highest participation rates, followed by Gyeongsang-do (20.1%).

Perception of FSMP classification and labeling

Perceptions of FSMP classification and labeling requirements are presented in Table 2. Overall, 93.5% of the respondents were aware that EN products are classified separately as FSMP and pharmaceuticals, with similar awareness across all professional groups (physicians 93.6%, nurses 93.2%, and dietitians 94.0%). However, awareness levels of the FSMP classification system under the Korea Food Code varied by profession. Dietitians showed the highest awareness, with 64.9% responding "aware," whereas the highest proportions of physicians (63.8%) and nurses (52.1%) responded "somewhat aware."

Understanding basic labeling information varied by professional group. When combining "fully understand" and "understand" responses, dietitians showed the highest comprehension at 98.7%, followed by nurses (86.3%) and physicians (85.1%). Overall satisfaction with current FSMP labeling was 66.2%. By professional group, dietitians (68.2%) and nurses (67.6%) showed similar satisfaction levels, whereas physicians showed lowest satisfaction level (53.2%).

Regarding areas needing improvement, "too much information, complex" (37.2%) and "font size too small to read" (34.1%) were the most frequently cited concerns. Nurses most frequently cited complexity (41.1%), whereas dietitians most frequently cited small font size (35.8%). Physicians uniquely reported higher rates

Table 1. Characteristics of study participants

Characteristic	Total (n=417)	Physician (n=47)	Nurse (n=219)	Dietitian (n=151)	P-value[a]
Age (yr)					0.417
20–29	37 (8.9)	2 (4.2)	18 (8.2)	17 (11.3)	
30–39	136 (32.6)	6 (12.8)	72 (32.9)	58 (38.4)	
40–49	147 (35.2)	24 (51.1)	73 (33.3)	50 (33.1)	
≥50	97 (23.3)	15 (31.9)	56 (25.6)	26 (17.2)	
Clinical experience (yr)					0.001*
<3	57 (13.7)	4 (8.5)	29 (13.2)	24 (15.9)	
≥3 and <5	47 (11.3)	4 (8.5)	25 (11.4)	18 (11.9)	
≥5 and <10	81 (19.4)	5 (10.6)	44 (20.1)	32 (21.2)	
≥10 and <20	153 (36.7)	21 (44.7)	75 (34.3)	57 (37.8)	
≥20	79 (18.9)	13 (27.7)	46 (21.0)	20 (13.2)	
Hospital type					<0.001*
Tertiary hospital	90 (21.6)	17 (36.2)	40 (18.3)	33 (21.8)	
General hospital	157 (37.6)	24 (51.1)	74 (33.8)	59 (39.1)	
Long-term care hospital	128 (30.7)	6 (12.7)	87 (39.7)	35 (23.2)	
Long-term care facility	42 (10.1)	0	18 (8.2)	24 (15.9)	
Region					0.016*
Seoul	118 (28.3)	19 (40.4)	65 (29.7)	34 (22.5)	
Gyeonggi-do	105 (25.2)	14 (29.8)	45 (20.5)	46 (30.5)	
Incheon	38 (9.1)	4 (8.5)	26 (11.9)	8 (5.3)	
Gangwon-do	4 (1.0)	0	2 (0.9)	2 (1.3)	
Chungcheong-do	18 (4.3)	1 (2.1)	10 (4.6)	7 (4.7)	
Gyeongsang-do	84 (20.1)	7 (15.0)	43 (19.6)	34 (22.4)	
Jeolla-do	38 (9.1)	1 (2.1)	26 (11.9)	11 (7.3)	
Jeju-do	12 (2.9)	1 (2.1)	2 (0.9)	9 (6.0)	

Values are presented as number (%).
[a]The P-values were derived from chi-square tests in each professional group.
*P<0.05 was considered statistically significant.

of "cannot easily find needed information" (19.1%) and "insufficient information provided" (8.5%). Regarding the usefulness of nutritional composition information for FSMP product selection, 77.9% of the respondents found it helpful. Nurses showed the highest positive response rate (81.3%), followed by dietitians (74.8%) and physicians (72.3%).

Current practices in enteral formula and ONS

Current practices in enteral formula prescription, administration, and patient education are presented in Table 3. Regarding prescription documentation, the most frequently recorded information across all professional groups was calories/volume (physicians 21.2%, nurses 24.7%, and dietitians 30.4%), followed by volume per feeding or daily volume (physicians 20.1%, nurses 22.2%, and dietitians 23.7%) and formula name (physicians 18.5%, nurses 19.4%, and dietitians 27.0%). Infusion rate was the least frequently documented item (physicians 9.2%, nurses 7.2%, and dietitians 3.9%).

Nurses were identified as the primary administrators of enteral formula across all groups by 59.2% physicians, 46.4% nurses, and 38.9% dietitians. Notably, dietitians reported family members or caregivers as primary administrators at a higher rate (47.1%) than physicians (29.6%) and nurses (30.8%).

Regarding responsibility for patient education, 59.8% of the nurses and 62.3% of the dietitians identified nurses as the primary educators; however, 59.6% of the physicians identified dietitians as the primary educators.

Physicians' criteria for enteral formula selection at admission and discharge are presented in Table 4. At admission, the most common selection criterion was NST consultation recommendations (50.8%), followed by products available through meal prescription (38.1%) and products available through medication prescription (11.1%). At discharge, NST consultation recommendations were the most common criterion (38.5%), followed by medication prescription products (32.7%) and meal prescription products (28.8%). Notably, the proportion prioritizing medication prescription products increased from 11.1% at admission to 32.7% at discharge.

Table 2. Healthcare professionals' perception of the classification and labeling requirements of FSMP

Variable	Category	Total (n=417)	Physician (n=47)	Nurse (n=219)	Dietitian (n=151)
FSMP classification					
EN products are classified separately as FSMP and pharmaceuticals	Yes	390 (93.5)	44 (93.6)	204 (93.2)	142 (94.0)
	No	27 (6.5)	3 (6.4)	15 (6.8)	9 (6.0)
FSMP classification system according to the Korea Food Code[a)]	Aware	207 (49.6)	13 (27.6)	96 (43.8)	98 (64.9)
	Somewhat aware	190 (45.6)	30 (63.8)	114 (52.1)	46 (30.5)
	Not aware	20 (4.8)	4 (8.5)	9 (4.1)	7 (4.6)
Labeling requirements					
Understanding of basic labeling information (e.g., product name, type, volume, and nutritional content)	Fully understand	80 (19.2)	4 (8.5)	30 (13.7)	46 (30.5)
	Understand	298 (71.5)	36 (76.6)	159 (72.6)	103 (68.2)
	Do not understand well	31 (7.4)	7 (14.9)	22 (10.0)	2 (1.3)
	Do not understand at all	8 (1.9)	0	8 (3.7)	0
Satisfaction with current FSMP labeling	Satisfied	276 (66.2)	25 (53.2)	148 (67.6)	103 (68.2)
	Not satisfied	93 (22.3)	14 (29.8)	44 (20.1)	35 (23.2)
	Do not know	48 (11.5)	8 (17.0)	27 (12.3)	13 (8.6)
Areas needing improvement in labeling	Font size too small to read	142 (34.1)	14 (29.8)	74 (33.8)	54 (35.8)
	Too much information, complex	155 (37.2)	15 (31.9)	90 (41.1)	50 (33.1)
	Difficult to understand terminology	38 (9.1)	4 (8.5)	22 (10.0)	12 (7.9)
	Cannot easily find needed information	51 (12.2)	9 (19.1)	23 (10.5)	19 (12.6)
	Insufficient information provided	8 (1.9)	4 (8.5)	0	4 (2.6)
	Others	5 (1.2)	-	1 (0.5)	4 (2.6)
	Not applicable	18 (4.3)	1 (2.1)	9 (4.1)	8 (5.3)
Usefulness of nutritional composition information for FSMP product selection	Helpful	325 (77.9)	34 (72.3)	178 (81.3)	113 (74.8)
	Not helpful	45 (10.8)	6 (12.8)	18 (8.2)	21 (13.9)
	Do not know	47 (11.3)	7 (14.9)	23 (10.5)	17 (11.3)

Values are presented as number (%)

FSMP, food for special medical purpose; EN, enteral nutrition.

[a)]Korea Food Code: food standards and specifications established by the Ministry of Food and Drug Safety, Korea.

Table 3. Current practices in enteral formula prescription, administration, and patient education by professional group

Category	Physician (n=47)	Nurse (n=219)	Dietitian (n=151)
What are the required documentation items when physicians prescribe enteral formula, excluding information on patient identification?[a)]			
Name of enteral formula	34 (18.5)	150 (19.4)	117 (27.0)
Calories (kcal)/volume (mL)	39 (21.2)	191 (24.7)	132 (30.4)
Route of administration	31 (16.8)	116 (15.0)	34 (7.8)
Volume per feeding (mL) or daily volume (mL)	37 (20.1)	172 (22.2)	103 (23.7)
Feeding method (e.g., continuous, intermittent, and bolus)	26 (14.1)	89 (11.5)	31 (7.1)
Infusion rate (e.g., initial rate or target rate)	17 (9.2)	56 (7.2)	17 (3.9)
Who is responsible for administering enteral formula to patients?[a)]			
Nurse	42 (59.2)	173 (46.4)	95 (38.9)
Nursing assistant	8 (11.3)	85 (22.8)	34 (13.9)
Family member or caregiver	21 (29.6)	115 (30.8)	115 (47.1)
Who is primarily responsible for educating patients on the use and consumption of enteral formula?			
Physician	2 (4.3)	22 (10.0)	7 (4.6)
Nurse	16 (34.0)	131 (59.8)	94 (62.3)
Dietitian	28 (59.6)	60 (27.4)	48 (31.8)
No response	1 (2.1)	6 (2.7)	2 (1.3)

Values are presented as number (%).

[a)]Multiple responses were allowed for each question.

Table 4. Criteria used for enteral formula selection by physicians at admission and discharge

Category	Physician (n=47)
What criteria do you use when selecting enteral formula prescriptions at admission?	
Prioritize products available through meal prescription	24 (38.1)
Determine based on NST consultation recommendations	32 (50.8)
Prioritize products available through medication prescription (e.g., Encover solution and Harmonilan solution[a])	7 (11.1)
What criteria do you use when selecting enteral formula prescriptions at discharge?	
Prioritize products available through meal prescription	15 (28.8)
Determine based on NST consultation recommendations	20 (38.5)
Prioritize products available through medication prescription (e.g., Encover solution and Harmonilan solution)	17 (32.7)

Values are presented as number (%). Multiple responses were allowed for each question.
NST, Nutrition Support Team.
[a]Encover solution and Harmonilan solution are commercially available enteral formulas prescribed as medications in South Korea.

Institutional characteristics and meal service by hospital type are presented in Table 5. The number of beds was highest in tertiary hospitals (1,111 ± 393 beds), followed by general hospitals (540 ± 214 beds); long-term care hospitals (255 ± 130 beds); and long-term care facilities (98 ± 35 beds). Length of stay was longest in long-term care hospitals (362 ± 362 days) and shortest in tertiary hospitals (7 ± 3 days).

Monthly meal service volume was highest in tertiary hospitals, with 28,029 ± 2,144 meals/month for regular diet meals; 16,355 ± 1,101 meals/month for therapeutic diet meals; and 4,408 ± 459 meals/month for enteral formula meals. Sterile diets were provided only in tertiary and general hospitals.

Daily enteral formula prescription volume ranged from 290 ± 177 to 1,985 ± 635 kcal/day in tertiary hospitals; 363 ± 218 to 1,905 ± 593 kcal/day in general hospitals; 794 ± 443 to 1,706 ± 340 kcal/day in long-term care hospitals; and 1,042 ± 306 to 1,308 ± 320 kcal/day in long-term care facilities.

Dietitians' considerations for enteral formula product selection for inventory are presented in Table S1. This item was administered to dietitians only. When selecting enteral formula products for the hospital inventory, dietitians rated hygiene as the most important factor (66.9% responded with "very important"), followed by safety (64.2%), patient compliance (62.3%), and nutrient composition (61.6%). More than one-half of the dietitians considered clinical efficacy (55.0%), convenience of delivery (52.3%), and cost (50.3%) as very important. By contrast, sensory evaluation received the lowest importance rating by dietitians. Sensory evaluation was considered very important by only 31.8%; 24.5% were "neutral," and 4.0% considered it "not important."

The provision of ONS in healthcare institutions is presented in Table S2. This item was administered to dietitians only. Among dietitian respondents, 84.1% reported that their hospitals provide ONS to patients, whereas 15.9% reported that their hospitals do not provide ONS. Regarding the provision form, the most common method was "included in the meal plan and provided in original packaging" (44.5%), followed by "provided separately from meals at the discretion of physicians or dietitians" (25.7%); "provided as a one-time sample during nutrition education" (12.6%); and "included in the meal plan and served in separate dishes" (11.0%).

Barriers and challenges in FSMP utilization

Reasons for enteral formula modification and barriers to product procurement are presented in Table 6. Diarrhea was the most common reason for enteral formula modification across all professional groups (physicians 39.3%, nurses 36.6%, and dietitians 36.9%). Aspiration risk was the second most reported reason among physicians (17.0%), nurses (13.0%) and dietitians (15.9%). Other reported reasons included total caloric requirements; malnourished patients; underlying diseases (e.g., diabetes, hemodialysis); vomiting; changes in disease status (e.g., hypoalbuminemia, renal function deterioration); change in treatment modality; and nutrient composition.

Reasons for delays in procuring enteral formula products varied by professional groups. Nurses most frequently reported "exceeds the reimbursement limit for enteral formula meal costs, making it difficult to use due to hospital budget constraints" (31.4%), whereas dietitians most frequently reported "difficulty in inventory management for products with low usage frequency" (40.1%). Physicians reported similar rates for budget constraints (23.0%), limited storage space (23.0%), and difficulties in inventory management (27.0%). Notably, dietitians reported higher rates of difficulties in inventory management for low-frequency products (40.1%) than physicians (27.0%) and nurses (27.0%). Conversely, nurses reported higher rates of budget constraints related to reimbursement limits (31.4%) than physicians (23.0%) and di-

Table 5. Institutional characteristics and meal service, including enteral formula, by hospital type

Category	Tertiary hospital (n=21)[a]	General hospital (n=39)	Long-term care hospital (n=18)	Long-term facility (n=12)
No. of beds[b]	1,111±393	540±214	255±130	98±35
Length of stay (day)	7±3	70±167	362±362	198±239
Monthly meal service (meals/mo)[c]				
Regular diet	28,029±2,144	14,379±1,285	7,083±830	3,374±481
Therapeutic diet	16,355±1,101	7,904±833	4,286±735	547±89
Enteral formula	4,408±459	2,250±313	3,131±602	456±62
Sterile diet	395±116	91±33	0	0
Daily enteral formula prescription volume over the past month (kcal/day)[d]				
Minimum	290±177	363±218	794±443	1,042±306
Maximum	1,985±635	1,905±593	1,706±340	1,308±320

Values are presented as mean±standard deviation.
[a]'n' indicates the number of dietitians who responded from each hospital type. Values differ from other tables due to exclusion of outliers. [b]Number of beds and length of stay are based on institutional data from April 2025. [c]Monthly meal service was calculated by multiplying daily average meal service (April 2025) by 30.4 days. [d]Mean of reported minimum and maximum daily prescription volumes for patients receiving enteral formula over the past month.

Table 6. Reasons for enteral formula modification and barriers to product procurement by professional groups

Category	Physician (n=47)	Nurse (n=219)	Dietitian (n=151)
What are the main reasons for changing the type of enteral formula after initiating enteral feeding?			
Diarrhea	44 (39.3)	191 (36.6)	109 (36.9)
Constipation	16 (14.3)	56 (10.7)	47 (15.9)
Abdominal distension	8 (7.1)	56 (10.7)	17 (5.8)
Abdominal pain	8 (7.1)	46 (8.8)	12 (4.1)
Aspiration risk	19 (17.0)	68 (13.0)	47 (15.9)
Infection	0	8 (1.5)	2 (0.7)
Fluid imbalance	5 (4.5)	41 (7.9)	20 (6.8)
Electrolyte imbalance	9 (8.0)	40 (7.7)	31 (10.5)
Others[a]	3 (2.7)	16 (3.1)	10 (3.4)
What are the reasons for delays in procuring enteral formula products at your hospital?			
Complex procurement process and procedures	19 (19.0)	60 (17.6)	51 (17.3)
Exceeds the reimbursement limit for enteral formula meal costs, making it difficult to use due to hospital budget constraints	23 (23.0)	107 (31.4)	64 (21.8)
Difficulty in obtaining information on enteral formula products not currently in stock	8 (8.0)	46 (13.5)	7 (2.4)
Limited storage space makes it difficult to store a variety of products	23 (23.0)	36 (10.6)	54 (18.4)
Difficulty in inventory management for products with low usage frequency	27 (27.0)	92 (27.0)	118 (40.1)

Values are presented as number (%). Multiple responses were allowed for each question.
[a]Others: total caloric requirements, malnourished patients, underlying diseases (e.g., diabetes and hemodialysis), vomiting, changes in disease status (e.g., hypoalbuminemia and renal function deterioration), change in treatment modality, and nutrient composition.

etitians (21.8%).

Needs and requirements for FSMP products

To assess healthcare professionals' needs for FSMP, surveys were conducted with 47 physicians and 151 dietitians. Regarding the need for enteral products in addition to those listed in the Korea Food Code, physicians rated high-calorie, high-protein products as the most needed, with 42/45 (93.3%) valid respondents indicating the product was "very needed" or "needed." High-calorie products and products for patients who were critically ill or had metabolic stress rated second, with 40/46 (87.0%) valid respondents each. Products for patients with inflammatory bowel disease (IBD) ranked fourth, with 39/47 (83.0%) valid respondents. High-protein products for pediatric patients ranking fifth, with 36/45 (80.0%) valid respondents.

Among dietitians, products for patients with IBD showed the highest demand, with 133/151 (88.1%) valid respondents indicating very needed or needed. High-calorie, high-protein products

ranked second, with 131/151 (86.8%) valid respondents. Products for wound healing ranked third, with 120/151 (79.5%) valid respondents. Products for pediatric patients who were critically ill or patients with metabolic stress ranked fourth, with 118/150 (78.7%) valid respondents. High-calorie products ranked fifth, with 118/151 (78.1%) valid respondents.

Both professional groups showed high demand for high-calorie, high-protein products and products for patients with IBD. Additionally, physicians showed high demand for products for patients who were critically ill or patients with metabolic stress, whereas dietitians showed additional high demand for products for wound healing.

Qualitative findings from FGI

FGI was conducted for the detailed analysis of FSMP utilization in clinical settings. A total of 24 participants from six healthcare institutions (three each in the capital region and noncapital regions) participated, including six physicians, six nurses, six pharmacists, and six dietitians. By hospital type, two tertiary hospitals (2,809 and 1,004 beds), two general hospitals (777 and 600 beds), and two long-term care hospitals (555 and 413 beds) participated. Four of the participating institutions operated NST. One of the tertiary hospitals operated a 30-member NST, divided into adult and pediatric teams due to a high proportion of pediatric patients, that performed approximately 500 consultations per month. The other tertiary hospital had a single 22-member team handling 500 consultations per month. The two general hospitals operated smaller NST teams of 4 and 18 members, performing 120 and 170 consultations per month, respectively. Monthly NST consultation numbers were based on May-July 2025 data.

The mean NST activity experience of participants was 9.9 years, with nurses having the longest experience (12.5 years), followed by physicians (11.2 years), dietitians (11.0 years), and pharmacists (4.8 years). Nurses showed the widest range of experience (5–25 years), followed by physicians (8–20 years), dietitians (3–23 years), and pharmacists (2–7 years). The two long-term care hospitals did not have formal NST structures; therefore, years of work experience were recorded instead of NST activity years.

NST operations in tertiary and general hospitals are governed by healthcare accreditation standards and the Ministry of Health and Welfare's "Intensive Nutrition Therapy Fee" reimbursement criteria, with team composition and professional roles institutionally defined. A multidisciplinary team comprising physicians, clinical dietitians, nurses, and pharmacists provides comprehensive nutrition management for hospitalized patients at risk of malnutrition, patients requiring EN, or patients requiring parenteral nutrition (PN). Professional roles are institutionally defined as follows: physicians determine diagnosis and treatment direction and bear final prescription responsibility; pharmacists manage the composition, stability, and interactions of medications and PN formulations; nurses monitor EN/PN administration and patient status; and dietitians develop intervention plans based on nutritional assessment and provide nutrition education to patients and caregivers.

Among the four institutions with formal NST structures, the frequency of rounds and conferences varied according to the circumstances of institutional operations. Generally, patient status was reviewed and adjusted through weekly team rounds and monthly conferences, and FSMP prescription and modification decisions were made comprehensively through multidisciplinary consultation. By contrast, long-term care hospitals are not required to establish NST under healthcare accreditation standards and are not eligible for the Ministry of Health and Welfare's "Intensive Nutrition Therapy Fee" reimbursement. Consequently, there are no institutionally mandated formal NST structure and defined professional roles. However, FGI results revealed that nutrition management is conducted individually according to hospital staffing and operational circumstances. Informal collaborative systems among attending physicians, nurses, dietitians, and pharmacists existed in practice. FSMP prescription, modification, and monitoring for patients receiving EN or PN were conducted through *ad hoc* consultations rather than regular rounds.

According to the literature review conducted as part of this study (as of August 2025), seven companies manufacture and sell FSMP in South Korea, with approximately 162 products available in the market. However, FGI results revealed that only a portion of these products is used in hospitals. The number of supplying companies ranged from 2 to 5 per participating institution, and the number of FSMP products in use ranged from 7 to 37. Tertiary hospitals used the most diverse range of products (14 and 37 products), followed by long-term care hospitals (12 and 15 products) and general hospitals (7 and 14 products). Products classified as pharmaceuticals, such as Encover (JW Pharmaceutical Co.) and Harmonilan (Yungjin Pharmaceutical Co.), which are separately procured and managed, were excluded from this analysis.

Thematic analysis of FGI data identified two major categories related to FSMP prescription criteria as follows: product selection and initial prescription and product modification (secondary prescription). Regarding product selection and initial prescription,

each institution primarily prescribed enteral feeding based on a patient's disease according to institutional dietary prescription guidelines. Dietary prescription guidelines presented criteria by disease name rather than product name. NST consultations reviewed formula appropriateness, prescription volume, and delivery rate, with adjustments made as needed according to treatment direction and clinical symptoms (e.g., diarrhea, vomiting, and reflux).

Regarding product modification (secondary adjustment), prescriptions were based on disease criteria but modified according to treatment direction and clinical symptoms (e.g., glycemic control issues, digestive intolerance, and difficulty reaching target volume), with changes made to formulation type, concentration, and fiber content. In long-term care hospitals, there were many cases of switching to high-calorie, high-protein formulations based on clinical indicators such as pressure ulcer and weight loss.

Although various FSMP formulations are utilized according to disease, treatment direction, and clinical symptoms, FGI participants noted that product utilization flexibility is not fully ensured due to limitations in formulation and volume options as well as economic and regulatory constraints. Semantic unit analysis identified commonly reported limitations.

The first limitation was product volume constraint. Participants reported that available volumes do not meet the diverse needs of patients. Ready-to-hang products are primarily limited to 400 mL, making stepwise volume increase during initial adaptation difficult and causing high wastage. For canned enteral products, which are generally fixed at 200 mL, some long-term care hospitals reported practices of prescribing and providing based on product volume.

The second limitation was insufficient diversity in available oral products. Participants reported that the monotonous taste and texture of the products led to decreased compliance with long-term consumption in patients with cancer, older patients, and patients with malnourishment. They indicated a need for new formulations, such as clear beverage types, rather than cloudy, viscous soy milk forms, warm porridge types, and stick-type jellies.

The third limitation was economic burden and regulatory constraint. High patient costs and lack of insurance coverage were identified as major barriers. Regulatory restrictions on product availability and procurement procedures were reported to further limit access to products.

The fourth limitation was restricted access to post-discharge care and follow-up management. Participants expressed concerns about patients' ability to continue FSMP consumption after discharge, citing difficulties in product procurement and absence of follow-up support systems.

The final limitation was limited patient and caregiver awareness. Lack of understanding about the importance and use of FSMP in patients and caregivers was identified as a barrier to optimal utilization and compliance. According to the participants, educational campaigns should raise awareness about FSMP consumption being a part of the treatment and an official platform must be established to compare and provide information on disease-specific formulations, ingredients, and costs.

According to FGI results, healthcare professionals perceived that the disease-centered product system alone cannot meet the demands of the patients' diverse clinical conditions and symptoms. Common suggestions for product development included development of symptom-specific refined products, diversification of product volumes and package sizes, and expansion of ONS varieties that better accommodate patient preferences and clinical needs.

DISCUSSION

This study highlights that despite the rapid growth of the FSMP market in South Korea, a significant gap exists between clinical needs and actual practice concerning healthcare professionals' perceptions and utilization patterns. The findings from the survey and FGI suggest the need for enhanced safety in prescription practices, standardization of nutrition delivery processes, and development of patient-centered products.

Incomplete documentation in EN prescription

Standardization and specificity in the prescription process of EN are needed, particularly regarding administration rate and method. Our results showed that although product names and volumes were well-documented, "infusion rate" was recorded in only 9.2% of the physicians' prescriptions. This low documentation rate was echoed by nurses (7.2%) and dietitians (3.9%), indicating that infusion rate decisions are rarely specified at the prescription stage. According to the ASPEN Safe Practices for EN Therapy by Boullata et al. [11], the administration method and rate are "critical elements" of an EN order to ensure patient tolerance and prevent complications such as aspiration. The absence of specific instructions forces nursing staff to rely on discretionary judgment, which may compromise safety. Therefore, institutional improvements, such as mandating infusion rate fields in computerized provider order entry systems, are necessary to prevent incomplete

orders [11].

Barriers to achieving adequate EN delivery

Systematic management of EN interruptions is required to address "underfeeding," where the prescribed nutrition is not fully delivered to the patient. In this study, diarrhea (36%–39%) was cited as the most frequent reason for modifying or discontinuing enteral formulas across all professional groups. Consistently, gastrointestinal intolerance was identified as a major barrier to adequate enteral intake in critical care settings [12].

However, in clinical practice, interruptions often occur due to "avoidable" factors in addition to gastrointestinal symptoms, such as fasting for diagnostic tests or procedures. Peev et al. [13] conducted a prospective observational study in surgical patients in the ICU and reported that approximately 26% of EN interruptions were avoidable, with the most common reasons being imaging studies where fasting was not required by radiologists. Patients who experienced at least one interruption in their EN infusions were approximately 3-fold more likely to be underfed (< 66% of the total prescribed calories) and accumulated significantly higher cumulative caloric deficits (5,834 ± 4,641 kcal vs. 3,066 ± 3,223 kcal; P = 0.001) compared with those without interruptions [13].

Kozeniecki et al. [14] identified the initiation and advancement of EN as the most common reason for suboptimal volume delivery in their tertiary medical ICU study, where patients achieved adequate intake (≥ 90% of the prescribed volume) on only 20% of the feeding days, with an overall mean intake of only 51% of the prescribed volume. EN was held on average 4.8 hr/day on days 2 to 6, with the top five reasons or interruption being anticipated extubation, fasting for bedside procedures, loss of enteral access, gastric residual volume concerns, and radiology suite procedures [14].

Therefore, rather than immediately stopping feeding upon onset of diarrhea or elevated gastric residual volume, standardized protocols should be implemented, such as adjusting infusion rate, utilizing prokinetic agents, or employing volume-based feeding strategies, that allow for increased rates to compensate for interruption time [11,14].

Discrepancy in professional roles for patient education

A notable discrepancy in professional roles regarding patient education and management was identified. Although 59.6% of the physicians believed that clinical dietitians should be responsible for patient education, in practice, nurses (59.8%) were the ones predominantly conducting it. This gap between perception and practice may contribute to suboptimal nutrition delivery.

Studies have emphasized that inadequate nutrition often stems from underprescription or delivery process errors, highlighting the need for standardized protocols and clear role delineation to mitigate these issues [12]. Notably, Peev et al. [13] reported that even among patients without EN interruptions, a significant caloric deficit accumulated, likely due to delayed initiation (33% of the patients started EN > 48 hours after ICU admission) and conservative "ramp-up" feeding protocols. This "purposeful" underprescription was often at the explicit request of surgical teams, underscoring the importance of multidisciplinary consensus and protocol adherence [13].

Given that proactive nutritional intervention improves clinical outcomes, policy support is essential to enable dietitians to lead nutrition assessment, education, and monitoring within a defined multidisciplinary framework.

Need for evidence-based feeding protocols

The implementation of evidence-based feeding protocols could address many barriers identified in this study. Our FGI results revealed that although tertiary and general hospitals operate NST governed by healthcare accreditation standards, long-term care hospitals lack institutionally mandated formal NST structures. This absence of standardized nutrition care protocols may contribute to practice variations observed across hospital types.

Studies have demonstrated that protocol implementation has a positive impact on the proportion of patients receiving adequate nutrition therapy, optimization of volume intake, and time to initiation of nutrition therapy [14,15]. Specifically, volume-based feeding protocols, which prescribe EN in mL/day and allow for increased infusion rates after interruption to make up for lost time, significantly increased EN delivery without increasing complications such as elevated gastric residual volume, emesis, aspiration, or pneumonia [14].

Product diversification for an aging society

Product diversification tailored to an aging society and the increasing demand for home care is imperative. The FGI results revealed that the limited variety in product volumes (primarily 400 mL for ready-to-hang products and 200 mL for canned products) and monotonous flavors significantly reduce patient compliance. Healthcare professionals expressed high demand for products not currently available, including high-calorie, high-protein formulations (93.3% of the physicians and 86.8% of the dietitians), products for IBD (83.0% of the physicians and 88.1% of the dietitians),

and products for wound healing (79.5% of the dietitians).

This suggests that developing products considering not only the disease state but also patient preferences, clinical symptoms, and convenience is essential for enhancing the therapeutic efficacy of FSMP.

Limitations

This study has several limitations. First, the cross-sectional survey design limits causal inferences about the correlations between identified barriers and nutritional outcomes. Second, we did not directly measure patient outcomes, such as caloric deficit, length of stay, or clinical complications, limiting our ability to quantify the clinical impact of identified barriers. Prospective studies must examine the correlation between FSMP utilization practices and patient outcomes to provide evidence for protocol development and policy interventions.

Conclusion

For FSMP to be recognized not merely as nutritional support but as an integral part of therapeutic treatment, we must establish a precise prescription system with mandatory documentation of infusion rates and feeding methods, introduce evidence-based protocols to prevent unnecessary feeding interruptions and optimize nutrition delivery, and define professional roles within a multidisciplinary framework.

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Conflicts of interest

None.

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Data availability

Data of this research are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary materials are available from https://doi.org/10.7762/cnr.2026.0002.

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CLINICAL NUTRITION RESEARCH

Effects of oral supplementation with whey protein concentrate and its hydrolysates on blood cholesterol levels and oxidative DNA damage in South Korean male smokers

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Objective: Cigarette smoking leads to oxidative stress and high cholesterolemia, which are key drivers of cardiovascular disease (CVD). Whey is known for its antioxidant and hypolipidemic properties. This study investigated whether whey protein concentrate (WPC) and hydrolysate of WPC (HWPC) can alleviate CVD risk in South Korean smokers by lowering oxidative stress and blood lipids.
Methods: A total of 25 male smokers were screened, of which 18 eligible participants (72.0%), randomly assigned to either the WPC (n=9) or the HWPC (n=9) group, completed the 8-week intervention. Before (week 0, baseline) and after the intervention, participants visited the laboratory for blood collection and anthropometric measurements (body weight, height, waist circumference, body fat mass, nutritional intake). Blood samples were analyzed for plasma lipid profiles, plasma fat-soluble antioxidants, and leukocyte oxidative DNA damage using the comet assay.
Results: There were no significant differences in anthropometric measurements, dietary food intake, plasma conjugated dienes, total radical-trapping antioxidant potential, and erythrocytes' glutathione peroxidase and catalase activities in both WPC and HWPC groups. However, we observed a significant decrease in the tail moments of leukocytes, low-density lipoprotein cholesterol, atherogenic index, and high coenzyme Q10 levels in both groups. In the WPC group, total cholesterol decreased, while plasma retinol, α-tocopherol, lycopene, α-carotene, and β-carotene increased.
Conclusion: WPC or HWPC significantly decreases blood cholesterol levels and oxidative DNA damage and increases plasma fat-soluble antioxidant levels. Thus, WPC or HWPC might be used as oral supplementation to lower the risk for CVD in South Korean male smokers.

Keywords: Whey protein concentrate; Whey protein hydrolysate; Smokers; Antioxidants; Hypocholesterolemic effect

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INTRODUCTION

Cigarette smoking is a risk factor for cardiovascular disease (CVD) [1,2]. Studies have reported an increase in serum total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) and a decrease in high-density lipoprotein cholesterol (HDL-C) in smokers [3,4], which are key drivers of CVD. Elevated LDL-C is the main contributor to the development of CVD [5]. Oxidative stress is also a significant CVD risk factor [6]. Smoking causes vascular injury and endothelial dysfunction by producing various oxidants [7,8]. Specifically, polycyclic aromatic hydrocarbons present in tobacco get metabolized in the body, producing reactive intermediates, which, in turn, form free-radical species and induce oxidative DNA damage. This oxidative stress results in cellular damage, such as double-strand DNA breaks [8,9], and increases the DNA damage response within atherosclerotic plaques [10,11]. Furthermore, previous studies have reported increased senescence in the leukocytes of smokers [12].

Smokers generally show decreased serum retinol, vitamin C, carotenes, and tocopherols compared to nonsmokers [7,13]. Although numerous *in vitro* studies have suggested that antioxidants lower oxidative DNA damage, the clinical effects of antioxidant supplementation in smokers remain inconclusive [14]. Some studies have indicated that dietary intake of antioxidants extracted from fruits and vegetables decreases oxidative stress markers in smokers [15,16]. However, other studies have shown that supplementation with specific antioxidants, such as vitamin C, vitamin E, and β-carotene, has varying results, ranging from the amelioration of oxidative DNA damage in lymphocytes [17] to partial or no significant effects [14,17-20]. Furthermore, although oral supplementation with antioxidants (vitamins C and E) was effective in decreasing endothelial dysfunction, the overall response was notably limited [18,19]. For instance, vitamin C supplementation effectively lowered plasma lipid peroxidation, as indicated by F2-isoprostanes levels, only among individuals with a high body mass index (BMI) [20].

Whey is a by-product of cheese manufacturing and contains proteins, lipids, vitamins, and minerals [21]. Milk lipids include tocopherols, retinol, and carotenoids [22-24]. Whey protein concentrate (WPC) has a high nutrition value [25]. Whey proteins include β-lactoglobulin and α-lactalbumin, bovine serum albumin, lactoferrin, and immunoglobulins [21]. WPC has been shown to decrease serum cholesterol in animals [26,27] and increase HDL-C in healthy humans [28]. Whey protein isolates decrease total-C and LDL-C in people with overweight and obesity [29]. In addition, whey is known for its antioxidant capacity, especially in *in vitro* assays [30-32] and animals [30,33]. Whey hydrolysates generated from whey β-lactoglobulin show free-radical–scavenging activity [32]. Albumin is the main contributor to the antioxidant properties of whey [34], while antioxidative vitamins in whey provide additional antioxidant properties [35].

Although studies have reported the antioxidant and hypolipidemic effects of whey protein, clinical *in vivo* data supporting its ability to decrease oxidative DNA damage remain scarce. Furthermore, evidence regarding the hypocholesterolemic effects of whey in human intervention studies is still inconclusive, given the distinct cholesterol metabolism in humans compared to animal models. In addition, research has not yet investigated the effects of whey on the health of smokers who are constantly exposed to oxidative stress and may be at higher risk for CVD. In this study, we investigated whether WPC or hydrolysate of whey protein concentrate (HWPC) can improve the lipid profile, alleviate oxidative DNA damage in leukocytes, and increase the levels of fat-soluble antioxidants in smokers.

METHODS

Ethics statement

This study was approved by the Kyungnam University Ethics Committee (No. KUIRB2013-16) and conducted in accordance with the Declaration of Helsinki. The procedures were explained in detail to all participants before the study began, and signed informed consent was obtained from them.

Preparation of WPC and HWPC

WPC (18% protein) was extracted from fresh cheddar cheese using spiral wound membrane–type ultrafiltration using membrane filters with a 20 kDa molecular weight cutoff. The extracted WPC was subjected to enzymatic hydrolysis by adding Neutrase (pH 7.0, Novo Nordisk Biochem Inc.) for 3 hours at 40 °C. The filtered whey hydrolysate retentate was further condensed, spray-dried, and then blended with sugar, citric acid, and xanthan gum (Table 1) [36].

Participant recruitment

A total of 25 healthy adult male smokers were voluntarily recruited from the area of Changwon (Gyeongsangnam-do, South Korea) and screened for their eligibility to participate in this study. All volunteers were administered a questionnaire asking about

Table 1. Composition of whey protein extracts used in the study

Component	WPC (%)	HWPC (%)
WPC	20.8	0.0
HWPC	0.0	20.8
Sugar	77.5	77.5
Citric acid	1.15	1.15
Pigment	0.275	0.275
Flavor	0.275	0.275
Total	100	100

WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate.

their age, present status of diseases, body weight, height, smoking, drinking, physical exercise, and intake of vitamin supplements. Those who consumed vitamin supplements or provided incomplete answers were excluded. Therefore, 20 participants (80.0%) were enrolled in the study, and 10 (50.0%) each were randomly assigned to either the WPC or the HWPC group. Toward the end of the study, 1 participant (10.0%) from each group was excluded due to failure to adhere to dietary supplementation. Finally, 18 of the 20 participants (90.0%) completed the 8-week intervention.

Study procedure

The participants were instructed to consume 24 g of powdered WPC or HWPC (reconstituted in 200 mL of water) every day for 8 weeks and were monitored regularly throughout the study period. Before (baseline) and after (at the end of) the intervention, the participants visited the laboratory for blood collection and anthropometric measurements. For anthropometry, body weight and height were measured using a weighing machine, waist circumference using a ruler, and body fat mass using a body fat analyzer (HBF-302, Omron). In addition, the participants' nutritional intake was assessed using the 24-hours dietary recall method and analyzed using a Computer-Aided Nutritional Analysis Program (CAN-Pro 4.0, Korea Nutrition Society).

Next, the participants were instructed to fast overnight, and blood samples were withdrawn the next day. For the comet assay, a portion of the whole blood was separated, and the remaining was collected in lithium-heparinic polystyrene tubes and centrifuged at 1,000 rpm for 10 minutes to obtain platelet-rich plasma. After taking aliquots, another round of centrifugation was performed at 3,000 rpm for 15 minutes, and the supernatant was aliquoted and stored at −80 °C until further use for lipid, vitamin, and total radical-trapping antioxidant potential (TRAP) analysis. Next, erythrocytes were collected and buffered with isosmotic phosphate buffer saline. After adding liquid nitrogen, the buffered erythrocytes were stored at −80 °C until further use for antioxidant enzyme activity analysis.

Plasma concentrations of lipids and conjugated dienes in LDL-C and TRAP

Plasma concentrations of total-C, HDL-C, and TG were determined using a photometric autoanalyzer (BTR 815, Biotron Scientific Instruments) and reagents obtained from InHwa Pharm. The plasma LDL-C concentration was calculated using the Friedewald equation [37], and baseline LDL-C conjugated diene (CD) levels were determined using a slightly modified method developed by Athotupa et al. [38]. Briefly, 100 μL of plasma was mixed with 700 μL of heparin citrate buffer (0.064 M trisodium citrate, 50,000 IU/L of heparin, pH 5.05) and incubated for 10 minutes. Next, centrifugation was performed at 2,500 rpm for 10 minutes, and the pellet was suspended in 100 μL of 0.1 M Na–phosphate buffer containing 0.9% NaCl (pH 7.4). From 100 μL of the suspension, lipids were extracted using chloroform-methanol in a 2:1 ratio, dried under nitrogen, and dissolved in cyclohexane. Absorbance was measured spectrophotometrically at 234 nm. Plasma TRAP was measured using the photometric method developed by Rice-Evans and Miller [6]. Absorbance was measured spectrophotometrically at 734 nm. Values were expressed as trolox equivalent antioxidant capacity and defined as the millimolar concentration of the trolox antioxidant capacity of a calibration curve.

Glutathione peroxidase and catalase activities in erythrocytes

GPx was determined using the method developed by Beutler. Briefly, 10 μL of hemolyzed erythrocytes was incubated with 1 mL of 0.1 M Tris-HCl buffer (pH 8.0) containing 20 μL of 0.1 M glutathione, 100 μL of 10 U/mL of glutathione reductase, and 100 μL of 2 mM decreased nicotinamide adenine dinucleotide phosphate (NADPH). After 10-minute incubation at 37 °C, 10 μL of tert-butyl hydroperoxide was added, and absorbance was measured spectrophotometrically at 340 nm for 90 seconds. The NADPH concentration was monitored by the rate of change in absorbance at 340 nm per minute (A340 nm/min). Catalase activity was measured using the method developed by Aebi et al. [39]. Briefly, 100 μL of hemolyzed erythrocytes was dissolved in 50 mL of 50 mM phosphate buffer (pH 7.0). Immediately after adding 1 mL of 30 nM H_2O_2 to the 2 mL mixture, the H_2O_2 concentration was monitored at 240 nm for 30 seconds at 20 °C.

Plasma concentrations of fat-soluble vitamins

Plasma retinol, α-carotene, β-carotene, lycopene, α-tocopherol,

γ-tocopherol, and coenzyme Q10 concentrations were assessed using reverse-phase high-pressure liquid chromatography (RP-HPLC) using the method developed by Jakob and Elmadfa [40]. Briefly, after precipitation of proteins with ethanol, plasma lipids were extracted with n-hexane. After evaporation, the dry residue was dissolved using 150 μL of methanol-dichlormethane (85:15, v/v). Next, 100 μL of the sample was used for analysis by injecting it into a Merck LiChrospher 100 RP18 guard column (10 μm, 250×4 mm) of a Dionex HPLC system (Summit HPLC) and running it at a flow rate of 1.0 mL/min. The absorption spectrum was detected at 325 nm for retinol, 295 nm for tocopherols, 450 nm for carotenoids and lycopene, and 270 nm for coenzyme Q10. The plasma concentration of each vitamin was determined based on the area under the curve using an external calibration curve. Fat-soluble vitamin concentrations in the plasma were corrected for the sum of plasma cholesterol (mmol/L) and TGs (mmol/L) because of their interdependency in the blood, as suggested by Thurnham et al. [41] and Horwitt et al. [42].

DNA damage determination using the alkaline comet assay

To isolate leukocytes, 70 μL of fresh whole blood was mixed with 1 mL of phosphate-buffered saline at pH 7.4 using Histopaque 1077 (Sigma) according to the manufacturer's instructions. A 10 μL aliquot of the cell suspension was mixed with 0.7% low-melting-point agarose, and 100 μL of the mixture was added to a slide previously coated with 0.5% normal-melting-point agarose. The slides were covered with a coverslip and solidified. Next, the coverslips were removed, and the slides were placed in lysis buffer (2.5 M NaCl, 100 mM EDTA, 10 mM Tris pH 10.0, and 1% sodium lauryl sarcosine; 1% Triton X-100; and 10% dimethyl sulfoxide) for 1 hour at 4 °C, protected from light. Subsequently, the slides were briefly washed in distilled water and placed in electrophoresis buffer (300 mM NaOH and 10 mM Na2EDTA, pH 13.0) for 40 minutes for DNA unwinding. Electrophoresis in the same buffer was performed at an electric current of 25 V/300±3 mA for 20 minutes at 4 °C. Next, the slides were rinsed three times with a neutralized buffer (0.4 M Tris, pH 7.5) for 5 minutes at 4 °C and dehydrated in absolute ethanol for 5 minutes. After drying at room temperature, the slides were stained with 50 μL of 20 μg/mL of ethidium bromide and covered with a coverslip. The tail intensity (equivalent to the percentage of DNA in the tail), tail length, and tail moment (tail length×tail intensity) in 50 cells each on two replicate slides were measured using a fluorescence microscope (Leica Wetzlar) equipped with a charge-coupled device camera (Nikon) and a Komet 4.0 comet image analysis system (Kinetic Imaging).

Statistical analysis

Statistical analysis was performed using IBM SPSS ver. 21.0 (IBM Corp.). All data were presented as the mean±standard error. Significance was determined using a paired t-test. $P<0.05$ was considered statistically significant.

RESULTS

Effects of WPC and HWPC dietary supplementation on anthropometry and blood lipid profiles

Results showed that compared to baseline, 8 weeks of oral intake of WPC or HWPC did not affect the participants' body weight, percentage of body fat mass, BMI, waist circumference, and waist-hip ratio (Table 2). However, plasma concentrations of total-C significantly decreased in the WPC group, while those of LDL-C significantly decreased in both WPC and HWPC groups, resulting in a decrease in the atherogenic index (AI) in both groups (Fig. 1A–1C). In contrast, the plasma TG concentration did not change in either group (Fig. 1D). These findings showed that without any significant changes in anthropometry, WPC and HWPC are effective in lowering blood LDL-C and AI levels.

Effects of WPC and HWPC dietary supplementation on plasma concentrations of fat-soluble antioxidant vitamins

The dietary intake of most of the nutrients did not significantly change during the study, except dietary retinol intake in the HWPC group (Table 3). However, plasma concentrations of retinol, α-tocopherol, lycopene, α-carotene, and β-carotene significantly increased postintervention in the WPC group, whereas plasma coenzyme Q10 levels increased in both WPC and HWPC groups (Fig. 2); γ-tocopherol levels were not affected in either group (data not shown). Considering that blood lipids affect fat-soluble vitamin levels, lipid standardization using either total-C or total-C and TGs was suggested to correct vitamin levels in the blood [43]. When corrected for total-C or for total-C and TGs, all tested fat-soluble antioxidant vitamins, even γ-tocopherol, remained significantly elevated in the WPC group but not in the HWPC group (data not shown). Overall, we observed that dietary supplementation with both WPC and HWPC commonly increases coenzyme Q10 levels, but WPC increases the plasma levels of additional fat-soluble antioxidants.

Table 2. Characteristics of study participants before and after 8-week WPC or HWPC dietary supplementation

Characteristic	WPC (n=9)			HWPC (n=9)			P-value[b]
	Before	After	P-value[a]	Before	After	P-value[a]	
Age (yr)	26.90±0.40			26.40±0.80			0.324
Weight (kg)	73.56±3.90	70.40±3.13	0.447	78.38±4.55	78.78±4.75	0.410	0.433
Body fat (%)	22.26±1.54	22.88±1.57	0.318	20.08±1.86	20.46±2.07	0.567	0.380
BMI (kg/m^2)	24.26±0.97	24.77±1.17	0.140	25.02±1.43	25.00±1.45	0.345	0.664
WHR	0.83±0.02	0.84±0.02	0.563	0.86±0.02	0.84±0.02	0.190	0.404
GOT (U/L)	22.30±1.90	28.11±2.96	0.061	27.67±2.49	40.44±9.70	0.200	0.106
GPT (U/L)	26.60±2.30	25.78±2.63	0.742	31.28±4.70	28.17±2.32	0.508	0.384
Physical activity frequency							
Every day/wk	2 (22.2)			2 (22.2)			0.924[c]
3–4 times/wk	3 (33.4)			4 (44.5)			
1–2 times/wk	2 (22.2)			2 (22.2)			
No physical activity	2 (22.2)			1 (11.1)			
Alcohol							
Yes	9 (100)			7 (77.8)			0.134[c]
No	0			2 (22.2)			
Alcohol intake (mL/day)	66.0±23.7			56.6±24.5			0.546[d]

Values are presented as mean±standard error or number (%).
WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate; BMI, body mass index; WHR, waist-hip ratio; GOT, glutamine oxaloacetic transaminase; GPT, glutamine pyruvic transaminase.
[a]Paired t-test (before-after); [b]independent t-test (WPC-HWPC before); [c]chi-square test (WPC-HWPC); [d]Mann-Whitney U-test (WPC-HWPC).

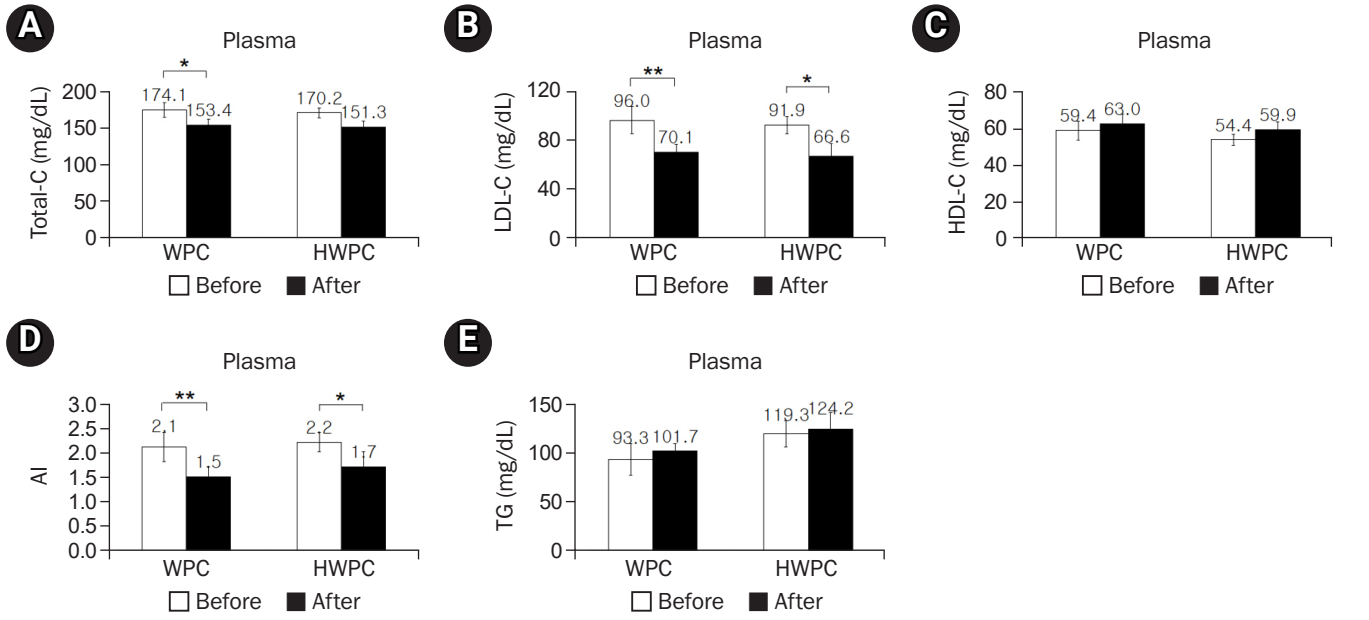

Fig. 1. Effects of 8-week dietary supplementation with WPC or HWPC on plasma concentrations of cholesterol, AI, and TG in South Korean male smokers. Plasma concentrations of total-C (A), LDL-C (B), HDL-C (C), AI (D), and TG (E) were compared between before (week 0, baseline) and after (8 weeks) oral supplementation with either WPC (n=9) or HWPC (n=9). Values are presented as mean±standard error. Total-C, total cholesterol; WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AI, atherogenic index (total-C−HDL-C)/HDL-C; TG, triglyceride. Significant difference within groups between baseline and 8 weeks later in the paired t-test (*P<0.05, **P<0.01).

Table 3. Comparison of energy and nutrient intake before and after 8-week WPC or HWPC dietary supplementation

Variable	WPC (n=9)			HWPC (n=9)			P-value[b]
	Before	After	P-value[a]	Before	After	P-value[a]	
Energy (kcal)	1,273.1±114.1	1,473.3±152.0	0.393	1,502.7±161.9	1,435.3±190.7	0.784	0.286
Carbohydrate (g)	174.6±9.7	225.5±24.7	0.062	226.4±31.1	219.0±36.8	0.873	0.167
Protein (g)	51.5±5.8	52.1±11.0	0.934	52.1±7.6	53.9±7.8	0.839	0.951
Lipid (g)	38.7±10.1	42.2±5.8	0.795	34.6±16.5	33.4±4.1	0.824	0.734
Fiber (g)	3.6±0.1	4.0±0.5	0.463	3.7±0.9	4.3±0.9	0.675	0.908
Calcium (mg)	268.2±22.0	298.0±68.8	0.729	420.9±62.5	295.6±54.8	0.194	0.114
Phosphorus (mg)	605.0±68.4	669.3±81.2	0.600[c]	740.2±114.7	683.4±94.0	0.612[c]	0.366[d]
Iron (mg)	8.7±0.5	8.3±1.0	0.753[c]	9.3±1.9	8.2±1.2	0.398[c]	0.731[d]
Sodium (mg)	3,490.4±616.3	3,645.4±708.2	0.722	3,647.4±677.1	2,946.8±517.0	0.416	0.869
Potassium (mg)	1,716.1±158.0	1,814.4±294.1	0.781	1,807.2±345.4	1,609.8±320.9	0.654	0.825
Zinc (mg)	6.2±0.4	6.5±0.7	0.600[c]	11.0±5.5	6.5±1.0	0.398[c]	0.945[d]
Vitamin A (μg RE)	443.2±89.3	542.7±139.9	0.437	336.8±96.7	496.2±162.3	0.409	0.442
Retinol (μg)	36.8±19.6	86.1±31.5	0.336	113.6±21.9	57.6±12.0	0.031	0.026
β-Carotene (μg)	2,420.7±540.5	2,588.6±729.9	0.779	1,296.1±474.2	2,458.3±993.9	0.350	0.144
Vitamin B1 (mg)	1.10±0.20	1.02±0.10	0.926	1.00±0.21	0.92±0.13	0.529	0.823
Vitamin B2 (mg)	0.76±0.17	0.83±0.16	0.755	0.97±0.18	0.69±0.08	0.133	0.420
Niacin (mg)	13.5±1.7	10.7±0.8	0.179	10.2±2.3	11.5±2.1	0.656	0.286
Vitamin C (mg)	68.3±14.2	39.5±7.5	0.140	53.9±11.2	54.1±18.1	0.993	0.437
Folic acid (μg)	165.0±34.6	162.2±33.5	0.953	160.2±30.4	147.3±34.4	0.751	0.918
Vitamin E (mg)	8.07±1.99	9.2±3.09	0.754	8.47±1.69	8.37±2.07	0.939	0.880

Values are presented as mean±standard error.
WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate; RE, retinol equivalents.
[a]Paired t-test (before–after); [b]independent t-test (WPC–HWPC before); [c]Wilcoxon signed-ranked test (before–after); [d]Mann-Whitney U-test (WPC–HWPC before).

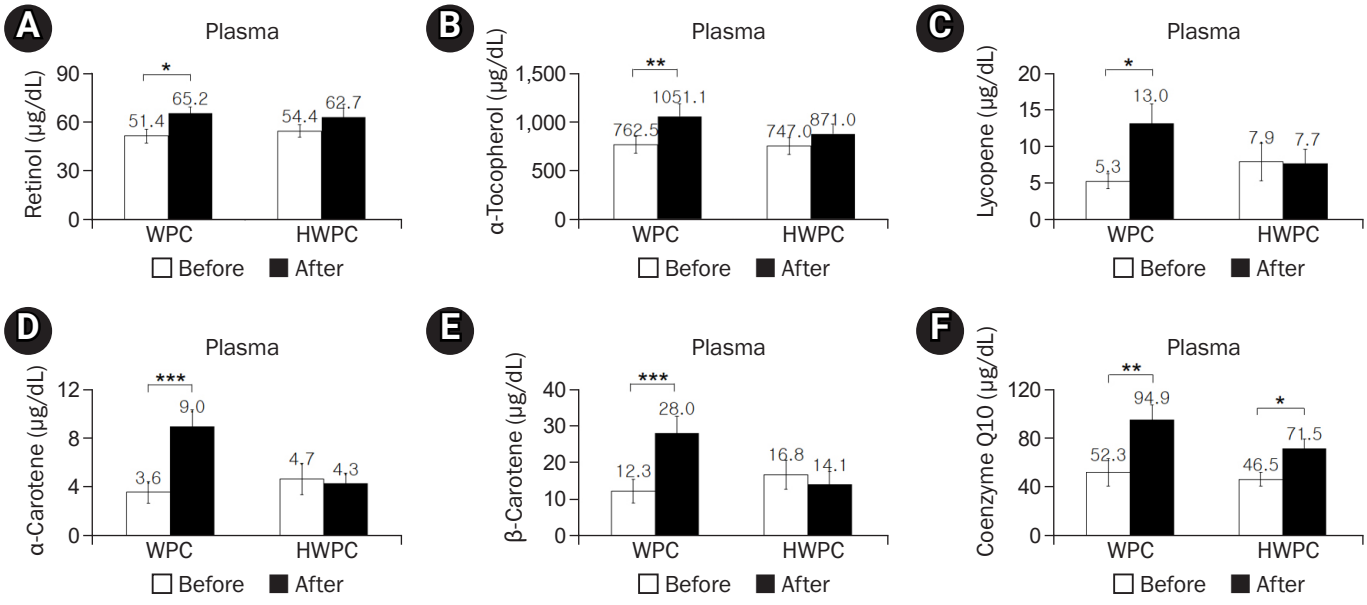

Fig. 2. Effects of 8-week dietary supplementation with WPC or HWPC on plasma concentrations of fat-soluble antioxidants in South Korean male smokers. Plasma concentrations of retinol (A), α-tocopherol (B), lycopene (C), α-carotene (D), β-carotene (E), and coenzyme Q10 (F) before (week 0, baseline) and after (8 weeks) oral supplementation with either WPC (n=9) or HWPC (n=9). Values are presented as mean±standard error. WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate. Significant difference within groups between baseline and 8 weeks later in the paired t-test (*P<0.05, **P<0.01, ***P<0.001).

Effects of WPC and HWPC dietary supplementation on oxidative markers on leukocytes, plasma, and erythrocytes

The mean tail moments of leukocytes significantly decreased in both WPC and HWPC groups (Fig. 3). However, there was no significant difference in plasma CDs and TRAP, as well as catalase and GPx activities in erythrocytes (Table 4). These findings show that dietary supplementation with WPC and HWPC is effective in lowering oxidative DNA damage in leukocytes but does not affect other plasma oxidative stress-related markers.

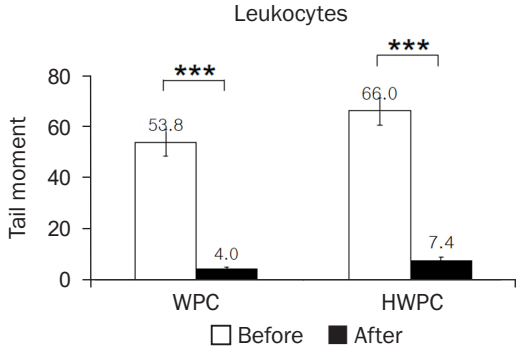

Fig. 3. Effects of 8-week dietary supplementation with WPC or HWPC on the tail moments of leukocytes. The tail moments (tail length×tail intensity) of leukocytes were compared before (week 0, baseline) and after (8 weeks) oral supplementation with either WPC (n=9) or HWPC (n=9). Values are presented as mean±standard error. WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate. Significant difference within groups between baseline and 8 weeks later in the paired t-test (***P<0.001).

Correlation analysis among plasma concentrations of fat-soluble antioxidants, plasma cholesterol levels, and leukocyte tail moments

Next, we examined the correlation among plasma cholesterol levels, leukocyte tail moments, and plasma concentrations of fat-soluble antioxidants (Table 5). The AI was positively correlated with total-C and LDL-C but negatively correlated with HDL-C. Leukocyte tail moments were positively correlated with total-C, LDL-C, and AI. Retinol, α-tocopherol, and coenzyme Q10 were positively correlated with HDL-C. Coenzyme Q10 was negatively correlated with leukocyte tail moments.

DISCUSSION

Principal findings

This is the first study to demonstrate that oral supplementation with WPC and HWPC is effective in lowering the AI and oxidative DNA damage, partly via modulating the plasma levels of fat-soluble antioxidants, especially coenzyme Q10, in smokers. In addition, we also noticed a WPC-specific effect in decreasing plasma total-C levels, along with increased plasma retinol, α-tocopherol, lycopene, α-carotene, and β-carotene levels.

Both WPC and HWPC lower LDL-C and AI in male smokers. This indicates that both WPC and HWPC may be protective against CVD development and hypocholesterolemia sustained after WPC hydrolysis. Earlier, whey hydrolysis was considered to increase the bioavailability and effectiveness of whey by removing its inactive part. However, whey hydrolysis does not appear to be more effective in improving blood cholesterol profiles, at least in South Korean male smokers with no apparent disorders. In addition, compared to HWPC, WPC is better at lowering plasma to-

Table 4. Plasma CD and TRAP, erythrocyte catalase, and GPx activities of study participants before and after 8-week WPC or HWPC dietary supplementation

Variable	WPC (n=9)			HWPC (n=9)			P-value[b]
	Before	After	P-value[a]	Before	After	P-value[a]	
Plasma							
CD (μM)	2.15±0.47	1.70±0.48	0.398[c]	2.74±0.51	2.37±0.62	0.161[c]	0.189[d]
TRAP (mM)	1.45±0.16	1.47±0.13	0.406[c]	1.47±0.26	1.52±0.10	0.106[c]	0.222[d]
Erythrocytic antioxidant enzymes							
CAT (K/g Hb)	82.98±7.59	80.04±5.70	0.374[c]	82.00±5.41	94.50±6.84	0.260[c]	0.387[d]
GPx (U/g Hb)	27.79±4.85	29.39±3.56	0.802	22.88±4.83	27.24±3.66	0.304	0.484

Values are presented as mean±standard error.
CD, conjugated diene; TRAP, total radical-trapping antioxidant potential; GPx, glutathione peroxidase; WPC, whey protein concentrate; HWPC, hydrolysate of whey protein concentrate; CAT, catalase; Hb, hemoglobin.
[a]Paired t-test (before–after); [b]independent t-test (WPC–HWPC before); [c]Wilcoxon signed-ranked test (before–after); [d]Mann-Whitney U-test (WPC–HWPC before).

Table 5. Correlation analysis of plasma cholesterol, AI, tail moment, and fat-soluble antioxidants

Variable	Total-C	HDL-C	LDL-C	AI	Tail moment	Retinol	α-Tocopherol	γ-Tocopherol	Lycopene	α-Carotene	β-Carotene
HDL-C	−0.058[a]										
LDL-C	0.879[b]	−0.463[b]									
AI	0.603[b]	−0.797[b]	0.837[b]								
Tail moment	0.374[c]	−0.157	0.390[c]	0.364[c]							
Retinol	−0.071	0.375[c]	−0.284	−0.276	−0.162						
α-Tocopherol	0.244	0.398[c]	0.021	−0.127	−0.188	0.695[b]					
γ-Tocopherol	−0.019	0.212	−0.164	−0.128	−0.190	0.561[b]	0.429[b]				
Lycopene	−0.013	−0.060	−0.019	0.038	−0.071	0.271	0.117	0.399[c]			
α-Carotene	0.228	0.113	0.166	0.040	−0.255	0.443[b]	0.612[b]	0.180	0.407[c]		
β-Carotene	0.159	0.070	0.166	0.027	−0.201	0.436[b]	0.559[b]	0.283	0.225	0.793[b]	
Coenzyme Q10	0.158	0.379[c]	−0.036	−0.222	−0.440[b]	0.528[b]	0.747[b]	0.225	0.121	0.634[b]	0.568[b]

AI, atherogenic index (total-C−HDL-C)/HDL-C; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Pearson correlation; [b]Correlation is significant at the 0.01 level (two-tailed); [c]Correlation is significant at the 0.05 level (two-tailed).

tal-C levels, indicating that hydrolysis might negatively affect some functional components of whey, contributing to this effect. Our findings related to the effects of WPC on cholesterol metabolism are in line with those of previous studies demonstrating the hypocholesterolemic effects of whey protein isolates in participants with overweight or obesity [29]. However, some studies have reported no significant effects of whey on cholesterol metabolism. This discrepancy might be due to the relative risk for CVD in the study populations. Male smokers and people with obesity have a higher risk for CVD compared to nonsmokers with a normal weight range and might be more responsive to the beneficial effects of whey. Overall, our data provide supporting evidence for the cholesterol-lowering effects of whey in humans.

The CVD risk in smokers is due to their constant exposure to cigarette smoke–induced oxidants, which, in part, cause endothelial dysfunction [6,7]. Therefore, lowering oxidative stress has been suggested as a way to prevent or lower CVD risk in smokers. However, reports on the beneficial effects of antioxidants in smokers are inconsistent [14-20]. To investigate the antioxidant effects of WPC and HWPC dietary supplementation on various aspects of the oxidative defense system in the body, we used the comet assay to detect oxidative DNA damage in leukocytes, along with measuring fat-soluble antioxidants as nonenzymatic antioxidant systems, CDs and TRAP as oxidative stress markers in plasma, and antioxidant enzyme activities in erythrocytes. Although WPC and HWPC did not significantly affect plasma CD and TRAP levels and erythrocytes' catalase and GPx activities, both WPC and HWPC had strong beneficial effects on fat-soluble antioxidant levels and leukocyte tail moments, an indicator for oxidative DNA damage in leukocytes. The lack of changes in plasma CD and TRAP levels or antioxidant enzyme activities in erythrocytes might suggest that WPC or HWPC might not be sufficient to induce changes in these parameters in smokers constantly exposed to cigarette smoke. No apparent beneficial effects of vitamin E supplementation on lipid peroxidation have been reported in young and healthy smokers [44,45]. However, in this study, some participants might not have reached a threshold of severe depletion in the enzymatic antioxidant defense system prior to the study; therefore, the additional protective effects of WPC or HWPC dietary supplementation might have been less pronounced. This potential variability in the baseline antioxidant status among participants is a factor that was not fully controlled and could influence the magnitude of the observed benefits.

In this study, a significant decrease in oxidative DNA damage in leukocytes proved the antioxidative effects of WPC and HWPC dietary supplementation on male smokers. We used the comet assay to determine oxidative DNA damage using surrogate cells, such as leukocytes [46]. In addition, correlation analysis indicated that tail moments and oxidative DNA damage markers are closely associated with plasma total-C, LDL-C, and AI levels. Therefore, the decrease in tail moments after supplementation with WPC and HWPC might be closely related to improving blood cholesterol levels in smokers. Similarly, oxidative DNA damage in leukocytes improved in smokers after supplementation with a mixture of antioxidant vitamins [17]. Our data might indicate the beneficial health effects of WPC and HWPC dietary supplementation on CVD, as well as other oxidative DNA damage–related disorders, such as cancer. In addition, the comet assay to determine oxidative DNA damage in circulating blood cells might be a good way to monitor the antioxidative effects of supplementation

with WPC or HWPC. Previously, the comet assay showed increased DNA damage in smokers [47]. Only when smoking was ceased did the comet assay show decreased oxidative DNA damage [46].

Our findings also indicate that supplementation with WPC or HWPC affects the levels of fat-soluble antioxidants, including retinol, α-tocopherol, γ-tocopherol, lycopene, α-carotene, β-carotene, and coenzyme Q10. Notably, coenzyme Q10 levels significantly increased in both groups, which might be linked to a concurrent decrease in plasma LDL-C levels, the AI, and leukocyte tail moments. Indeed, we observed a strong negative correlation between coenzyme Q10 and leukocyte tail moments, although there were no significant correlations with LDL-C and AI. Previous studies have shown that coenzyme Q10 supplementation protects against oxidative DNA damage in lymphocytes [48,49] and decreases lipid peroxidation in patients with coronary artery disease [50]. However, no significant effects of coenzyme Q10 on oxidative DNA damage markers in smokers have been reported [51].

The increases observed in fat-soluble antioxidants in this study could be attributed to either the inherent micronutrient content of WPC and HWPC or the enhanced preservation capacity of antioxidants in the plasma induced by these two supplements. Due to logistical limitations, we were unable to analyze the specific vitamin and coenzyme Q10 contents of WPC and HWPC samples. Consequently, it is unclear whether the increased plasma antioxidants levels were directly derived from supplementation with WPC and HWPC or resulted from secondary metabolic improvements. Further investigation is required to clarify the exact role of coenzyme Q10 in the antioxidative and hypocholesterolemic effects observed in smokers.

Conclusion

After 8 weeks of oral supplementation with WPC or HWPC, South Korean male smokers have decreased plasma LDL-C levels, resulting in a decrease in the AI and alleviation of leukocyte oxidative DNA damage, along with increased plasma coenzyme Q10 levels. In particular, WPC leads to a further reduction in plasma total-C levels, while simultaneously increasing the concentrations of fat-soluble antioxidants, such as retinol, α-tocopherol, lycopene, α-carotene, and β-carotene. These findings might support the hypocholesterolemic and antioxidative roles of WPC and HWPC in smokers, suggesting the use of WPC and HWPC as dietary supplements to aid in the prevention of CVD in these populations.

ARTICLE INFORMATION

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Authors' contributions

Conceptualization: EP, JYP, SML. Data curation: EP. Formal analysis: EP. Investigation: EP. Methodology: EP. Project administration: EP, SML. Resources: JYP. Software: JYP. Supervision: EP. Validation: SML. Visualization: EP, SML. Writing - original draft: EP, JYP, SML. Writing - review & editing: EP, JYP, SML. All authors read and approved the final manuscript.

Conflicts of interest

Eunju Park is the current editor-in-chief of this journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Data availability

Data of this research are available from the corresponding author upon reasonable request.

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CLINICAL NUTRITION RESEARCH

Comparative nutritional assessment of vegetarian and nonvegetarian ready-to-eat foods

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Objective: This study aimed to assess the nutritional adequacy of vegetarian ready-to-eat convenience foods, focusing on gimbap, rice ball, and sandwich products.
Methods: We examined 114 vegetarian and 414 nonvegetarian ready-to-eat products and compared their energy and nutrient contents to gain useful insights for consumers when making informed choices and for producers when developing nutritionally balanced vegetarian convenience foods.
Results: Compared with nonvegetarian products, vegetarian convenience foods had a significantly greater carbohydrate content per serving and significantly lower protein, sodium, and cholesterol contents. Although vegetarian gimbap was significantly more costly than the nonvegetarian gimbap, its cholesterol and saturated fat contents were significantly lower. Vegetarian rice balls had a significantly lower trans fat content than their nonvegetarian counterparts. Sandwiches in the vegetarian options had a significantly higher sugars content but had significantly lower protein and sodium contents than those in the nonvegetarian options. Vegetarian convenience foods did not meet one-third of the daily nutrient reference values for a single meal, similar to their nonvegetarian counterparts, but their sodium content exceeded the daily reference value. However, unlike the nonvegetarian options, the sodium content of vegetarian sandwiches did not exceed the daily value.
Conclusion: Vegetarian convenience foods contain higher levels of carbohydrates and sugars and lower levels of protein, sodium, and cholesterol than nonvegetarian convenience foods. Foods such as vegetarian gimbap, rice balls, and sandwiches do not provide sufficient energy or nutrients to meet the nutritional requirements for a single meal. Creating nutritionally balanced vegetarian convenience foods should be the focus when developing new vegetarian food products.

Keywords: Nutrients; Vegetarian diet; Food labeling; Fast foods

INTRODUCTION

Veganism is a broad concept that not only adheres to a plant-based diet but also avoids products containing animal-derived ingredients or produced through animal-exploiting processes [1]. Vegetarian diets are classified according to the degree to which animal-derived foods are restricted. These include strict vegan diets, which completely exclude all animal products; ovo-lacto vegetarian diets, which allow eggs and dairy but exclude meat; pescatarian diets, which avoid all meat except for fish and seafood; and flexi-

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tarian diets, which occasionally include meat [2].

Interest in and adoption of vegetarianism have been steadily increasing locally and globally. In 2020, the global vegetarian population reached approximately 180 million, while the local population was between 1 and 1.5 million [3]. Ethical and environmental concerns, as well as health-related considerations, prompt certain individuals to choose a vegetarian lifestyle [4]. From a sustainability perspective, vegetarianism helps reduce greenhouse gas emissions, improve land use efficiency, and minimize biodiversity loss, making it an increasingly important approach to sustainable food consumption [5]. Furthermore, plant-based diets are typically lower in saturated fat and cholesterol but richer in dietary fiber, phytochemicals, vitamin C, folate, and magnesium than animal-based diets, thereby beneficial in preventing cardiovascular diseases and certain types of cancer [6]. However, highly processed plant-based foods may contain excessive amounts of added sugars, sodium, and saturated fats, potentially increasing the risk of metabolic disorders [7].

Home meal replacements (HMRs) are processed food products designed to shorten meal preparation time. HMRs are typically classified into four categories according to the level of preparation needed: ready-to-eat (RTE; consumed immediately upon purchase), ready-to-heat (requiring minimal heating), ready-to-end-cook (requiring substantial heating), and ready-to-cook (containing preprocessed ingredients and still requiring partial or complete cooking) [8]. Economic growth and rising national income have notably reshaped consumer lifestyles, driving rapid expansion of the HMR market to meet the increasing consumer demand for convenient and time-saving options [9]. Additionally, since the onset of the COVID-19 pandemic in 2019, the consumption of convenience foods has continued to increase [10].

In modern society, where lifestyles prioritizing convenience and simplicity have become ever more common, nutritional research on the convenience of vegetarian foods has become increasingly important, given the increasing number of individuals adopting vegetarian diets for various reasons. While previous studies have examined vegetarian consumer motivations for food selection, satisfaction, perceptions, and dietary habits [11,12], the nutritional contents of commercially available vegetarian convenience foods remain uninvestigated, indicating a significant gap in the literature. In particular, research on RTE foods, which are designed for immediate consumption and frequently chosen by modern consumers, should be prioritized.

This study aimed to conduct a nutritional evaluation of vegetarian convenience foods to provide evidence-based insights for consumers selecting convenience food products. Hence, we compared and analyzed the nutritional composition (energy, carbohydrate, protein, fat, trans fat, saturated fat, cholesterol, sodium, and sugars contents) of vegetarian and nonvegetarian convenience foods available on the local market.

METHODS

Ethics statement

This study did not involve human participants or animal subjects and was based solely on publicly available product label information; therefore, institutional review board approval was not required.

Study targets

We conducted a survey from December 2024 to February 2025 to evaluate the nutritional content of vegetarian convenience foods, particularly RTE foods. Using the search terms "gimbap," "rice balls," "triangular gimbap," "sandwiches," and "hamburgers" on local portal sites and convenience store applications, we identified 528 products currently available on the market. Of these, 114 were vegetarian convenience foods, and 414 were nonvegetarian. By product type, 155, 120, and 253 were gimbap, rice ball, and sandwich products, respectively.

Survey contents and methods

Data on product type, storage method, weight, nutritional content per unit weight (including energy, carbohydrate, protein, fat, trans fat, saturated fat, cholesterol, sodium, and sugars contents), and price were collected from the labels printed on the packaging. Vegetarian convenience foods were classified as vegan, ovo-lacto vegetarian, or pescatarian according to the ingredient lists and allergen information provided on the labels. To evaluate the nutritional adequacy of a single meal composed of vegetarian versus nonvegetarian convenience foods, we calculated the proportion of one-third of the daily reference value provided by a single serving.

Statistical analysis

Descriptive statistics, including means, standard deviations, and frequencies, were obtained from the survey data. The nutritional contents of vegetarian and nonvegetarian convenience foods were compared using Student t-test. To compare nutritional contents across different types of convenience foods and vegetarian categories, we used one-way analysis of variance. When significant differences were identified, we conducted post hoc analysis using

Duncan's new multiple range test. All statistical data were analyzed using IBM SPSS ver. 30.0 (IBM Corp.). A P-value below 0.05 was considered statistically significant.

RESULTS

General characteristics of vegetarian and nonvegetarian RTE foods

Table 1 summarizes the basic and nutritional characteristics of vegetarian and nonvegetarian convenience foods. Across all products, the mean serving size was 190.0 g, while the mean price per serving was 3,643.3 South Korean won (KRW), with no significant differences noted between vegetarian and nonvegetarian items. The carbohydrate content per serving was significantly higher among vegetarian convenience foods than among nonvegetarian products (53.0 g vs. 48.0 g, $P < 0.05$). Conversely, the protein (10.3 g vs. 12.4 g, $P < 0.001$), sodium (748.6 mg vs. 901.7 mg, $P < 0.001$), and cholesterol (30.4 mg vs. 44.6 mg, $P < 0.01$) contents were significantly lower in vegetarian products. Among the types of vegetarian convenience foods, gimbap had the highest average weight per serving (245.6 g), followed by sandwiches (175.2 g) and rice balls (135.3 g, $P < 0.001$). Sandwich-type (4,479.6 KRW, 437.1 kcal) and gimbap-type (4,216.9 KRW, 400.7 kcal) products had significantly higher price and energy contents than rice ball-type items (1,663.0 KRW, 249.5 kcal; $P < 0.001$ for both). Gimbap products also had significantly higher levels of carbohydrate, protein, and sodium, whereas sandwiches contained significantly higher levels of fat, sugars, cholesterol, and saturated fat.

Nutrient contents of vegetarian and nonvegetarian gimbaps

Table 2 lists the energy and nutrient contents of vegetarian and nonvegetarian gimbap, categorized by vegetarian diet type. The vegetarian gimbap had significantly lower contents of cholesterol (24.0 mg vs. 43.9 mg, $P < 0.01$) and saturated fat (2.2 g vs. 3.1 g, $P < 0.05$) per serving than nonvegetarian gimbap. Per 100 g, the cholesterol (10.0 mg vs. 17.4 mg, $P < 0.05$) and saturated fat (0.8 g vs. 1.3 g, $P < 0.05$) contents were also significantly lower in the vegetarian gimbap than in the nonvegetarian gimbap, whereas the carbohydrate content was significantly greater (25.9 g vs. 24.5 g, $P < 0.05$). Fat content, both per serving and per 100 g, showed significant differences according to vegetarian type; however, differences between individual types were not significant.

Table 1. General characteristics of vegetarian and nonvegetarian ready-to-eat foods

Characteristic	Total (n=528)	Vegetarian foods (n=114)					Nonvegetarian foods (n=414)					t-value (P-value)[c]
		Total	Gimbap (n=42)	Rice ball (n=25)	Sandwich (n=47)	F-value (P-value)[b]	Total	Gimbap (n=113)	Rice ball (n=95)	Sandwich (n=206)	F-value (P-value)	
Serving size (g)	190.0±63.3	192.4±85.4	245.6±100.1[a]c	135.3±46.6[a]	175.2±56.5[b]	19.50 (<0.001)	189.4±55.8	248.6±40.2[b]	133.1±32.1[a]	182.8±38.5[b]	249.29 (<0.001)	0.35 (0.73)
Price (KRW)	3,643.3±1973.2	3,765.1±1,762.7	4,216.9±1,351.5[b]	1,663.0±383.0[a]	4,479.6±1,679.0[b]	38.15 (<0.001)	3,609.7±2028.0	3,739.7±837.2[b]	1,664.6±459.7[a]	4,435.4±2,314.8[c]	86.16 (<0.001)	0.74 (0.46)
Energy (kcal)	387.8±142.2[d]	382.6±183.4	400.7±214.6[b]	249.5±92.7[a]	437.1±155.2[b]	10.33 (<0.001)	389.2±128.8	416.8±86.5[b]	237.9±71.2[a]	443.9±113.9[c]	148.82 (<0.001)	−0.44 (0.66)
Carbohydrate (g)	49.0±17.5	53.0±24.5	63.9±31.4[b]	40.2±10.7[a]	49.6±16.5[a]	9.16 (<0.001)	48.0±15.0	60.9±13.4[c]	37.9±9.3[a]	45.6±13.1[b]	96.03 (<0.001)	2.04 (0.04)
Protein (g)	12.0±5.5	10.3±5.4	12.8±5.4[c]	6.0±2.6[a]	10.4±5.2[b]	15.53 (<0.001)	12.4±5.4	13.2±3.4[b]	6.7±3.6[a]	14.6±5.1[b]	107.49 (<0.001)	−3.65 (<0.001)
Fat (g)	16.6±11.2	15.0±12.4	13.1±13.0[b]	7.2±5.6[a]	21.9±11.2[c]	14.73 (<0.001)	17.1±10.4	15.5±12.7[b]	7.4±4.4[a]	22.4±8.2[c]	92.17 (<0.001)	−0.34 (0.73)
Sugar (g)	9.5±8.0	10.4±10.2	10.6±12.6[b]	3.2±2.5[a]	14.0±8.5[b]	10.59 (<0.001)	9.2±7.3	10.0±9.9[b]	4.1±3.1[a]	11.2±5.7[b]	37.36 (<0.001)	1.11 (0.27)
Sodium (mg)	868.7±392.6	748.6±524.4	995.2±724.7[b]	562.4±256.4[a]	627.3±289.4[a]	8.46 (<0.001)	901.7±341.1	1,104.2±334.4[c]	612.9±239.8[a]	923.9±291.8[b]	73.53 (<0.001)	−3.73 (<0.001)
Cholesterol (mg)	41.7±45.1	30.4±47.0	24.0±35.7[a]	8.1±10.1[a]	51.1±61.5[b]	8.07 (<0.001)	44.6±44.2	43.9±37.9[b]	16.2±22.7[a]	58.2±48.6[c]	34.02 (<0.001)	−2.93 (0.003)
Saturated fat (g)	4.7±4.1	4.5±5.3	2.2±2.5[a]	1.3±1.2[a]	8.3±6.1[b]	32.87 (<0.001)	4.7±3.6	3.1±2.4[a]	1.6±1.7[a]	7.1±3.3[c]	153.51 (<0.001)	−0.43 (0.67)
Trans fat (g)	0.3±1.2	0.3±0.8	0.5±1.3	0.1±0.2	0.2±0.4	2.02 (0.14)	0.4±1.3	0.4±1.7[ab]	0.6±1.7[b]	0.2±0.3[a]	3.65 (0.03)	−0.53 (0.60)

Values are presented as mean±standard deviation.
KRW, Korean won.
[a]Values with different superscripts within a row are different by Duncan's new multiple range test; [b]P-value was determined by one-way analysis of variance; [c]P-value was determined by Student t-test; [d]Energy and nutrient content per serving.

Table 2. Nutrient contents of the vegetarian and nonvegetarian gimbaps

Characteristic	Total (n=155)	Vegetarian gimbap (n=42)	Nonvegetarian gimbap (n=113)	t-value (P-value)[a]	Vegetarian type			F-value (P-value)[b]
					Vegan (n=16)	Ovo-lacto vegetarian (n=4)	Pescatarian (n=22)	
Per serving								
Weight (g)	247.8±62.0	245.6±100.1	248.6±40.2	−0.19 (0.85)	224.1±34.3	266.5±62.6	257.4±132.6	0.60 (0.56)
Energy (kcal)	412.4±133.3	400.7±214.6	416.8±86.5	−0.47 (0.64)	327.6±59.3	422.0±185.3	450.1±275.3	1.57 (0.22)
Carbohydrate (g)	61.7±19.9	63.9±31.4	60.9±13.4	0.60 (0.55)	60.7±9.6	61.5±12.7	66.6±42.7	0.17 (0.84)
Protein (g)	13.1±4.1	12.8±5.4	13.2±3.4	−0.51 (0.61)	10.8±3.0	14.5±5.8	14.0±6.4	1.88 (0.17)
Fat (g)	14.8±12.8	13.1±13.0	15.5±12.7	−1.05 (0.30)	5.7±3.3	16.4±11.1	17.8±15.5	4.92 (0.01)
Sugar (g)	10.2±10.6	10.6±12.6	10.0±9.9	0.29 (0.77)	7.3±10.4	10.8±10.8	12.9±14.2	0.92 (0.41)
Sodium (mg)	1,074.6±472.8	995.2±724.7	1,104.2±334.4	−1.28 (0.20)	730.6±257.2	1,083.8±407.2	1,171.6±931.1	1.82 (0.18)
Cholesterol (mg)	38.5±38.2	24.0±35.7	43.9±37.9	−2.95 (0.002)	5.0±11.8	24.9±43.5	24.0±35.7	4.53 (0.02)
Saturated fat (g)	2.9±2.5	2.2±2.5	3.1±2.4	−2.15 (0.03)	1.1±1.2	2.1±2.1	3.0±3.0	2.69 (0.08)
Trans fat (g)	0.4±1.6	0.5±1.3	0.4±1.7	0.17 (0.86)	0.2±0.3	1.4±2.4	0.6±1.4	1.64 (0.21)
Per 100 g								
Energy (kcal)	166.5±27.3	162.4±34.1	168.0±24.3	−0.98 (0.33)	149.4±32.1	153.6±31.0	173.4±33.6	2.63 (0.08)
Carbohydrate (g)	24.9±3.8	25.9±4.3	24.5±3.6	2.04 (0.04)	27.4±4.3	23.3±2.9	25.4±4.3	1.96 (0.15)
Protein (g)	5.4±1.4	5.3±1.3	5.4±1.4	−0.44 (0.66)	4.9±1.4	5.3±1.0	5.5±1.2	0.99 (0.38)
Fat (g)	6.1±5.5	5.3±5.0	6.3±5.6	−1.03 (0.30)	2.6±1.6	5.9±2.8	7.2±6.1	4.49 (0.02)
Sugar (g)	4.1±4.6	4.4±5.7	4.0±4.2	0.40 (0.69)	3.9±7.2	3.6±3.0	4.8±4.9	0.16 (0.86)
Sodium (mg)	432.3±130.3	400.3±140.3	444.2±125.0	−1.88 (0.06)	333.5±120.3	402.7±97.5	448.4±144.6	3.48 (0.04)
Cholesterol (mg)	15.4±14.9	10.0±14.9	17.4±14.4	−2.80 (0.01)	2.3±5.4	9.7±16.7	15.8±17.2	4.42 (0.02)
Saturated fat (g)	1.1±0.9	0.8±0.8	1.3±0.9	−2.46 (0.01)	0.5±0.6	0.7±0.6	1.1±0.9	2.59 (0.09)
Trans fat (g)	0.2±0.7	0.2±0.6	0.2±0.8	0.18 (0.86)	0.1±0.2	0.6±1.1	0.3±0.6	1.56 (0.22)

Values are presented as mean±standard deviation.
[a]P-value was determined by Student t-test; [b]P-value was determined using one-way analysis of variance.

Nutrient contents of vegetarian and nonvegetarian rice balls

Table 3 presents the energy and nutrient contents of the vegetarian and nonvegetarian rice balls, categorized by vegetarian diet type. The trans fat content per serving and per 100 g was significantly lower in vegetarian rice balls than in nonvegetarian rice balls (0.1 g vs. 0.6 g, $P < 0.05$; 0.1 g vs. 0.5 g, $P < 0.01$). Regarding the vegetarian type, the pescatarian rice balls had significantly greater weight per serving (154.2 g vs. 102.5 g) and saturated fat content per 100 g (1.1 g vs. 0.3 g) than the vegan rice balls ($P < 0.05$ for both).

Nutrient contents of vegetarian and nonvegetarian sandwiches

Table 4 presents the nutritional content differences between vegetarian and nonvegetarian sandwiches, as well as among various types of vegetarian sandwiches. The vegetarian sandwiches had significantly higher sugars content per serving (14.0 g vs. 11.2 g

Table 3. Nutrient contents of vegetarian and nonvegetarian rice balls

Characteristic	Total (n=120)	Vegetarian rice ball (n=25)	Nonvegetarian rice ball (n=95)	t-value (P-value)[a]	Vegetarian type			F-value (P-value)[b]
					Vegan (n=6)	Ovo-lacto vegetarian (n=4)	Pescatarian (n=15)	
Per serving								
Weight (g)	133.6±35.4	135.3±46.6	133.1±32.1	0.22 (0.83)	102.5±8.8[c]a	113.5±25.7[a]b	154.2±50.7[b]	3.93 (0.03)
Energy (kcal)	240.3±75.9	249.5±92.7	237.9±71.2	0.68 (0.50)	189.2±33.1	207.0±48.5	284.9±102.1	3.33 (0.05)
Carbohydrate (g)	38.4±9.6	40.2±10.7	37.9±9.3	1.09 (0.28)	34.5±3.2	32.8±5.9	44.5±11.6	3.74 (0.04)
Protein (g)	6.6±3.4	6.0±2.6	6.7±3.6	−0.95 (0.35)	4.3±0.5	5.3±1.0	6.9±3.0	2.48 (0.11)
Fat (g)	7.3±4.7	7.2±5.6	7.4±4.4	−0.12 (0.91)	4.0±2.7	6.2±2.7	8.8±6.5	1.77 (0.19)
Sugar (g)	3.9±3.0	3.2±2.5	4.1±3.1	−1.30 (0.20)	4.0±2.2	2.3±1.7	3.1±2.8	0.58 (0.57)
Sodium (mg)	602.3±243.1	562.4±256.4	612.9±239.8	−0.92 (0.36)	421.7±61.8	523.8±182.6	629.0±300.9	1.52 (0.24)
Cholesterol (mg)	14.5±20.9	8.1±10.1	16.2±22.7	−1.75 (0.08)	1.7±4.1	8.3±6.5	10.6±11.7	1.78 (0.19)
Saturated fat (g)	1.5±1.6	1.3±1.2	1.6±1.7	−0.96 (0.34)	0.4±0.6	0.8±0.6	1.7±1.3	3.67 (0.04)
Trans fat (g)	0.5±1.6	0.1±0.2	0.6±1.7	−2.85 (0.01)	0.3±0.4	0.0±0.0	0.0±0.1	2.52 (0.10)
Per 100 g								
Energy (kcal)	179.6±24.6	183.4±13.0	178.6±26.8	0.86 (0.39)	183.5±15.1	182.3±9.9	183.6±13.6	0.01 (0.99)
Carbohydrate (g)	29.3±5.0	30.6±3.8	28.9±5.2	1.48 (0.14)	33.7±2.4	29.1±2.6	29.7±3.9	3.31 (0.06)
Protein (g)	4.9±2.2	4.4±0.8	5.0±2.5	−1.24 (0.22)	4.3±0.7	4.7±01.0	4.3±0.9	0.38 (0.69)
Fat (g)	5.3±2.7	4.9±2.2	5.4±2.8	−0.78 (0.44)	3.8±2.1	5.3±1.2	5.2±2.4	1.05 (0.37)
Sugar (g)	2.9±1.9	2.5±1.9	3.0±1.8	−1.23 (0.22)	4.0±2.2	2.1±1.8	2.0±1.6	2.72 (0.09)
Sodium (mg)	446.9±117.6	417.3±113.5	454.7±118.0	−1.42 (0.16)	411.6±55.0	474.2±195.1	404.4±108.3	0.59 (0.57)
Cholesterol (mg)	10.2±12.6	6.4±9.2	11.2±13.2	−1.70 (0.09)	1.4±3.4	6.7±3.4	8.3±11.1	1.27 (0.30)
Saturated fat (g)	1.1±0.9	0.8±0.6	1.1±1.0	−1.73 (0.09)	0.3±0.5[a]	0.8±0.6[a]b	1.1±0.5[b]	4.80 (0.02)
Trans fat (g)	0.4±1.3	0.1±0.2	0.5±1.4	−2.88 (0.004)	0.2±0.4	0.0±0.0	0.0±0.1	2.48 (0.11)

Values are presented as mean±standard deviation.
[a]P-value was determined by Student t-test; [b]P-value was determined by one-way analysis of variance; [c]Values with different superscripts within a row are different by Duncan's new multiple range test.

per serving, $P<0.05$) and per 100 g (8.5 g vs. 6.1 g per 100 g, $P<0.05$) than the nonvegetarian sandwiches. Conversely, their protein content (10.4 g vs. 14.6 g per serving, $P<0.001$; 5.9 g vs. 8.0 g per 100 g, $P<0.001$) and sodium content (627.3 mg vs. 923.9 mg per serving, $P<0.001$; 349.3 mg vs. 504.7 mg per 100 g, $P<0.001$) were significantly lower. Meanwhile, their saturated fat content per 100 g was significantly higher than that of nonvegetarian sandwiches (4.9 g vs. 3.9 g, $P<0.05$). Moreover, serving weights and sodium content per serving significantly differed among vegetarian sandwiches according to vegetarian type. Vegan sandwiches had the highest serving weight (213.0 g, $P<0.05$) and sodium content per serving (806.0 mg, $P<0.01$). Energy, carbohydrate, fat, and saturated fat contents per 100 g also varied significantly by vegetarian type, with the highest values noted in ovo-lacto vegetarian sandwiches (280.5 kcal, 32.5 g carbohydrates, 13.6 g fat, and 6.2 g saturated fat). Meanwhile, pescatarian sandwiches had the highest sodium content per 100 g (411.7 mg).

Nutritional adequacy of vegetarian and nonvegetarian RTE foods

Table 5 lists the results comparing the nutritional adequacy of vegetarian and nonvegetarian RTE products, evaluated as single meals against one-third of the daily reference values. Both vegetarian and nonvegetarian products were generally below the reference values for energy and most nutrients. However, the sodium content of gimbap in both the vegetarian and nonvegetarian versions exceeded the reference value. While sandwiches exceeded the reference values for fat and saturated fat, no significant differences were found between the vegetarian and nonvegetarian options. The sodium content of the vegetarian sandwiches was below the reference value, whereas that of the nonvegetarian sandwiches exceeded it, showing a statistically significant difference ($P<0.001$).

Table 4. Nutrient contents of vegetarian and nonvegetarian sandwiches

Characteristic	Total (n=253)	Vegetarian sandwich (n=47)	Nonvegetarian sandwich (n=206)	t-value (P-value)[a]	Vegetarian type			F-value (P-value)[b]
					Vegan (n=5)	Ovo-lacto vegetarian (n=27)	Pescatarian (n=15)	
Per serving								
Weight (g)	181.4±42.4	175.2±56.5	182.8±38.5	−0.88 (0.38)	213.0±13.4[c)b]	157.0±62.9[a]	195.3±38.7[ab]	3.92 (0.03)
Energy (kcal)	442.6±122.3	437.1±155.2	443.9±113.9	−0.34 (0.73)	481.0±108.8	438.7±183.4	419.5±110.9	0.29 (0.75)
Carbohydrate (g)	46.2±13.8	49.6±16.5	45.6±13.1	1.70 (0.09)	69.0±8.5	49.9±17.2	45.6±13.9	1.79 (0.18)
Protein (g)	13.8±5.4	10.4±5.2	14.6±5.1	−5.08 (<0.001)	12.2±4.9	9.6±5.4	11.3±5.0	0.85 (0.43)
Fat (g)	22.3±8.7	21.9±11.2	22.4±8.2	−0.31 (0.75)	28.0±11.3	21.8±12.8	21.1±6.7	0.31 (0.73)
Sugar (g)	11.7±6.4	14.0±8.5	11.2±5.7	2.17 (0.03)	11.2±7.0	15.2±9.4	12.7±7.2	0.68 (0.51)
Sodium (mg)	868.8±312.9	627.3±289.4	923.9±291.8	−6.30 (<0.001)	806.0±189.6[b]	506.5±298.2[a]	785.3±182.7[a]	6.99 (0.002)
Cholesterol (mg)	57.0±50.8	51.1±61.5	58.2±48.6	−0.69 (0.50)	5.0±0.0	47.2±61.0	69.1±65.3	1.09 (0.35)
Saturated fat (g)	7.3±4.0	8.3±6.1	7.1±3.3	1.38 (0.17)	4.8±1.6	9.9±7.3	6.6±3.0	2.47 (0.10)
Trans fat (g)	0.2±0.3	0.2±0.4	0.2±0.3	0.27 (0.79)	0.5±0.1	0.2±0.4	0.2±0.2	0.60 (0.56)
Per 100 g								
Energy (kcal)	245.7±48.5	254.6±65.1	243.6±43.8	1.10 (0.28)	226.8±55.4[a]	280.5±60.9[b]	217.2±55.5[a]	6.23 (0.004)
Carbohydrate (g)	25.2±7.4	25.9±13.1	25.0±5.3	0.45 (0.66)	13.2±8.2[a]	32.5±7.8[b]	18.1±12.1[a]	12.95 (<0.001)
Protein (g)	7.6±2.3	5.9±2.4	8.0±2.2	−5.82 (<0.001)	5.7±2.1	6.1±2.7	5.7±1.9	0.12 (0.88)
Fat (g)	12.1±4.7	11.2±6.5	12.4±4.2	−1.18 (0.24)	5.4±7.9[a]	13.6±4.7[b]	8.7±6.9[ab]	6.20 (0.004)
Sugar (g)	6.5±3.7	8.5±5.7	6.1±3.0	2.76 (0.01)	5.4±3.6	10.1±6.4	6.5±3.6	3.06 (0.06)
Sodium (mg)	475.8±128.4	349.3±119.3	504.7±112.1	−8.47 (<0.001)	378.7±88.8	309.2±121.6	411.7±97.2	4.26 (0.02)
Cholesterol (mg)	30.9±28.3	24.5±33.7	32.3±26.8	−1.72 (0.09)	1.0±1.3	27.4±36.2	27.1±32.9	1.39 (0.26)
Saturated fat (g)	4.1±2.1	4.9±3.2	3.9±1.6	2.13 (0.04)	2.3±0.8[a]	6.2±3.6[b]	3.4±1.5[a]	6.98 (0.002)
Trans fat (g)	0.1±0.2	0.1±0.1	0.1±0.2	−0.66 (0.51)	0.1±0.1	0.1±0.2	0.1±0.1	0.16 (0.86)

Values are presented as mean±standard deviation.
[a)]P-value was determined by Student t-test; [b)]P-value was determined by one-way analysis of variance; [c)]Values with different superscripts within a row are different by Duncan's new multiple range test.

DISCUSSION

Given that convenience-oriented lifestyles have become more widespread and that interest in vegetarianism continues to grow, this study evaluated whether the nutrients found in vegetarian RTE convenience foods are adequate. Results showed that vegetarian convenience foods contain higher levels of carbohydrates and sugars but lower levels of protein, sodium, and cholesterol than their nonvegetarian counterparts. Similar nutritional trends were observed in specific product categories, including gimbap, rice balls, and sandwiches.

In general, vegetarian diets, particularly vegan diets, exclude animal-based foods such as meat and fish; therefore, their nutritional characteristics are distinct from those of typical omnivorous diets. Shridhar et al. [13] investigated the nutritional intake of 6,555 adults and reported that vegetarians, who do not consume eggs,

Table 5. Percentage of one-third of the daily value per serving for energy and nutrients in vegetarian and nonvegetarian ready-to-eat foods

Characteristic	Gimbap			Rice ball			Sandwich		
	Vegetarian (n=42)	Nonvegetarian (n=113)	t-value (P-value)[a]	Vegetarian (n=25)	Nonvegetarian (n=95)	t-value (P-value)[a]	Vegetarian (n=47)	Nonvegetarian (n=206)	t-value (P-value)[a]
Energy	60.1±32.2	62.5±13.0	−0.47 (0.64)	37.4±13.9	35.7±10.7	0.58 (0.57)	64.9±23.4	62.8±17.6	0.63 (0.53)
Carbohydrate	59.2±29.1	56.4±12.4	0.60 (0.55)	37.3±9.9	35.1±8.6	1.09 (0.28)	38.0±21.8	40.7±13.2	−0.78 (0.44)
Protein	70.0±29.6	72.1±18.6	−0.51 (0.61)	32.7±14.3	36.7±19.6	−0.95 (0.35)	55.7±28.6	75.6±30.7	−3.79 (<0.001)
Fat	72.5±72.4	85.9±70.4	−1.05 (0.30)	40.2±31.0	40.8±24.6	−0.12 (0.91)	101.7±73.2	115.1±43.4	−1.15 (0.25)
Sugar	31.8±37.7	30.1±29.6	0.29 (0.77)	9.6±7.5	12.2±9.3	−1.30 (0.20)	42.7±25.9	28.4±16.5	3.45 (<0.001)
Sodium	149.3±108.7	165.6±50.2	−1.28 (0.20)	84.4±38.5	91.9±36.0	−0.92 (0.36)	90.9±42.8	129.3±45.4	−4.92 (<0.001)
Cholesterol	24.0±35.7	43.9±37.9	−2.95 (0.003)	8.1±10.1	16.2±22.7	−1.75 (0.08)	45.6±61.0	67.3±57.4	−2.14 (0.03)
Saturated fat	43.2±50.4	62.2±48.1	−2.15 (0.03)	25.1±24.5	32.0±33.2	−0.96 (0.34)	172.0±123.0	132.1±70.6	2.04 (0.05)

Values are presented as mean±standard deviation.
[a]P-value was determined using Student t-test.

fish, poultry, and meat, had higher intakes of carbohydrates, dietary fiber, and folate but consumed lower amounts of fat, protein, vitamin B12, and zinc than nonvegetarians. A vegetarian diet is characterized by low levels of saturated fat and cholesterol and high levels of dietary fiber, phytochemicals, vitamin C, folate, and magnesium; thus, it has been associated with a reduced risk of cardiovascular disease and certain cancer types [6]. This association is a key factor when evaluating vegetarianism as a health-promoting dietary pattern [14-16]. This study revealed that some vegetarian RTE foods contain low levels of cholesterol and saturated fat, consistent with the findings of previous research.

Contrary to the health benefits of a vegetarian diet, highly processed vegetarian foods often contain elevated levels of sugars and sodium, increasing the risk of metabolic diseases [7]. In this study, vegetarian RTE foods had significantly greater contents of carbohydrate and sugars than nonvegetarian products, while the sodium content was lower. When the nutritional adequacy of vegetarian RTE foods as a single meal was evaluated by comparing their nutrient content with dietary reference intake values, both the carbohydrate and sugars contents did not meet the recommended values. While the sodium content in vegetarian sandwiches remained within the recommended limits, that in nonvegetarian sandwiches exceeded the reference value. Therefore, vegetarian RTE foods may be more nutritionally appropriate in terms of sodium content. The nutritional evaluation of local vegetarian RTE products examined in this study may differ from that of vegetarian diets or foreign vegetarian RTE products; therefore, conducting comparative studies on this topic is warranted.

Consuming vegetarian diets may lead to deficiencies in nutrients such as protein, zinc, iron, vitamin B12, and vitamin D [17-19]. Although we did not assess vitamin and mineral contents, we found that the protein content of vegetarian RTE foods was significantly lower than that of nonvegetarian products, consistent with previous findings. Owing to this scientific evidence, concerns have been raised regarding the potential of developing nutritional deficiencies among growing children who follow vegetarian diets [20,21]. This concern is particularly relevant, given that the foods evaluated in this study (gimbap, rice balls, and sandwiches) are commonly consumed by children and adolescents during critical growth periods, underscoring the need for proper nutritional management. We evaluated the protein adequacy of these RTE foods as a single meal and found that both vegetarian and nonvegetarian versions of gimbap, rice balls, and sandwiches failed to meet the recommended protein intake standards. Notably, rice balls supplied below 50% of one-third of the daily protein reference value. RTE foods are consumed either as a full meal, partial meal, or snack. Given that this study compared the nutritional characteristics of individual products by using one-third of the daily reference value, further research is needed to examine whether nutritional adequacy can be achieved when incorporating plant-based products into real-world meals.

Therefore, when children and adolescents consume gimbap, rice balls, or sandwiches as a single meal, pairing them with other foods that can help supplement protein intake is important. Al-

though the differences between dietary types were not statistically significant, the protein content tended to be lowest in vegan products, followed by ovo-lacto vegetarian and pescatarian products. Therefore, when developing RTE vegetarian products, considering potential nutritional deficiencies and tailoring formulations are essential to meet the nutritional requirements.

Vegetarian diets not only offer health and nutritional benefits but also potentially address the climate crisis [22], making them increasingly relevant to environmental education. In countries such as Germany, France, Denmark, and South Korea, vegetarian meal options have been introduced in school cafeterias [23]. Furthermore, Poinsot et al. [24] assessed the nutritional adequacy of vegetarian and nonvegetarian diets in France. Despite having low levels of vitamin B12, vitamin D, vitamin B2, and calcium, vegetarian diets were considered to have a generally favorable nutritional profile. This finding was attributed to the appropriate inclusion of eggs and dairy products, depending on the vegetarian diet type. Dahmani et al. [25] reported no significant differences between the proportions of vegetarian and nonvegetarian school meal menus that met nutritional adequacy standards in French elementary schools. They found that 87.5% of vegetarian menus and 88.5% of nonvegetarian menus met the standards, indicating that both types of menus were nutritionally adequate.

Choi et al. [26] also compared vegetarian and nonvegetarian meal menus provided in an elementary school service in South Chungcheong Province. Vegetarian meals had lower protein and vitamin B1 contents but higher vitamin A and calcium levels than nonvegetarian meals. This study also emphasizes the need to develop a wider variety of vegetarian menus that meet nutritional requirements. With the increasing prevalence of convenience-oriented lifestyles and growing interest in vegetarianism, developing more nutritionally balanced vegetarian convenience foods that reflect the specific nutritional profile of plant-based diets is needed.

Limitations

This study has several limitations in terms of generalizability. Despite a thorough investigation, the variety of vegetarian RTE products was limited; consequently, the number of items included for the analysis was insufficient. Certain categories of RTE foods contained very few vegetarian options; thus, our analysis was merely focused on gimbap, rice balls, and sandwiches. The nutritional content and adequacy of vegetarian diets were evaluated primarily according to the energy and macronutrients specified on nutritional labels. Future research should expand to analyze and assess micronutrients such as vitamin B12, iron, calcium, and zinc, which are critically discussed in relation to vegetarian diets. Nevertheless, we were able to identify the nutritional characteristics of vegetarian RTE foods. These findings may help consumers make more appropriate product choices and may support the development of more nutritious vegetarian products. The development of such products is particularly important, given the rising demand for vegetarian options and the widespread consumption of convenience foods.

Conclusion

Vegetarian RTE convenience foods contain higher carbohydrate and sugars levels and lower protein, sodium, and cholesterol levels than nonvegetarian convenience foods do. Vegetarian versions of gimbap, rice balls, and sandwiches are deficient in energy or nutrients, failing to meet the nutritional requirements of a single meal. Thus, future product development should aim to produce nutritionally balanced vegetarian convenience foods.

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Conceptualization: MKC. Formal analysis: JP, SRH. Investigation: JP. Methodology: JP, MKC. Supervision: MKC. Writing - original draft: JP, SRH, MKC. Writing - review & editing: JP, SRH, MKC. All authors read and approved the final manuscript.

Conflicts of interest

Mi-Kyeong Choi is an editorial board member of this journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Data availability

Data of this research are available from the corresponding author upon reasonable request.

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CLINICAL NUTRITION RESEARCH

Effects of propolis supplementation on blood glucose and lipid profiles in individuals with metabolic syndrome and type 2 diabetes: a systematic review and meta-analysis

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Objective: Propolis has been suggested as a complementary therapy for improving glycemic control and lipid metabolism. However, evidence from clinical trials remains inconsistent. This systematic review and meta-analysis aimed to provide a clear and updated assessment of the effects of propolis supplementation on fasting blood sugar (FBS) and lipid profiles in individuals with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS).

Methods: A comprehensive search was conducted on the PubMed, Scopus, Cochrane Library, and Web of Science databases through December 2024 to identify randomized controlled trials (RCTs) evaluating the impact of propolis supplementation on FBS and lipid parameters. Eligible data were pooled using a random-effects model, and weighted mean differences (WMDs) were calculated as pooled effect sizes.

Results: A total of 12 RCTs were included, encompassing 736 participants. Propolis supplementation significantly reduced FBS (WMD, −12.08 mg/dL; 95% confidence interval [CI], −19.13 to −5.04; P=0.001) and triglyceride (TG) levels (WMD, −25.40 mg/dL; 95% CI, −44.21 to −6.59; P=0.008) without significantly affecting the levels of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Conclusion: These findings suggest that propolis supplementation may modestly improve glycemic control and reduce TG levels in individuals with T2DM and MetS. However, the limited number of available studies and relatively small sample sizes highlight the need for large, high-quality RCTs to verify these findings and clarify the metabolic effects of propolis.

Keywords: Propolis; Bee glue; Diabetes mellitus; Metabolic syndrome; Meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common endocrine disorder wherein the body either cannot use insulin effectively or the pancreas produces insufficient insulin [1,2]. The global prevalence of T2DM is rising rapidly, and the disease is forecasted to affect 642

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million individuals by 2040 [3]. In addition to affecting the health of individuals, T2DM imposes an onerous burden on healthcare systems [4]. The costs of treating T2DM and its complications, such as cardiovascular disease, kidney damage, nerve disorders, and eye problems, are substantial [5]. Metabolic syndrome (MetS), characterized by obesity, high cholesterol, insulin resistance, and hypertension, is linked to an increased risk of developing T2DM [6]. Current strategies for managing T2DM and MetS include dietary modifications, regular exercise, weight loss, and medication [7,8]. Although effective, these approaches are often challenging to maintain over the long term because lifestyle changes can be difficult and medications may cause side effects [9-12]. This drawback underscores the need for complementary strategies that can support individuals alongside standard treatments.

Natural supplements are increasingly gaining attention for their health benefits [13,14]. Honeybee products, such as propolis, have shown promise owing to their bioactive compounds, accessibility, and minimal side effects [15-17]. Propolis, a sticky substance that bees use to protect their hives, has been used in traditional medicine for centuries to aid healing, reduce inflammation, and combat infections [18,19]. Contemporary studies suggest that it may also help control blood sugar [20], improve lipid profiles [21], and positively affect anthropometric measurements [22] and blood pressure [23].

Several clinical trials have investigated the effects of propolis on glucose and lipid levels in patients with T2DM and MetS [24-35], but the results remain inconsistent. Some studies have reported improvements in metabolic parameters [30,32,34], while others have reported no significant changes [29,31,35]. Given these conflicting findings, this systematic review and meta-analysis aimed to clarify the effects of propolis supplementation on blood sugar and lipid levels in individuals with T2DM and MetS.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Cochrane handbook for systematic reviews of interventions [36]. To ensure high methodological quality, we also adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37].

Search strategy

A comprehensive search was conducted to identify randomized controlled trials (RCTs) that evaluated propolis supplementation in individuals with T2DM or MetS. The PubMed, Cochrane Library, Web of Science, and Scopus databases were searched for studies published up to December 31, 2024. The following search terms were used: "propolis," "bee glue," "bee bread," "insulin resistance syndrome," "syndrome X," "metabolic syndrome," "Reaven's syndrome," "type 2 diabetes mellitus," "diabetes mellitus," and "hyperglycemia." MeSH terms, truncations, variations, and acronyms were applied to maximize search coverage. The reference lists of all included studies, as well as relevant systematic reviews and meta-analyses, were manually screened to identify additional eligible trials.

Study selection

All identified articles were initially screened by title and abstract, followed by full-text review to determine eligibility. Two independent authors screened the studies separately, and any discrepancies were resolved through discussions with a third reviewer. Literature screening was performed using the EndNote X8 reference manager (Clarivate). The inclusion criteria for studies were as follows: (1) RCTs conducted in adults (aged ≥ 18 years) with T2DM or MetS; (2) investigation of propolis supplementation for a minimum duration of 1 week, with a control or placebo group included in the study design; (3) reporting of at least one relevant outcome, such as fasting blood sugar (FBS) levels or lipid profiles; (4) studies published in English. The exclusion criteria were as follows: (1) studies conducted in children, pregnant women, or lactating women; (2) studies reporting insufficient data; (3) trials that assessed propolis in combination with other compounds; (4) gray literature, including theses and conference abstracts. If the same trial was covered by multiple publications, the most comprehensive report was selected as the main reference.

Data extraction

Data were collected from all eligible articles using a standardized extraction form. One researcher performed the initial extraction, and the extracted data were independently verified by two additional reviewers. Any discrepancies were resolved through discussion. The extracted data included participant characteristics (sample size, gender, and age), study details (author, year, country, propolis dose and formulation, type of intervention, and treatment duration), main outcomes (FBS, total cholesterol [TC], triglyceride [TG], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), and key information for risk of bias assessment. For studies that reported data only in graphical form, numerical values were obtained using GetData

Graph Digitizer version 2.26 (Informer Technologies Inc.). The corresponding authors were contacted for clarification in cases of missing information.

Quality assessment

The risk of bias in the included studies was assessed using Cochrane Collaboration's Risk of Bias tool [36]. This tool examines seven domains: (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other potential sources of bias. Each domain was categorized as having a low, unclear, or high risk of bias. The evaluation was conducted independently by two researchers, and any disagreements were resolved through discussion and consensus.

Statistical analysis

All analyses were conducted using STATA ver. 11.0 (StataCorp.). Outcomes are reported as weighted mean differences (WMDs) with 95% confidence intervals (CIs), calculated using the generic inverse variance method. A random-effects model was utilized to account for the expected heterogeneity across studies. Statistical heterogeneity was evaluated using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Subgroup analyses were performed to investigate the potential effects of intervention duration and study location on the outcomes. Sensitivity analyses were conducted using the leave-one-out method to assess the robustness of the findings. Publication bias was evaluated using Egger's test, and a P-value ≤ 0.05 was considered as the threshold for statistical significance.

RESULTS

Literature search

Searches conducted on four electronic databases yielded a total of 487 records, of which 373 remained after duplicates were removed using EndNote. Title and abstract screening resulted in the selection of 26 articles for full-text assessment. Of these, 14 studies were excluded for the following reasons: investigating propolis in combination with other substances (n = 2), no reporting on the outcomes of interest (n = 2), absence of an appropriate control group (n = 1), no participation of individuals with T2DM or MetS (n = 9). Ultimately, 12 studies met the inclusion criteria and were included in the final analysis. The study selection process is illustrated in Fig. S1 [24-35].

Study selection and risk of bias assessment

Overall, 12 RCTs published between 2015 and 2024 and encompassing 736 participants were included in this meta-analysis [24-35]. According to Cochrane Collaboration's Risk of Bias tool [36], two studies were rated as having fair quality [28,35] and one as having weak quality [27], while the remaining trials demonstrated good methodological quality [24-26,29-34]. Detailed characteristics of the studies and their quality assessments are presented in Table 1 and Table S1, respectively.

Pooled estimates for FBS

The overall effect of propolis on FBS is presented as a forest plot in Fig. 1. Eleven studies evaluated the impact of propolis supplementation on FBS [24-28,30-35]. Overall, propolis significantly reduced FBS compared with the control group (WMD, −12.08 mg/dL; 95% CI, −19.13 to −5.04; P = 0.001). Despite considerable heterogeneity among the studies ($I^2 = 79.4\%$, $P < 0.001$), sensitivity analysis showed that the results were not influenced by any single study. Subgroup analysis revealed a significant reduction in FBS only in studies with > 8 weeks of intervention and in those conducted in West Asian countries. However, heterogeneity remained high in all subgroups. The subgroup analysis results are presented in Table S2.

Pooled estimates for blood lipid levels

Fig. 2 depicts the overall impact of propolis supplementation on TC. Seven studies examined the effect of propolis on TC [24,26,29-32,34]. The findings indicate that propolis supplementation did not lead to a significant reduction in TC compared with the control group (WMD, −4.62 mg/dL; 95% CI, −13.88 to 4.65; P = 0.32). Considerable heterogeneity was noted among the studies ($I^2 = 82.7\%$, $P < 0.001$). Sensitivity analyses showed that the overall results were stable and not influenced by the exclusion of any single study. Subgroup analyses on the basis of intervention duration and study location also revealed no significant reductions in any group, while the level of heterogeneity remained high. Detailed findings from the subgroup analyses are provided in Table S2.

The effect of propolis supplementation on TG is presented as a forest plot in Fig. 3. Six studies assessed the impact of propolis on TG levels [24,28,30-32,34]. The overall results indicated that propolis supplementation significantly reduced TG levels (WMD, −25.40 mg/dL; 95% CI, −44.21 to −6.59; P = 0.008). Heterogeneity among the studies was low and not statistically significant ($I^2 = 39.0\%$, P = 0.14). However, a sensitivity analysis demonstrat-

Table 1. Randomized controlled trials included in the present systematic review and meta-analysis

Study	Country	Intervention	Control	Sample size	Sex	Mean age (yr)	Trial duration (wk)	Subject
Gholami et al. (2024) [28]	Iran	900 mg/day propolis + diet	Placebo + diet	84	Male/female	52	12	MetS
Yousefi et al. (2023) [33]	Iran	1,500 mg/day propolis	Placebo	60	Male/female	50	8	T2DM
Sajjadi et al. (2023) [31]	Iran	500 mg/day propolis	Placebo	62	Male/female	54	12	MetS
Moayedi et al. (2023) [29]	Iran	500 mg/day propolis	Placebo	30	Female	53	8	T2DM
Ochoa-Morales et al. (2023) [30]	Mexico	600 mg/day propolis	Placebo	24	Male/female	47	12	T2DM
Afsharpour et al. (2019) (Iran) [24]	Iran	1,500 mg/day propolis	Placebo	60	Not reported	50	8	T2DM
Zakerkish et al. (2019) [34]	Iran	1,000 mg/day propolis	Placebo	94	Male/female	55	12	T2DM
Gao et al. (2018) [27]	China	900 mg/day propolis	Control	61	Male/female	59	18	T2DM
Samadi et al. (2017) [32]	Iran	900 mg/day propolis	Placebo	66	Male/female	54	12	T2DM
El-Sharkawy et al. (2016) [25]	Egypt	400 mg/day propolis	Placebo	50	Male/female	50	24	T2DM
Zhao et al. (2016) [35]	China	900 mg/day propolis	Control	65	Male/female	60	18	T2DM
Fukuda et al. (2015) [26]	Japan	226 mg/day propolis	Placebo	80	Male/female	69	8	T2DM

MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.

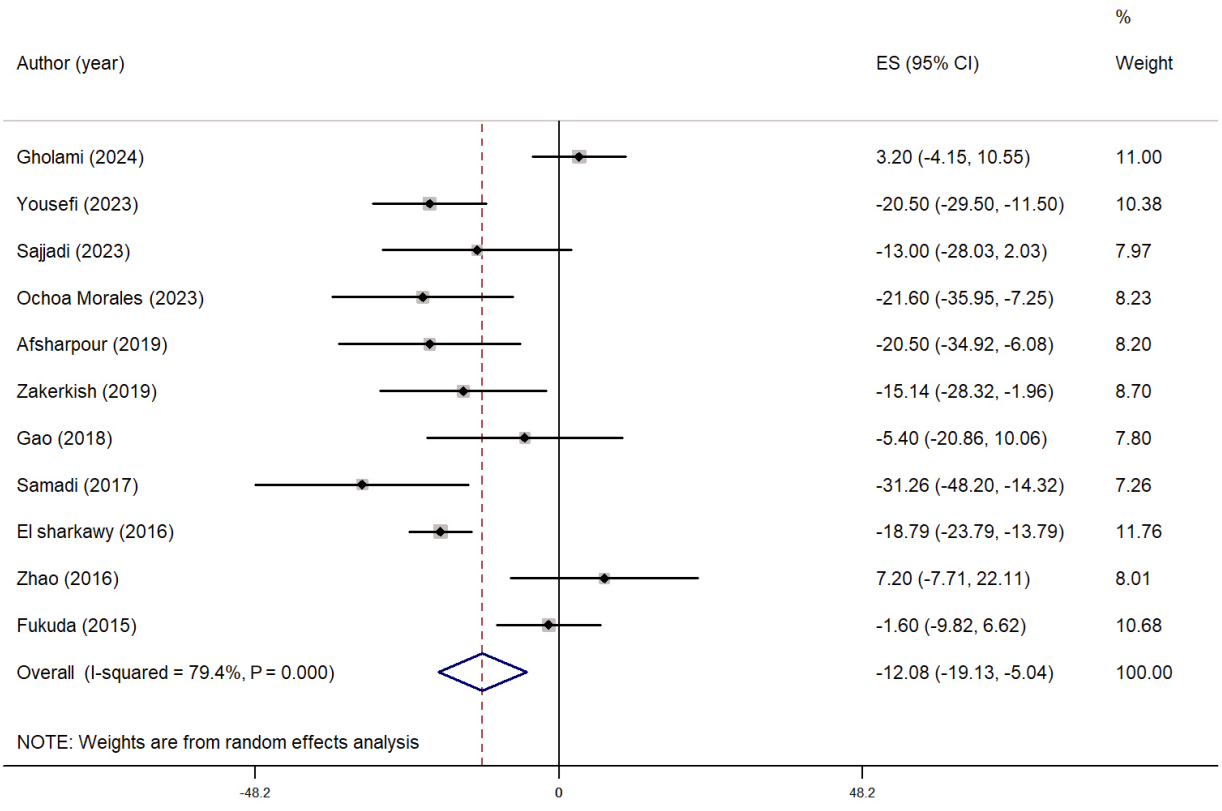

Fig. 1. Forest plot illustrating the effect of propolis supplementation on fasting blood sugar in individuals with type 2 diabetes mellitus and metabolic syndrome [24-28,30-35]. ES, effect size; CI, confidence interval.

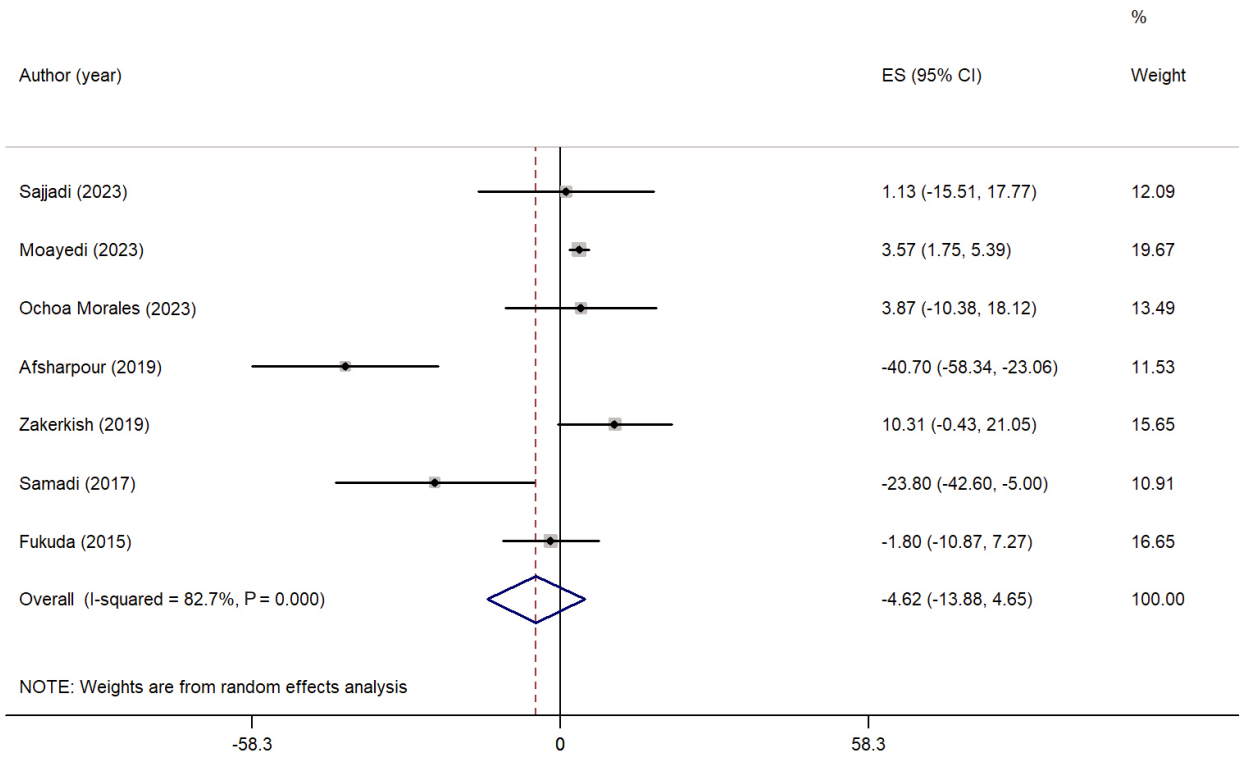

Fig. 2. Forest plot illustrating the effect of propolis supplementation on total cholesterol in individuals with type 2 diabetes mellitus and metabolic syndrome [24,26,29-32,34]. ES, effect size; CI, confidence interval.

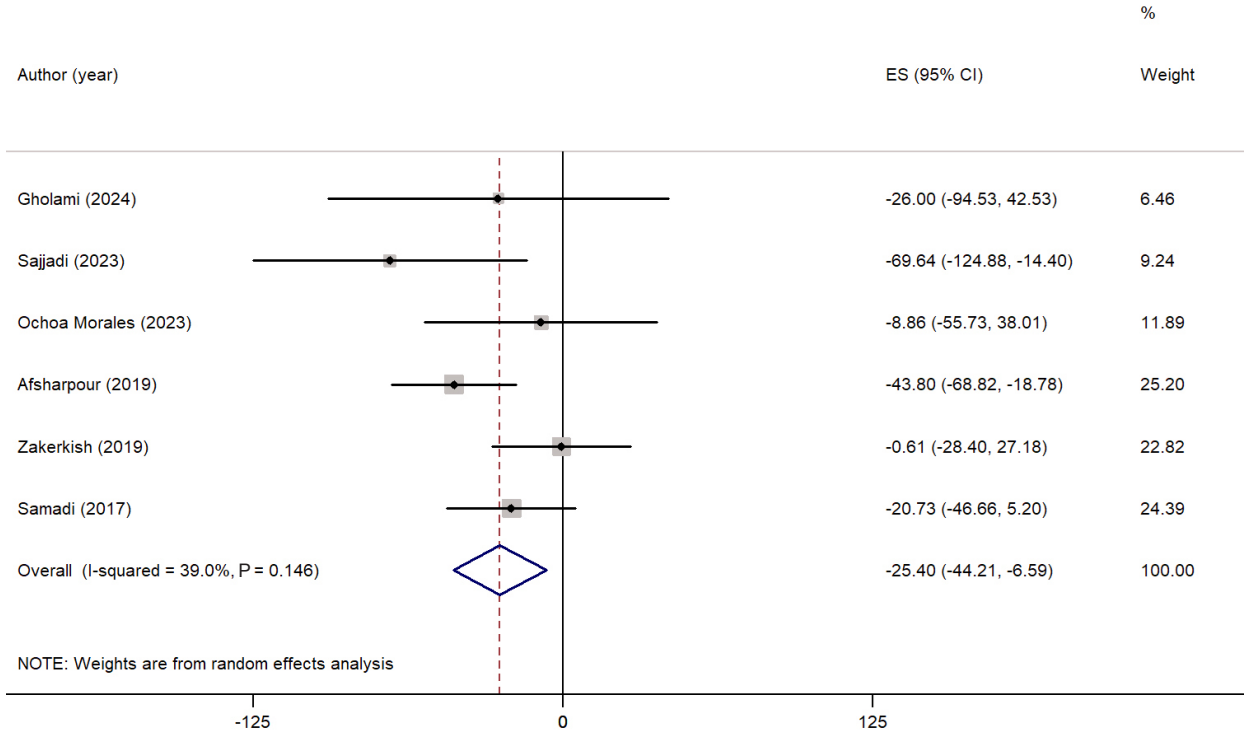

Fig. 3. Forest plot illustrating the effect of propolis supplementation on triglyceride levels in individuals with type 2 diabetes mellitus and metabolic syndrome [24,28,30-32,34]. ES, effect size; CI, confidence interval.

ed that excluding the study conducted by Afsharpour et al. [24] resulted in a nonsignificant effect (WMD, −18.29 mg/dL; 95% CI, −37.76 to 1.16). Subgroup analysis could not be performed due to insufficient data.

Fig. 4 summarizes the impact of propolis on LDL-C levels. A meta-analysis of seven studies revealed a nonsignificant reduction in LDL-C levels in the propolis group compared with the control group (WMD, −9.92 mg/dL; 95% CI, −19.96 to 0.12; P = 0.05) [24,26,29-32,34]. However, considerable heterogeneity was noted among the studies (I^2 = 91.9%, P < 0.001). No significant reduction was observed when examining subgroups based on intervention duration. Nevertheless, studies conducted in West Asian countries reported a significant decrease in LDL-C levels. Heterogeneity was relatively low among studies from non-West Asian countries and those with interventions lasting longer than 8 weeks. Sensitivity analysis indicated that excluding studies by Sajjadi et al. [31] (WMD, −11.04 mg/dL; 95% CI, −21.91 to −0.17), Ochoa-Morales et al. [30] (WMD, −11.58 mg/dL; 95% CI, −22.85 to −0.32), and Zhao et al. [35] (WMD, −11.87 mg/dL; 95% CI, −23.30 to −0.45) resulted in a significant reduction, suggesting that these studies had a considerable impact on the overall results. A summary of all subgroup analyses is presented in Table S2.

The overall effect of propolis on HDL-C is illustrated as a forest plot in Fig. 5. Eight studies were included in the analysis of HDL-C levels [24,26,28-32,34]. Propolis supplementation did not result in a significant improvement in HDL-C compared with the control group (WMD, 0.94 mg/dL; 95% CI, −0.71 to 2.59; P = 0.26). High heterogeneity was observed across the studies (I^2 = 53.1%, P = 0.03). However, sensitivity analysis showed that the results remained consistent and were not significantly affected by the exclusion of any individual study. No significant changes in HDL-C levels were noted in any subgroup analysis. Nevertheless, lower heterogeneity was found in studies conducted in non-West Asian countries and in studies with intervention durations ≤ 8 weeks. Detailed findings from the subgroup analysis are presented in Table S2.

Publication bias

Publication bias was assessed using Egger's test. No evidence of publication bias was found in studies examining the effect of propolis supplementation on FBS (P = 0.96), TC (P = 0.19), TG (P = 0.75), LDL-C (P = 0.89), and HDL-C (P = 0.76).

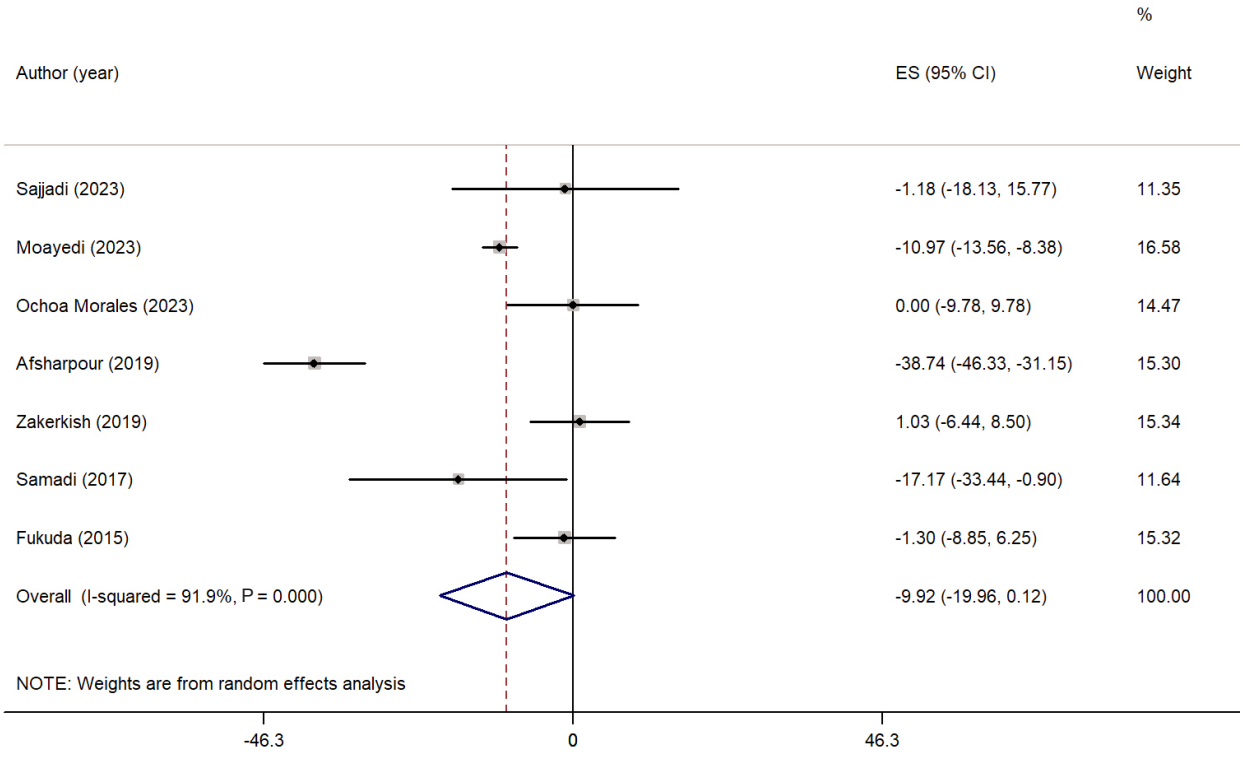

Fig. 4. Forest plot illustrating the effect of propolis supplementation on low-density lipoprotein in individuals with type 2 diabetes mellitus and metabolic syndrome [24,26,29-32,34]. ES, effect size; CI, confidence interval.

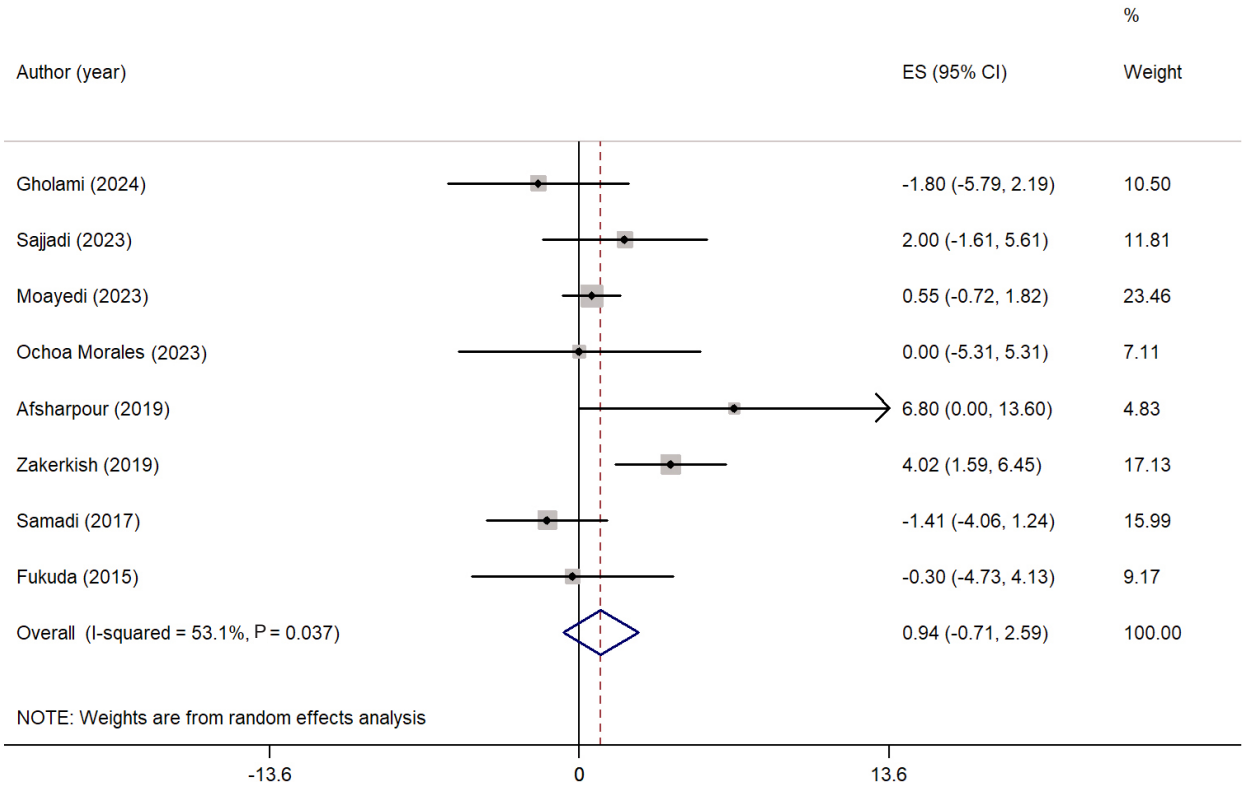

Fig. 5. Forest plot illustrating the effect of propolis supplementation on high-density lipoprotein in individuals with type 2 diabetes mellitus and metabolic syndrome [24,26,28-32,34]. ES, effect size; CI, confidence interval.

DISCUSSION

The results of this meta-analysis of 12 RCTs indicate that propolis supplementation significantly lowers FBS and TG levels in individuals with T2DM and MetS without significantly affecting other lipid parameters. The considerable heterogeneity among the included studies points toward notable differences in study design, participant characteristics, intervention duration, and propolis composition, necessitating the exercise of caution while interpreting the pooled results. Sensitivity analysis revealed that the outcomes for serum TG changed significantly when individual studies were excluded. Additionally, no evidence of publication bias was found for any of the outcomes.

Subgroup analyses revealed that significant reductions in FBS were observed only in studies conducted in West Asian countries and in interventions lasting more than 8 weeks. While the overall pooled effect of propolis supplementation on LDL-C was not statistically significant, a significant reduction was observed in trials conducted in West Asian countries. These findings likely reflect regional differences in dietary habits, baseline metabolic status, genetic factors, and the botanical composition of propolis, all of which may influence its bioactive profile and metabolic efficacy [38,39]. Longer intervention durations may provide more sustained modulation of inflammatory pathways, oxidative stress, and insulin signaling mechanisms, all of which mediate the glycemic benefits of propolis [20,40,41]. Overall, these findings indicate that the metabolic effects of propolis can vary based on contextual and biological factors, highlighting the importance of considering regional characteristics and treatment duration when evaluating the efficacy of propolis.

Although the precise mechanisms underlying the metabolic effects of propolis are not fully understood, previous investigations have suggested several plausible pathways. Individuals with T2DM and MetS often experience chronic hyperglycemia, elevated TG levels, and insulin resistance, which collectively contribute to impaired glucose and lipid metabolism. These baseline metabolic disturbances create conditions in which bioactive compounds, such as those in propolis, may exert measurable effects [16,21,39,41,42].

Propolis is rich in polyphenolic compounds, including flavonoids, phenolic acids, and other bioactive constituents that exhibit antioxidant and anti-inflammatory properties [42]. These com-

pounds may help mitigate oxidative stress and suppress inflammatory signaling, two key factors driving insulin resistance and hypertriglyceridemia in T2DM and MetS [43,44]. Propolis has been shown to enhance glucose uptake in peripheral tissues by activating insulin-sensitive transporters such as glucose transporter type 4. Moreover, it has been shown to improve glycolysis in liver and muscle cells and suppress hepatic gluconeogenesis, which can collectively cause FBS levels to decrease [17,20,39].

Regarding lipid metabolism, propolis may influence hepatic lipid synthesis, increase fatty acid oxidation, and regulate lipoprotein metabolism, thereby lowering TG levels [20,45]. By attenuating systemic inflammation and the oxidative modification of lipoproteins, propolis may help improve lipid homeostasis in these high-risk populations [21]. Clinical evidence further supports its role in downregulating inflammatory markers, such as tumor necrosis factor alpha and C-reactive protein, both of which are closely linked to insulin resistance and dyslipidemia [43]. Together, these antioxidant, anti-inflammatory, and metabolic regulatory activities of propolis provide a mechanistic rationale for the modest improvements in FBS and TG levels observed in individuals with T2DM and MetS.

The current study has some limitations. First, due to the limited number of available studies, we were unable to perform sex-specific analyses or investigate the effects of different types of propolis and their bioactive compounds. Second, the generalizability of our findings may be limited, given that most of the included research was conducted in Iran and East Asian countries. Third, we could not fully identify the sources of heterogeneity in the case of some metabolic outcomes, necessitating caution while interpreting the results. Fourth, this review was not prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO), which presents a potential methodological limitation. Nevertheless, all procedures were conducted systematically following the PRISMA guidelines.

In conclusion, propolis supplementation modestly improves FBS and TG levels in patients with T2DM and MetS. However, these findings should be interpreted with caution, given the heterogeneity among the included studies and the small sample sizes. More large-scale, well-designed RCTs using standardized propolis preparations are required to verify these findings and clarify the underlying mechanisms.

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None.

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Data availability
Data of this research are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary materials are available from https://doi.org/10.7762/cnr.2025.0004.

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Review Article

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CLINICAL NUTRITION RESEARCH

Effects of meal sequence intervention on blood glucose response in healthy adults: a systematic review

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Objective: Achieving glycemic control is essential in the prevention and management of metabolic disorders, with several dietary strategies having been proposed. Meal sequence, which is defined as the order of food consumption while maintaining the overall composition and intake, may attenuate postprandial glycemic responses. This systematic review aimed to assess the effects of meal sequences on postprandial glycemic responses in healthy adults and explore its potential as a preventive strategy for glycemic control.

Methods: Literature published between January 2015 and March 2025 in PubMed, Cochrane Library, Web of Science, KoreaMed, and RISS was searched using the keywords "healthy adult," "food order," "meal sequence," and "glucose response."

Results: Among the 2,442 records identified, one randomized controlled trial, four randomized crossover studies, and one repeated-measures design with a total of 107 participants aged 20–36.7 years met the inclusion criteria. Most of the studies reported that consuming vegetables, fruits, or protein-rich foods before carbohydrate-rich foods reduced postprandial glucose responses and incremental area under the curve compared with mixed or carbohydrate-first meals. These effects were also noted in randomized controlled trials and randomized crossover design.

Conclusion: Our findings indicate that adjusting the order of food consumption can effectively mitigate acute postprandial glucose responses in healthy individuals. Further large-scale and long-term randomized controlled trials across diverse populations and standardized protocols are warranted to strengthen the evidence base.

Keywords: Meal sequence; Blood glucose; Glycemic control; Insulin; Healthy volunteers

INTRODUCTION

Blood glucose control plays an important role in maintaining metabolic health and preventing chronic diseases. Persistent hyperglycemia increases the risk of developing type 2 diabetes mellitus and contributes to the development of cardiovascular disease, kidney disease, and neuropathy [1-3], which not only reduces quality of life but also has significant socioeconomic burden [4,5].

The World Health Organization and the American Diabetes Association have highlighted diabetes prevention and early intervention as critical public health strategies, shifting focus beyond treatment-centered approaches [6,7]. Several studies have shown that lifestyle modifications can effectively prevent or delay the onset of diabetes in individuals with prediabetes, which is characterized by

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borderline elevations in blood glucose levels [8-10]. Therefore, preventive strategies for glycemic management have become increasingly important.

Dietary strategies for glycemic control have mostly focused on macronutrient composition and the amount and type of carbohydrates consumed as postprandial blood glucose responses reportedly vary depending on the intake and ratio of carbohydrates, protein, fat, and dietary fiber [11-14]. Meal sequence, which is the order of consumption of food groups, has gained increasing attention as a novel intervention strategy for glycemic control. Consuming fiber- and protein-rich foods before carbohydrates attenuates postprandial glucose responses, potentially through mechanisms such as delayed gastric emptying and enhanced glucagon-like peptide-1 (GLP-1) secretion [15].

Compared to consuming carbohydrate-rich food first, consuming protein or vegetables beforehand significantly decreased postprandial glucose and insulin responses. Lee et al. [16] reported that consuming proteins first lowered the incremental area under the curve (iAUC) and incremental glucose peak (iGp) by up to 55% and 1.9 mmol/L in normal-weight adults, and by 41.2% and 1.0 mmol/L in overweight/obese individuals, respectively. Additionally, a protein-vegetable–first sequence reduced the iAUC by 38.8% and iGp by 45.8%, with similar benefits seen in the vegetable-first group. These results indicate that modifying either the composition or the order of meals may be an effective dietary approach for managing postprandial glycemia.

However, most studies in this area are limited by small sample sizes, short intervention durations, and heterogeneity in study design, meal composition, and outcome measurements. Therefore, this study aimed to systematically review the literature regarding the effects of meal sequence on postprandial blood glucose responses in healthy adults and explore its potential as a dietary strategy for glycemic control.

METHODS

Study design

This study systematically reviewed the effects of meal sequence on blood glucose responses in healthy adults. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Search strategy and study selection

Using KoreaMed, RISS, PubMed, Cochrane Library, and Web of Science Domestic, and international literature were searched from March 17 to March 24, 2025, targeting studies published between January 2015 and March 2025. Studies were included if they included meal sequence interventions in healthy adults and evaluated blood glucose responses. The main search terms included "healthy adult," "food order," "meal sequence," "glucose response," and "glucose excursion" (Table 1, Table S1).

The inclusion criteria were as follows: (1) study population were adults aged ≥19 years; (2) included meal sequence interventions; and (3) analyzed postprandial blood glucose or related hormone responses. Studies were excluded if (1) they included individuals aged <19 years, animals, patients with medical conditions, or postmenopausal women, (2) were unrelated to the research topic (e.g., interventions not related to food intake, or outcomes unrelated to glucose metabolism), (3) were not published in Korean or English, (4) were reviews, letters, editorials, or other non-original research, and (5) had inaccessible full texts.

"Healthy adults" was defined according to the eligibility criteria in the included studies. Specifically, healthy adults were defined as individuals aged ≥19 years without any metabolic, genetic, or chronic diseases as indicated in the original studies. Participants were required to have a normal glycemic status, no history of medication intake that affected glucose or insulin metabolism, and no clinical conditions predisposing them to altered postprandial glycemic responses. The exclusion criteria also comprised current smokers, individuals with gastrointestinal disorders or previous gastrointestinal surgery, and those with food allergies relevant to the test interventions. Body mass index (BMI) was not a primary exclusion criterion due to the variability in BMI ranges across the included studies.

All phases of the systematic review, including literature search, study selection, data extraction, and synthesis, were conducted by a single investigator (JK) under the supervision of a faculty member specializing in nutrition who provided methodological guidance and oversight throughout the review process. To reduce potential bias and ensure methodological rigor, screening and extraction were guided by predefined eligibility criteria and standardized forms.

Data on study design, participant characteristics, meal compo-

Table 1. Description of PICO

Criteria	Determinant
Population (P)	Healthy adults
Intervention (I)	Meal Sequence
Comparison (C)	Healthy adults who received a general meal sequence
Outcome (O)	Blood glucose response and related hormones

sition and sequence, intervention methods, outcome variables, measurement techniques, and primary findings were systematically extracted. All extracted data and study classifications underwent iterative verification to ensure the accuracy and internal consistency of the results.

Risk-of-bias assessment

After completing the study selection process, the methodological quality of the included studies was evaluated using two risk-of-bias assessment tools. For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2.0 for individually randomized parallel-group trials (RoB2-IRPG) was used. For studies employing randomized crossover or repeated-measures designs, the Cochrane Risk of Bias 2.0 for crossover trials (RoB2-crossover) was used. All evaluations were performed using an intention-to-treat approach, focusing on the effect of assignment to intervention. The RoB 2.0 tool comprises five bias domains, namely bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measuring the outcome, and bias in selecting the reported result. Each signaling question was rated as "yes," "probably yes," "probably no," "no," or "no information." Based on the responses to these questions, domain-level judgments were determined using the domain-specific algorithms provided by the RoB 2.0 framework and were classified as low risk of bias, some concerns, or high risk of bias.

RESULTS

Search results and general characteristics

Overall, 2,442 articles were retrieved, and 598 duplicates were removed. After screening the titles and abstracts of the remaining 1,844 articles, 1,728 were further excluded for not meeting the inclusion criteria. The full texts of the 116 remaining articles were reviewed, and six studies were included in the final analysis (Fig. 1).

Among the six studies, one was an RCT, four were randomized crossover studies, and one used a repeated-measures design. The studies were performed in Indonesia, the United Arab Emirates, Singapore, and Japan and included 107 participants with a mean age ranging from 20 to 36.7 years. The intervention periods ranged from 3 to 7 days. Four studies had a washout period of 3 to 10 days, while two studies administered the intervention continuously. The meal sequence interventions involved consuming vegetables or fruits, meat, or rice first, or consuming all meal components together. Postprandial glucose responses were analyzed us-

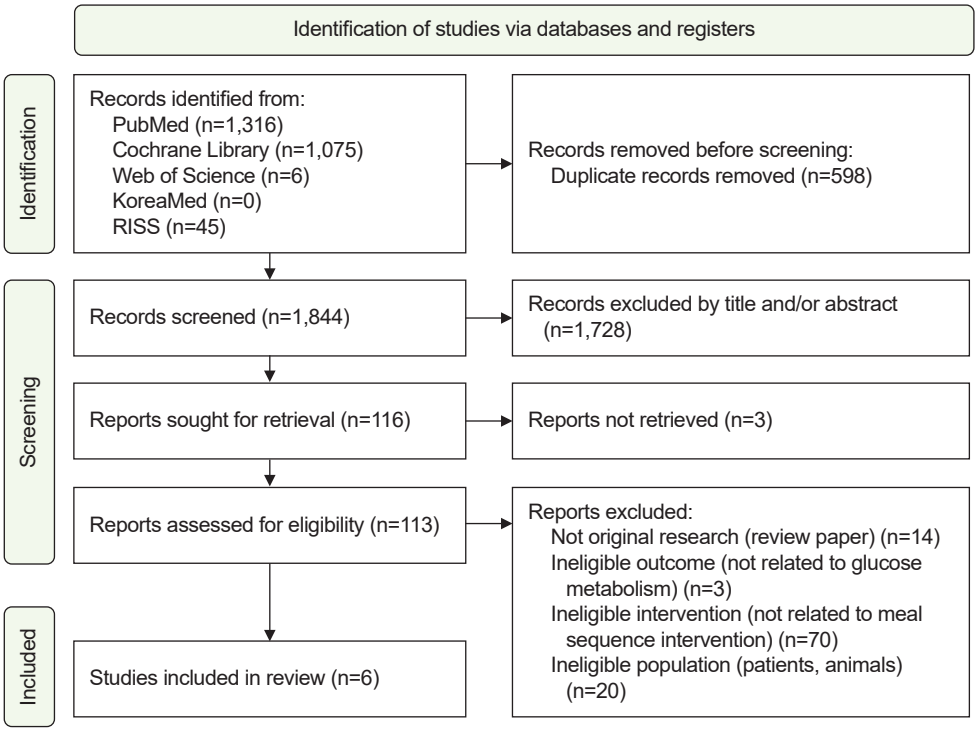

Fig. 1. Flowchart of the study selection process.

ing blood glucose levels, and several studies also assessed levels of incretin hormones, such as insulin, GLP-1, and gastric inhibitory polypeptide (GIP). The detailed characteristics and results of each study are shown in Table 2, with additional methodological details shown in Table S2.

Risk-of-bias assessment

The results of the risk-of-bias assessment for the six included studies are shown in Fig. 2. Regarding bias arising from the randomization process, five studies (83.3%) had some concerns, and one study (16.7%) had a high risk of bias. Regarding bias due to deviations from intended interventions, five studies (83.3%) had a low risk of bias, while one study (16.7%) had some concerns. Regarding bias due to missing outcome data, all studies had a low risk of bias. Regarding bias in the measurement of the outcome, five studies (83.3%) had a low risk of bias, and one study (16.7%) had some concerns. Regarding bias in selecting the reported result, four studies (66.6%) had a low risk of bias, one study (16.7%) had some concerns, and one study (16.7%) had a high risk of bias.

Effects of meal sequence intervention on blood glucose responses

Across the included studies, consuming vegetables, fruits, or meat before carbohydrates was generally linked to lower postprandial glucose levels or reduced glycemic variability compared to consuming rice first or eating all components together.

Nagoro et al. [18] performed a 3-day intervention involving 30 healthy adults in Indonesia. Postprandial glucose levels at 1 hour were significantly lower in the banana-only and banana–broccoli groups than in the rice-only control group ($P < 0.001$). Nishino et al. [19] studied eight healthy Japanese adults over 3 days with a 7-day washout period. The group that consumed salad–pork–carbohydrate-rich foods (rice, steamed pumpkin, and orange) in sequence had significantly lower blood glucose ($P < 0.05$) and insulin ($P < 0.01$) levels at 30 minutes postprandially compared to the group that consumed carbohydrate-rich foods–salad–pork. Additionally, there was a significant difference among the three groups in serum insulin levels (AUC_{0-120}; $P = 0.0449$). Sun et al. [20] performed a 5-day intervention with a 7-day washout period on 16 healthy Chinese adults in Singapore. The group that consumed vegetables–chicken breast–rice in sequence had significantly lower glucose levels at 15, 30, and 45 minutes postprandially compared to the group that consumed all items together and the group that consumed rice first ($P < 0.05$). At 30 minutes postprandially, serum insulin levels were significantly lower in the vegeta-

Table 2. Characteristics of the included studies

Study	Design	Subject (male:female)	BMI (kg/m^2)	Mean age (yr)	Region	Intervention	Outcome variable	Key finding
Nagoro et al. [18] (2019)	Randomized control trial	Healthy adults 30 (12:18)	C (n=6): 27.1±2.7 T1 (n=6): 23.2±1.9 T2 (n=6): 26.0±4.9 T3 (n=6): 25.2±3.4 T4 (n=6): 29.4±4.4	36.7±3.5	Indonesia	Comparison of different meal sequence patterns (rice-only, rice-first, and vegetable-first)	Primary outcome: blood glucose	Primary outcome: Fruit- and vegetable-first consumption (T1, T3) resulted in significantly lower postprandial blood glucose levels at 1 h compared with rice-first consumption (C) ($P<0.001$)

(Continued on the next page)

Table 2. Continued

Study	Design	Subject (male:female)	BMI (kg/m^2)	Mean age (yr)	Region	Intervention	Outcome variable	Key finding
Nishino et al. [19] (2018)	Randomized crossover	Healthy adults 8 (4:4)	20.30±1.10	20±1.2	Japan	Comparison of different meal sequence patterns (carbohydrate-first, carbohydrate-last, and vegetable-first)	Primary outcome: blood glucose Secondary outcome: serum insulin, HbA1c	Primary outcome: VMC resulted in significantly lower postprandial blood glucose levels at 30 min compared with CVM (P<0.01); Serum glucose $AUC_{0\text{-}120}$ tended to differ among the three meal sequence groups, with the highest values observed in the CVM and the lowest in the VMC Secondary outcome: VMC resulted in a significantly lower change in insulin level at 30 min compared with CVM (P<0.05); VMC resulted in significantly lower serum insulin $AUC_{0\text{-}120}$ compared with CVM (P=0.0449)
Sun et al. [20] (2020)	Randomized crossover	Healthy adults 16 (13:3): Chinese ethnic background	22.0±2.0	25.8±4.8	Singapore	Comparison of different meal sequence patterns (rice-first, meat-first, vegetable-first, mixed eating)	Primary outcome: blood glucose Secondary outcome: serum insulin, GLP-1, GIP	Primary outcome: V-M-R resulted in significantly lower postprandial blood glucose levels at 15, 30, and 45 min compared with mixed and rice-first consumption (VMR, R-VM) (P<0.05) Secondary outcome: V-MR and V-M-R resulted in significantly lower serum insulin concentrations at 30 min compared with R-VM (P<0.05); Mixed, meat-first, and rice-first (VMR, M-VR, R-VM) consumption resulted in significantly lower plasma total GLP-1 concentrations at 60 min compared with V-M-R consumption (P<0.05).
Shaheen et al. [21] (2024)	Randomized crossover	Healthy adults 18 (7:11): Arab ethnicity (15), Emirati (3)	25.4±2.3	31.1±8.6	United Arab Emirates	Comparison of different sequence patterns (rice-last, mixed eating)	Primary outcome: blood glucose Secondary outcome: serum insulin	Primary outcome: VPF resulted in significantly lower postprandial blood glucose concentration in 30 min compared with SMM (P=0.001) Secondary outcome: Meal sequence did not result in significant differences in the insulinogenic index between the test meals
Kurotobi et al. [22] (2025)	Randomized crossover	Healthy adults 29 (21:8)	21.9±2.8	32.7±6.6	Japan	Comparison of different meal sequence patterns (rice-last, mixed eating)	Primary outcome: blood glucose	Primary outcome: Non–rice-first consumption (−5 dish, −10 dish, −15 dish) resulted in significantly lower postprandial blood glucose levels over 4 hours compared with mixed and rice-first consumption (+15 dish, 0 dish) (P<0.05); Non–rice-first consumption (−15 beef) resulted in significantly lower 4-hour mean postprandial blood glucose compared with mixed eating (0 beef) (P<0.05)

(Continued on the next page)

Table 2. Continued

Study	Design	Subject (male:female)	BMI (kg/m^2)	Mean age (yr)	Region	Intervention	Outcome variable	Key finding
Matsuo et al. [23] (2023)	Repeated measures	Healthy adults 6 (3:3)	20.8±1.5	21.3±0.5	Japan	Comparison of different meal sequence patterns (rice-first, meat-first, vegetable-first, mixed eating)	Primary outcome: blood glucose	Primary outcome: Meat-first consumption (MVR) resulted in significantly lower postprandial blood glucose concentration at all measured time points except 120 min compared with other meal sequences (P<0.05); Vegetable-first consumption (VMR) did not result in significant differences in postprandial blood glucose concentrations at any time point except 90 min

C, rice only; T1, banana→rice→broccoli; T2, banana, broccoli→rice; T3, banana→broccoli→rice; T4, rice→banana, broccoli; BMI, body mass index; HbA1c, hemoglobin A1c; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; AUC, area under the curve; VMC, vegetable→meat→carbohydrate; CVM, carbohydrate→vegetable→meat; V-MR, vegetable→meat, rice; V-M-R, vegetable→meat→rice; R-VM, rice→vegetables, meat; VMR, vegetable, meat, rice together; M-VR, meat→vegetables, rice; R-VM, rice→vegetables, meat; VPF, vegetables and protein first followed by carbohydrates; SMM, standard mixed meal; MVR, meat→vegetable→rice.

bles-first group than in the rice-first group (P < 0.05). Shaheen et al. [21] performed a 2-day intervention with a 7- to 10-day washout period on 18 healthy Arab adults. Blood glucose levels at 30 minutes postprandially were significantly lower in the group that consumed chicken breast and salad first followed by rice compared to the group that consumed a mixed meal (P = 0.001). Kurotobi et al. [22] performed a 7-day intervention on 29 healthy Japanese adults using continuous glucose monitoring over 4 hours. The group that consumed nonrice foods first had significantly lower postprandial glucose levels compared to the group that consumed rice first or mixed-intake groups (P < 0.05). Notably, the −15 beef group had the lowest average postprandial glucose levels, indicating a potential benefit of consuming noncarbohydrate foods first.

In contrast, Matsuo et al. [23], using a repeated-measures design, reported that consuming meat first significantly reduced blood glucose levels at all-time points except at 120 minutes postprandially (P < 0.05). However, no significant differences were noted when vegetables were consumed first, except at 90 minutes.

In summary, most studies showed lower postprandial glucose responses when fiber- or protein-rich foods were consumed before carbohydrates, although the magnitude and consistency of effects varied across meal sequence conditions.

DISCUSSION

Across the six included studies, consuming vegetables, fruits, or protein first generally resulted in lower postprandial blood glucose levels or reduced glycemic variability compared to consuming a mixed meal or carbohydrates first. RCTs and crossover studies generally showed significant reductions in postprandial glucose levels and iAUC when vegetables were consumed first before carbohydrate-rich foods.

Meal sequence interventions represent a straightforward strategy to improve acute postprandial glucose responses by simply altering the order of food consumption while maintaining similar overall meal compositions and energy intake. Consumption of fiber-rich vegetables, fruits, and protein-rich foods first is emphasized, and several physiological mechanisms explain these effects. Viscous dietary fibers absorb water and form high-viscosity gels in the gastrointestinal tract, thereby delaying gastric emptying and nutrient transit through the small intestine. This mechanism reduces the interaction of nutrients with digestive enzymes, modulating glucose absorption rates and mitigating the elevation of postprandial blood glucose; this is supported by previous studies.

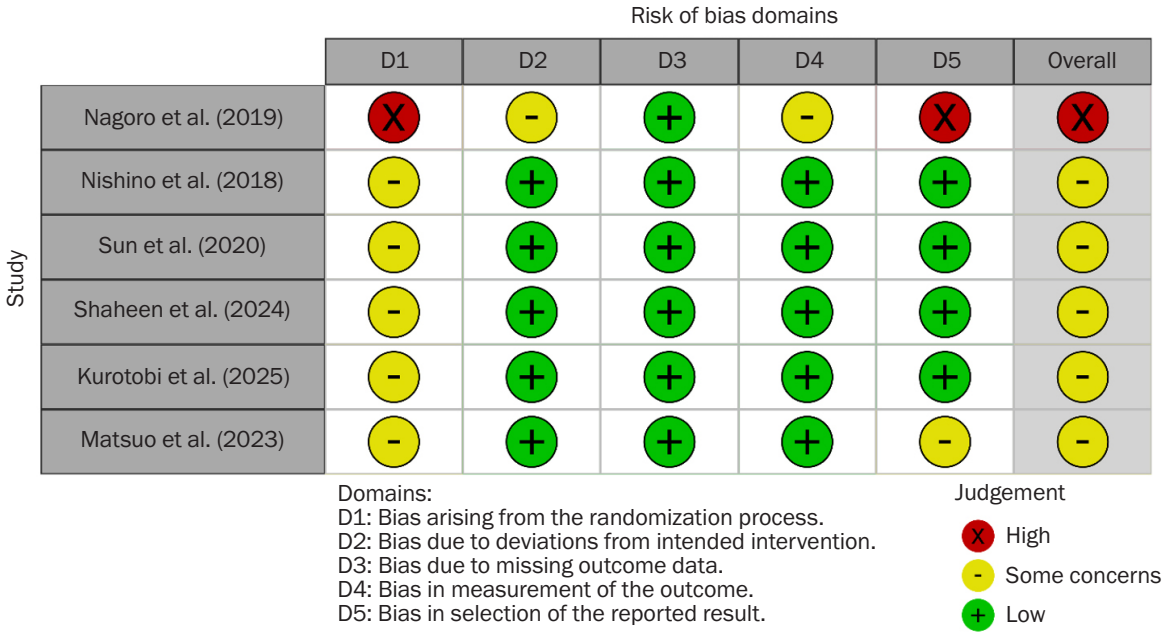

Fig. 2. Risk-of-bias assessment of the included studies.

From 22 RCTs in patients with type 2 diabetes, Mao et al. [24] reported that dietary fiber intake significantly improved glycemic indices and insulin sensitivity. Similarly, Lu et al. [25] reported that viscous dietary fiber supplementation in patients with type 2 diabetes significantly reduced hemoglobin A1c and fasting blood glucose levels. Giuntini et al. [26] also summarized that soluble fibers, such as β-glucan, psyllium, glucomannan, and pectin, regulate glycemic responses by increasing gastric viscosity, thereby slowing gastric emptying and intestinal transit. Additionally, fermentation by the gut microbiota generates short-chain fatty acids that attenuate hepatic gluconeogenesis and stimulate GLP-1 and peptide tyrosine tyrosine (PYY) secretion, thereby enhancing insulin secretion and satiety. These findings strongly support the observed improvements in postprandial glycemia when vegetables and fruits are consumed first during a meal.

Protein intake also contributes to the regulation of postprandial glycemic response. In their review, Anjom-Shoae et al. [27] reported that amino acids and peptides derived from protein-rich foods stimulate gastrointestinal L cells, thereby promoting GLP-1, GIP, and PYY secretion. Protein also delays gastric emptying, thereby attenuating postprandial glucose responses. RCTs that employed protein preloads before carbohydrate ingestion also reported a significant reduction in glucose iAUC in both healthy individuals and those with type 2 diabetes. In a randomized crossover trial, Ma et al. [28] reported that a whey protein preload in patients with type 2 diabetes significantly delayed gastric emptying, increased GLP-1, GIP, and cholecystokinin secretion, and reduced glucose iAUC to nearly half of the control condition. In another randomized crossover trial involving healthy individuals and patients with type 2 diabetes, Ekberg et al. [29] similarly reported that a protein-enriched meal significantly reduced the glucose iAUC and insulin-to-glucagon ratio compared with a carbohydrate-enriched meal.

While the feasibility of a meta-analysis was thoroughly assessed, the included studies had substantial methodological and clinical heterogeneity that was evident in study designs (e.g., RCTs, randomized crossover, and repeated-measures designs), intervention protocols (meal composition and intake sequence), and outcome measures, including postprandial glucose levels, iAUC, and hormonal responses. Additionally, inconsistencies in measurement time points across the studies precluded robust quantitative synthesis. Thus, a narrative synthesis was used to interpret the findings as a meta-analytic approach was deemed inappropriate due to the high degree of heterogeneity.

This review has several limitations. First, the heterogeneity in study designs and outcome measures limited direct comparisons and synthesis results. Second, most of the studies only measured short-term acute responses, making it difficult to extrapolate the findings to long-term glycemic control or diabetes-related complication prevention in real-world settings. Third, as the partici-

pants were primarily healthy Asian adults, further studies to validate these effects in Western populations and other demographic groups are warranted.

Nevertheless, this review consolidates recent evidence on meal sequence interventions in healthy adults and highlights the fact that simply modifying the order of food intake may effectively attenuate postprandial glycemic variability. By adhering to the PRISMA guidelines, the review systematically performed literature search, study selection, and data extraction and compared results across diverse study designs and outcomes, thereby supporting the potential for clinical and public health applications. Future studies should strengthen the evidence base by using standardized protocols for meal composition consumption order and performing long-term RCTs that encompass diverse ages, ethnicities, and metabolic conditions.

In conclusion, this systematic review suggests that meal sequence interventions may attenuate acute postprandial blood glucose responses in healthy adults. The effects were most evident when vegetables, fruits, or protein-rich foods were consumed before carbohydrate-rich foods and may be mediated by physiological mechanisms such as delayed gastric emptying, reduced intestinal glucose absorption, and enhanced incretin secretion. However, due to the short intervention durations, small sample sizes, and limited population diversity, the results should be interpreted as evidence of acute postprandial effects rather than long-term glycemic control or disease prevention. Future research should include large-scale, long-term RCTs across diverse populations and use standardized protocols to strengthen the evidence base and inform clinical and public health applications.

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Conflicts of interest

Seungmin Lee is an editorial board member of this journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Data availability

Data of this research are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary materials are available from https://doi.org/10.7762/cnr.2025.0027.

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Case Report

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CLINICAL NUTRITION RESEARCH

Nutritional management of an adolescent undergoing bariatric surgery: a case report

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This case report describes the nutritional management and long-term outcomes of an adolescent undergoing bariatric surgery. A 13-year-old female patient with morbid obesity complicated by nonalcoholic steatohepatitis (NASH), impaired glucose tolerance (IGT), and polycystic ovary syndrome (PCOS) underwent sleeve gastrectomy in July 2021. The patient achieved significant weight loss, with a body mass index decreasing from 42.0 to 23.4 kg/m² and reaching a total weight loss of 45.9% by the fourth postoperative year. Remission of NASH, IGT, and PCOS was observed after 1 year. Postoperatively, vitamin D deficiency developed, whereas other biochemical parameters remained within normal reference ranges. Adherence to recommended nutritional supplementation was suboptimal; however, with continuous nutritional education and regular follow-up, the patient ultimately established and maintained a balanced dietary pattern. The case highlights the effectiveness of bariatric surgery in achieving sustained weight loss and improving obesity-related comorbidities in adolescents, while underscoring the critical role of continuous nutritional management, patient education, and individualized multidisciplinary care in supporting long-term postoperative success.

Keywords: Bariatric surgery; Diet, Food, and Nutrition; Adolescent; Case reports

INTRODUCTION

The prevalence of obesity among adolescents has increased steadily worldwide, accompanied by a rising burden of obesity-related comorbidities, including hypertension, type 2 diabetes (T2D), insulin resistance, obstructive sleep apnea (OSA), polycystic ovary syndrome (PCOS), dyslipidemia, and nonalcoholic fatty liver disease. Bariatric surgery has emerged as an effective therapeutic option for adolescents with morbid obesity. According to the American Society for Metabolic and Bariatric Surgery, bariatric surgery is indicated in adolescents with a body mass index (BMI) of ≥ 35 kg/m^2 or ≥ 120% of the 95th percentile for age and sex with significant comorbidities, such as OSA, T2D, nonalcoholic steatohepatitis (NASH), or hypertension, or in those with a BMI of ≥ 40 kg/m^2 [1]. At our institution, bariatric surgery is performed in adolescents with a BMI of ≥ 35 kg/m^2 or a BMI of ≥ 30 kg/m^2 with accompanying comorbidities, after confirmation of completed skeletal growth.

Following bariatric surgery, adolescents are at risk for various nutrition-related complications resulting from alterations in the gastrointestinal tract and postoperative dietary restrictions. These complications include vomiting, anorexia, altered bowel habits, and dumping syndrome. Accordingly, a structured postoperative dietary progression from liquids to a regular diet, combined with

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ongoing counseling by a clinical dietitian, is essential to reduce symptoms and prevent nutritional deficiencies. In addition, sustained lifestyle modifications play a central role in achieving effective weight loss and long-term weight maintenance, underscoring the importance of ongoing nutritional management [2-4]. Previous studies have reported postoperative deficiencies in key nutrients, including protein, vitamin B_{12}, folate, vitamin D, calcium, and iron. However, most available evidence is derived from adult populations, and data specific to adolescents remain limited [5].

Currently, evidence-based guidelines for nutritional management in adolescent bariatric patients are lacking, largely due to insufficient empirical data. This case report aims to describe the nutritional interventions implemented in an adolescent undergoing bariatric surgery, evaluate clinical and nutritional outcomes, and share practical experience. By doing so, this report seeks to contribute to the body of evidence and support the development of standardized nutritional management strategies for adolescents undergoing bariatric surgery.

Ethics statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital with a waiver of informed consent (No. 3-2025-0318).

CASE REPORT

The patient was a 13-year-old girl diagnosed with morbid obesity complicated by NASH, impaired glucose tolerance (IGT), and amenorrhea secondary to PCOS. At the preoperative evaluation, her height was 175.9 cm, body weight was 130 kg, and BMI was 42.0 kg/m^2. Despite previous attempts at weight loss through dietary modification, exercise, and traditional herbal medicine, she did not achieve clinically meaningful weight loss. Preoperative assessment of the epiphyseal growth plates confirmed completion of bone growth. Based on her BMI and associated comorbidities, she met the institutional criteria for adolescent bariatric surgery and subsequently underwent sleeve gastrectomy in July 2021.

Nutritional management provided by the clinical dietitian at the Gangnam Severance Hospital is outlined in Table 1. The patient received nutritional counseling during outpatient visits for approximately 30 minutes at each outpatient visit, scheduled at 2 weeks and at 1, 3, 6, and 12 months post-surgery, followed by annual follow-up visits. Counseling focused on diet monitoring, nutrient adequacy, eating behaviors, physical activity, and long-term adherence to lifestyle modifications. Biochemical, anthropometric, and dietary intake data were collected longitudinally from the preoperative period through 4 years postoperatively using medical records and interviews. To ensure consistency, all dietary assessments were conducted by the same clinical dietitian using the 24-hour recall method, supported by food models to improve portion size estimation. Energy and protein intakes were calculated manually using the food exchange lists for Koreans [6]. Preoperative and postoperative biochemical parameters are summarized in Table 2. Postoperatively, the patient developed vitamin D

Table 1. Standard dietary progression following bariatric surgery at Gangnam Severance Hospital

Periods after surgery	Recommended type of foods	Recommended nutrient intake
Preoperative period	Balanced low-calorie diet	Energy: Female: 1,200–1,500 kcal Male: 1,500–1,800 kcal Protein: 60–80 g/day
	Very low-calorie diet when BMI >45 kg/m^2	Energy: 600–800 kcal Protein: 60–80 g/day
Until 2 wk	Liquid diet Allowed: gruel, soup, soymilk, yogurt, liquid protein supplements, oral nutritional supplements	Energy: 600–800 kcal Protein: 60–80 g/day
2–4 wk	Pureed diet Allowed: porridge added protein sources and vegetables, soft protein foods (eggs and tofu)	Energy: 800–1,000 kcal Protein: 60–80 g/day
4–6 wk	Soft diet Allowed: protein foods (fish and meat), soft vegetables	Energy: 800–1,000 kcal Protein: 60–80 g/day
After 6 wk	Balanced regular diet Most foods are allowed, but it is recommended to avoid foods high in fat and sugar	Energy: 1,000–1,400 kcal Protein: 60–80 g/day

BMI, body mass index.

deficiency, defined as a serum 25-hydroxyvitamin D_3 level below 20 ng/mL [4], while other biochemical parameters remained within the reference ranges. Changes in anthropometric measures following bariatric surgery are presented in Fig. 1, and longitudinal trends in energy and protein intake are presented in Fig. 2.

Preoperative assessment (1 month before surgery)

One month before surgery, the patient reported consuming three meals per day with an estimated total daily energy intake of 2,500 kcal. Her dietary pattern was characterized by frequent snacking, regular consumption of sugar-sweetened beverages, and a preference for fast food. During the preoperative nutritional assessment, the patient was educated on the role of dietary modification and caloric reduction in preoperative weight management and surgical preparedness.

Admission for surgery

Despite the preoperative goal of weight reduction, the patient gained 4 kg before surgery, increasing the BMI from 42.0 to 43.3 kg/m^2. She underwent sleeve gastrectomy on July 26, 2021. The patient was maintained on nothing by mouth on the day of surgery and on postoperative day (POD) 1. Sips of water were initiated on POD 2, followed by a clear liquid diet on POD 3 and advancement to a full liquid diet on POD 4. The patient was discharged on POD 5. On POD 4, the clinical dietitian provided education regarding post-discharge dietary management, including continuing a full liquid diet until the first outpatient follow-up visit, guidance on protein and micronutrient supplementation, and strategies for managing postoperative gastrointestinal symptoms, including dumping syndrome, nausea, vomiting, diarrhea, and constipation.

Table 2. Biochemical profiles before and after bariatric surgery

Biochemical parameter	1 mo before surgery	Day of surgery	Duration after surgery						
			2 wk	1 mo	3 mo	6 mo	1 yr	2 yr	3 yr
Hematological marker									
Hemoglobin (g/dL)	11.9	11.4	14.2	12.7	12.3	13.6	11.6	12.4	11.7
Hematocrit (%)	35.9	34.9	44.7	39.8	39.3	42.6	36.6	38.3	35.6
Iron (μg/dL)	-	-	-	-	134	117	112	131	134
Ferritin (ng/mL)	-	-	-	-	81.7	98.0	22.5	31.1	17.3
TIBC (μg/dL)	-	-	-	-	327	356	331	314	321
Vitamins and minerals									
Vitamin B1 (nmol/L)	-	-	-	-	4.1	5.6	2.9	10.9	4.6
Vitamin B12 (pg/mL)	-	-	-	-	673	508	339	332	397
Folate (ng/mL)	-	-	-	-	3.8	4.0	4.6	4.8	5.4
25-Hydroxyvitamin D_3 (ng/mL)	-	-	-	-	11.6	10.7	20.0	-	12.5
PTH (pg/mL)	-	-	-	-	-	-	-	36.2	37.1
Calcium (mg/dL)	8.7	8.2	9.6	9.3	9.7	10.1	8.8	9.5	9.2
Phosphorus (mg/dL)	3.6	3.5	5.1	4.8	4.7	5.9	4.8	4.5	3.8
Metabolic and lipid profile									
Fasting glucose (mg/dL)	69	133	92	84	84	87	76	78	79
HbA1c (%)	5.9	-	-	-	5.0	5.1	5.0	5.0	4.9
Insulin (μU/mL)	56.6	-	-	-	30.7	47.6	12.0	-	11.5
C-peptide (ng/mL)	5.36	-	-	-	3.36	4.66	2.84	-	1.88
Total cholesterol (mg/dL)	161	153	246	167	181	187	133	142	133
LDL cholesterol (mg/dL)	106	-	-	-	136	136	78	62	75
HDL cholesterol (mg/dL)	30	-	-	-	35	35	41	49	47
Triglyceride (mg/dL)	120	-	-	-	105	120	72	60	45
AST (U/L)	37	110	68	106	38	24	13	12	12
ALT (U/L)	67	155	142	92	52	27	8	9	8
Blood pressure (mmHg)									
Systolic	132	140	114	120	-	102	-	121	103
Diastolic	70	70	87	60	-	50	-	54	59

TIBC, total iron binding capacity; PTH, parathyroid hormone; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase.

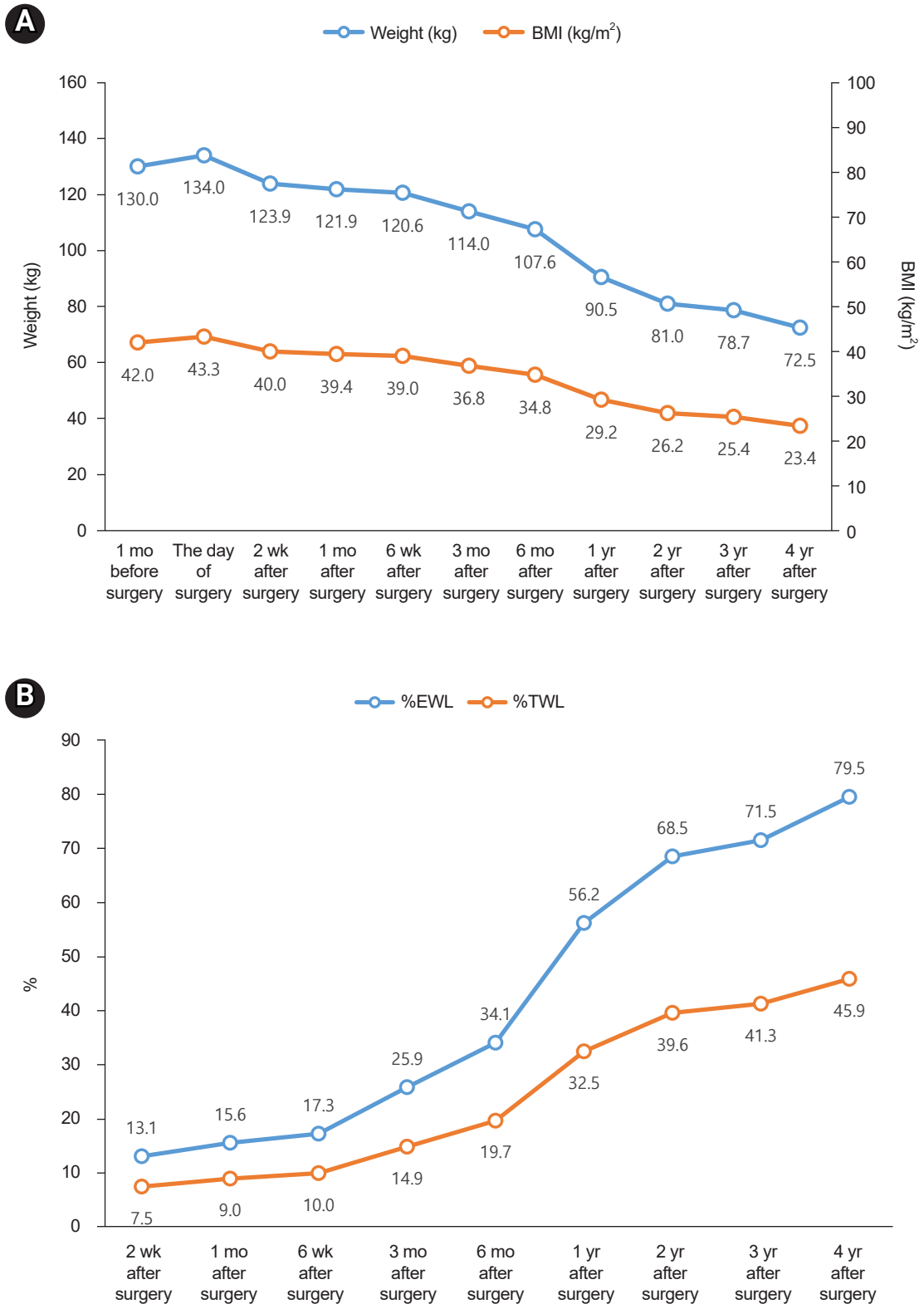

Fig. 1. Anthropometric changes after bariatric surgery. (A) Changes in weight and BMI. (B) Changes in %EWL and %TWL. BMI, body mass index; %EWL, excess weight loss=[(initial weight−postoperative weight)/(initial weight−ideal weight)]×100; %TWL, total weight loss=(initial weight−postoperative weight)/initial weight×100.

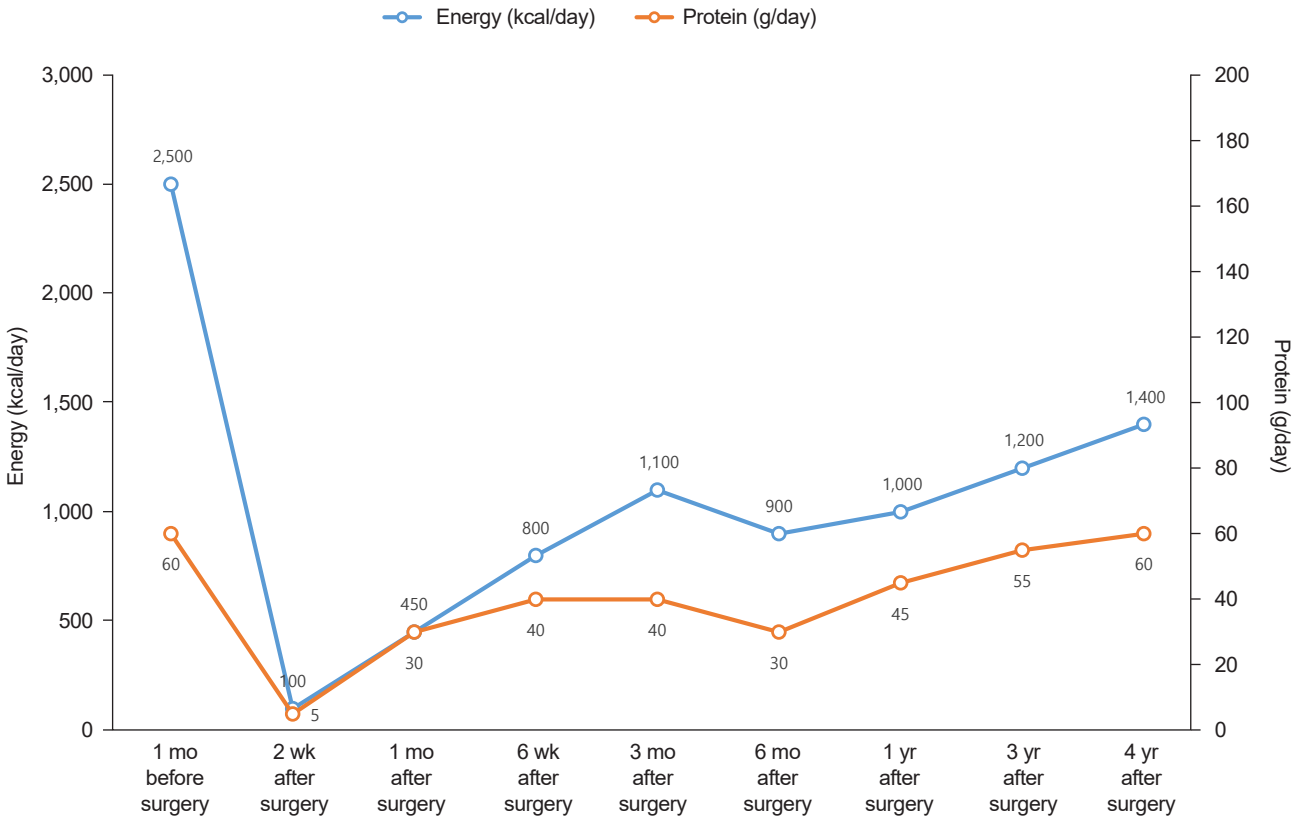

Fig. 2. Changes in energy and protein intake.

Two weeks post-surgery

Two weeks after surgery, the patient presented to the emergency room with dizziness and was admitted for evaluation and management. Following discharge, her reported energy intake was approximately 100 kcal per day due to intolerance to the prescribed liquid diet and limited acceptance of available options. Nutritional counseling was reinforced to emphasize the importance of adherence to the liquid diet during the early postoperative period. Alternative liquid food options were suggested to improve tolerance and caloric intake. The patient was subsequently discharged.

One month post-surgery

One month after surgery, the patient advanced prematurely to a regular diet despite prior instructions to maintain a soft diet. This prompted re-education on appropriate dietary modifications to prevent complications. By the first postoperative month, the patient had achieved a weight loss of 9.0%, approaching the target of 10% total weight loss (TWL).

Six weeks post-surgery

Six weeks after surgery, the patient was adhering to a soft diet and was advised to gradually transition to a regular diet. However, her protein intake was insufficient at 40 g/day. Despite recommendations for protein supplements, she reported poor tolerance related to personal preferences. Consequently, she was counseled to consume soft, protein-rich foods, such as eggs and tofu. Additionally, she was encouraged to initiate regular exercise.

Three months post-surgery

Three months after surgery, the patient reported consuming three meals per day. Each meal included 30 to 40 g of rice and half a serving of protein. Snacks primarily included dairy products and fruits, with occasional consumption of chips or fast food. The estimated daily energy intake was approximately 1,100 kcal. The patient had initiated a routine of walking for 30 minutes daily after lunch. By 3 months after surgery, the patient achieved a TWL of 14.9%, which was below the target of 20%. Accordingly, the patient was advised to reduce snack intake and increase the intensity of physical activity.

Six months post-surgery

Six months after surgery, the patient had increased portion sizes at her three main meals to approximately 100 g of rice and one serving of protein per meal while eliminating all snacks. Consequently, her estimated total daily energy intake decreased to approximately 900 kcal. The patient continued her 30-minute walking regimen. She was advised to maintain the current dietary pattern and exercise routine.

One year post-surgery

One year post-surgery, the patient relocated to Canada, leading to changes in her dietary patterns and physical activity levels. Her typical breakfast included half a bowl of cereal with milk, lunch consisted of half a sandwich, and dinner comprised one to two servings of protein with vegetables. Physical activity included daily 30-minute walks and participation in Taekwondo sessions twice weekly. By the 1-year follow-up, the patient had achieved a TWL of 32.5%, exceeding the target of 30%. She was encouraged to continue her current dietary pattern and exercise regimen.

Three years post-surgery

Three years post-surgery, the patient reported consuming three meals per day, each approximating 1/2 to 1/3 of a standard school meal serving. Additionally, she consumed one to two eggs daily as snacks. The patient participated in supervised personal training sessions two to three times per week, each lasting 1 hour. She was advised to maintain her current dietary and exercise habits.

Four years post-surgery

Four years post-surgery, the patient had increased meal portions to 2/3 of a standard school meal serving per meal and eliminated snacks. She discontinued personal training and instead engaged in walking for approximately 30 minutes after lunch. She was advised to maintain her current dietary pattern and physical activity routine. Over the 4-year postoperative period, the patient achieved a TWL of 57.5 kg, with body weight reducing from 130 to 72.5 kg and BMI decreasing from 42.0 to 23.4 kg/m^2. Despite initial difficulty in adjusting to the post-surgical diet, the patient ultimately established a balanced and sustainable eating pattern. At 1 year after surgery, follow-up assessments demonstrated remission of NASH and IGT, and the menstrual cycle had resumed regularity. The patient developed vitamin D deficiency after surgery. Although supplementation was recommended, she reported frequent nonadherence. Annual bone mineral density assessments were conducted, and all results remained within the normal reference range.

DISCUSSION

In this case study, the patient achieved a TWL of 41.3% and a BMI reduction of 16.6 kg/m^2 by 3 years after surgery, which increased to 18.6 kg/m^2 by the 4th year. These outcomes are consistent with previous research findings. The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, a large multicenter prospective cohort of adolescents undergoing bariatric surgery, reported a mean TWL of 27% over the first 3 years, corresponding to a BMI reduction of 13 kg/m^2 [7]. Similarly, Alqahtani et al. [8] reported a mean BMI reduction of 17.9 kg/m^2 at ≥4 years following sleeve gastrectomy in children and adolescents.

Long-term studies indicate that weight regain occurs in approximately 50% of patients after bariatric surgery [9]. Data from the Teen-LABS cohort suggest that adolescents typically experience a significant weight loss of approximately 30% in the first postoperative year, followed by a gradual and modest weight regain, resulting in a sustained reduction of 22% to 27% at 5 years [10]. In contrast, our patient demonstrated a remarkably stable and progressive weight loss over 4 years. This favorable trajectory appears to be closely related to consistent postoperative follow-up and repeated nutritional counseling, which supported the development of structured eating habits, portion control, and sustained lifestyle modification.

Furthermore, the patient experienced remission of NASH, IGT, and PCOS by the fourth year post-surgery. Previous studies have demonstrated high remission rates for comorbidities such as T2D (90.0%), dyslipidemia (76.6%), hypertension (80.7%), OSA (80.8%), and asthma (92.5%) after at least 5 years of follow-up [11]. These findings highlight the metabolic benefits of bariatric surgery in adolescents and reinforce its role as an effective intervention not only for weight reduction but also for the resolution of obesity-related comorbidities.

Despite these benefits, bariatric surgery is associated with an increased risk of nutritional deficiencies, particularly in adolescent patients. A systematic review and meta-analysis reported postoperative nutrient deficiencies, with prevalence rates of low serum levels of albumin, ferritin, vitamin D, and vitamin B_{12} of 10%, 49%, 41%, and 20%, respectively. Additionally, 23% of adolescents experienced iron deficiency, and 10% developed calcium deficiency [5]. Another study reported that the most common postoperative deficiencies in adolescents were vitamin D (92.3%), albumin (51.8%), anemia (15.9%), zinc (11.1%), and vitamin B_{12} (8.0%)

[12]. Our patient developed vitamin D deficiency post-surgery, whereas other nutritional parameters remained within normal ranges. The etiology of vitamin D deficiency following bariatric surgery is multifactorial and includes preoperative baseline deficiency, inadequate supplementation, and malabsorption related to altered bile salt metabolism, potential intestinal bacterial overgrowth, and the anatomical redirection of the small intestine [13]. Although vitamin D supplementation was recommended by the clinical dietitian, adherence was poor. A previous study reported high rates of nonadherence to vitamin supplementation following adolescent bariatric surgery, with common barriers including forgetfulness and difficulty swallowing pills [14]. Consistent with these findings, our patient also demonstrated poor adherence to pre-surgery weight loss efforts, a liquid diet in the early postoperative phase, and protein and vitamin supplementation. However, with ongoing education and repeated nutritional counseling, the patient ultimately established and maintained a balanced dietary pattern. These observations underscore the importance of ongoing education, close monitoring, and individualized support to improve adherence and achieve long-term success after adolescent bariatric surgery.

This study is limited by its design as a single case report involving only one patient, which limits the generalizability of the findings. Nevertheless, the detailed longitudinal follow-up provides meaningful insight into the nutritional challenges and adherence issues that may emerge at different postoperative stages. Future studies with larger adolescent cohorts, as well as comparative analyses between adolescent and adult populations, are needed to better delineate age-related differences in surgical outcomes, nutritional deficiencies, and optimal postoperative care.

In conclusion, a multidisciplinary approach is essential for adolescents undergoing bariatric surgery. Continuous nutritional management and individualized care are critical to achieving durable weight loss, preventing nutritional deficiencies, and maintaining long-term adherence to postoperative treatment guidelines.

ARTICLE INFORMATION

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Conceptualization: YY, HL, SMA. Data curation: YY. Investigation: YY. Visualization: YY. Writing–original draft: YY. Writing–review & editing: YY, HL, SMA. All authors read and approved the final manuscript.

Conflicts of interest

Hosun Lee is an editorial board member of this journal, but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Data availability

Data of this research are available from the corresponding author upon reasonable request.

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Case Report

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CLINICAL NUTRITION RESEARCH

Reversing 20 years of diabetes using the carnivore diet in India: a case report

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Diabetes has been well established as one of the deadliest chronic diseases globally. Currently, India is known as the diabetes capital of the world although this disease had been documented in the country for centuries. Current treatment strategies center around oral hypoglycemic drugs, insulin, and the standard 'diabetic diet.' Nonetheless, millions continued to suffer from this chronic disease and its multiple complications. We herein present a case involving a male patient suffering from diabetes for 20 years despite being on medications and a diabetic diet who finally achieved remission of diabetes and hypertension by removing carbohydrates and following a carnivore diet.

Keywords: Type 2 diabetes mellitus; Carbohydrate-restricted diet; Hypertension; Remission induction; Case reports

INTRODUCTION

Diabetes mellitus (DM) is one of the most dangerous chronic noncommunicable diseases, with millions across the globe suffering from its complications. Type 2 DM accounts for almost 95% of all DM cases. Estimates have shown that 588.7 million people (age, 20–79 years) were found to be suffering from DM in 2024. Currently, India ranks second behind China in terms of the number of people with DM, with 89.8 million cases having been documented [1]. Contrary to popular belief, westernization did not cause the emergence of DM in India, considering that this condition had already existed within the country. In fact, two of the first physicians of India, namely Charakha and Sushruta, had described DM in 300 to 400 AD [2]. Osler [3], in his book, described DM as a syndrome caused by a disturbance in carbohydrate metabolism due to various causes, one of which being excess carbohydrate intake. His treatment recommendation was to wean off carbohydrates and place patients on a diet containing 200 g of protein and 135 g of fats, which is akin to a very low carbohydrate ketogenic diet in modern times. In as early as 1797, Rollo [4] revealed that restricting carbohydrates and increasing meat consumption resolved glycosuria in two of his patients.

The American Diabetes Association has focused on glucose lowering drugs while appropriately recommending the reduction of overall carbohydrate consumption. However, they do promote the consumption of fruits, grains, legumes, low fat meat, and dairy, which is counterproductive [5]. Accordingly, low carbohydrate (< 130 g/day) and ketogenic diets (< 50 g/day) have reentered discussions and are being advocated by clinicians and physicians worldwide [6]. A "carnivore diet," which has been touted as the most potent ketogenic diet, eliminates all plant foods and contains high fat, moderate protein, and negligible carbohydrates, which

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emulates diets historically prescribed by Osler [3], Rollo [4], and Newiss [7].

We herein present a case involving a 58-year-old male patient who presented to our department with chronic diabetes for 20 years and a diagnosis of renal cell carcinoma. He was advised to be put on insulin to which he did not consent. We put him on a carnivore diet which led to reversal of his diabetes and hypertension in approximately 4 months.

Ethics statement

Written informed consent was obtained from the family for publication of this case report.

CASE REPORT

A 58-year-old male patient suffering from type 2 DM and hypertension for 20 years visited our department in January 2024 asking for assistance after being advised to start insulin therapy and dialysis. All available records for the last 20 years were reviewed. The patient did not smoke and occasionally consumed alcohol.

His father had suffered from a brain hemorrhage, whereas his mother died due to a sudden cardiac arrest. He had been diagnosed with type 2 DM in May 2004 at 39 years of age with an hemoglobin A1c (HbA1c) of 7%. At this time, he was normotensive with a blood pressure of 110/70 mmHg. His fasting blood sugar (FBS) and postprandial (PP) blood sugar levels were 157 and 150 mg/dL, respectively. His triglyceride (TG)/high-density lipoprotein (HDL) ratio was marginally elevated at 2.90, while his low-density lipoprotein was 137 mg/dL. The patient was initiated on oral metformin (sustained release) before dinner and oral repaglinide (1 mg) three times a day before meals. He was also placed on rosuvastatin (10 mg orally) once daily. The patient, who was an avid golfer, was also advised to continue exercising and consume a diabetic diet. In particular, the patient was advised to consume eight meals a day, which amounted to approximately 260 g of carbohydrates, 74 g of protein, and 63 g of fat.

In June of 2008, a routine checkup reached an HbA1c of 9.0%, FBS of 240 mg/dL, PP blood sugar of 282 mg/dL, and TG/HDL ratio of 4.62. His ultrasound examination also suggested a fatty liver. As such, he was advised to continue the diet and exercise. However, his medications were changed to a combination tablet of metformin (500 mg) and glimepiride (2 mg) twice a day along with oral ramipril (2.5 mg) once daily and a combination capsule of atorvastatin (10 mg) and aspirin (150 mg) once before bedtime.

In August of 2008, he was admitted due to severe back and chest pain and was investigated for a suspected acute coronary syndrome. At discharge, he was diagnosed with uncontrolled DM, dyslipidemia, and severe myalgia. He had an HbA1c of 9.3%, creatine phosphokinase of 445 IU/L (range, 38–174 IU/L), and a TG/HDL ratio of 7.44. He was discharged on oral glimepiride (2 mg) twice daily, metformin (1 g twice daily), and a combination of atorvastatin (10 mg) and aspirin (150 mg) once after dinner. Moreover, he was advised to continue with the conventional diabetic diet.

A routine checkup in January 2011 revealed an FBS of 180 mg/dL, HbA1c of 11.3%, total cholesterol of 218 mg/dL, TG/HDL ratio of 3.64, and low-density lipoprotein of 142 mg/dL. His treadmill test came back negative, and electrocardiography showed normal findings. He was then prescribed a combination drug of metformin (1,000 mg) and glimepiride (2 mg prolonged release) twice daily, saxagliptin (5 mg) once daily, rosuvastatin (10 mg) once before sleeping, and ramipril (2.5 mg) once daily. In March 2011, the patient had a follow-up HbA1c of 8.7% and was advised to continue the same medications along with the diabetic diet.

On the next follow-up in January of 2013 at 47 years of age, he had an HbA1c of 8.9%, microalbuminuria, and fatty liver. He was also diagnosed with early cataract and diabetic retinopathy. The patient was then prescribed glimepiride (4 mg) once before breakfast, metformin (1,000 mg) twice a day, saxagliptin (5 mg) once a day, ramipril (2.5 mg) once daily, and rosuvastatin (10 mg) once daily and was advised to continue with the diabetic diet similar to previous visits.

On his next follow-up in April 2014, he had a PP blood sugar of 293 mg/dL, an HbA1c of 8.7%, and a TG/HDL ratio of 1.4. He was also diagnosed with hypertension, with a blood pressure of 150/90 mmHg. Kidney function and liver function tests were within normal limits. He was advised to continue the diabetic diet and increase walking. The patient was now prescribed glimepiride (4 mg) before breakfast and dinner, a combination of metformin (1 g) and sitagliptin (50 mg) before breakfast and dinner, and pioglitazone (15 mg) before dinner on alternate days. He was also advised to increase ramipril to 5 mg and continue with rosuvastatin (10 mg).

A follow-up with his cardiologist in May 2018 revealed a BP of 146/94 mmHg, pulse rate of 80/min, and normal systemic examination results. He had an FBS of 135 mg/dL, HbA1c of 7.5%, serum creatinine of 0.84 mg/dL, TG/HDL ratio of 1.55, and grade 1 prostatomegaly. He was advised to continue ramipril (5 mg) and rosuvastatin (10 mg), as well as continued with all other oral hypoglycemic agents as previously prescribed.

On June 3, 2021, the patient went to his next follow-up, which revealed a BP of 136/86 mmHg, pulse rate of 74/min, and FBS of 134 mg/dL. During this visit, he was found to have chronic kidney disease with a serum creatinine of 1.33, estimated glomerular filtration rate (eGFR) of 55 mL/min/1.73 m^2, and HbA1c of 12.2%. He was then prescribed ramipril (10 mg) before breakfast, cilnidipine (10 mg) after dinner, metformin (1 g) twice daily with meals, a combination of empagliflozin (25 mg) and linagliptin (5 mg) before breakfast, gliclazide (60 mg) once before breakfast, and rosuvastatin (10 mg) after dinner. He was planned for insulin therapy at a later date and was advised to strictly consume a diabetic diet. A month thereafter, blood tests revealed an HbA1c of 10.7%, serum creatinine of 1.2 mg/dL, and TG/HDL ratio of 5.66. A combination of hydrochlorothiazide (12.5 mg) and ramipril (10 mg) in place of a single ramipril was then added to his prescription. By September 2021, his HbA1c was 6.9%, and he was advised to continue with the previous prescription.

In 2022, the patient underwent cataract surgery on both eyes. In December 2023, blood tests revealed an FBS of 130 mg/dL, PP blood sugar of 180 mg/dL, HbA1c of 8%, hemoglobin of 9.6 g/dL, TG/HDL ratio of 1.88, serum creatinine of 1.9 mg/dL, and eGFR of 39 mL/min/1.73 m^2. His prescription was revised to gliclazide (30 mg) once a day, with the rest remaining the same as that in 2021. He was further diagnosed with chronic kidney disease and was advised visit a nephrologist. His medications were continued as documented in Table 1.

On January 11, 2024, the patient was diagnosed with stage 4 chronic kidney disease with serum creatinine of 2.1 mg/dL, serum urea of 60.3 mg/dL, eGFR of 35.8 mL/min/1.73m^2, and an HbA1c of 7.7%. He was advised to immediately undergo dialysis and was prescribed oral megestrol (160 mg). After his gliclazide dose was increased to 6 mg once a day, he was advised to continue with the combination of empagliflozin (25 mg) and linagliptin (5 mg) and was prescribed long-acting insulin subcutaneously once a day. He was also advised to undergo abdominal ultrasound.

The patient then contacted us on January 12, 2024 as he was reluctant to receive insulin therapy and was not interested in dialysis. Thereafter, we placed him on no carbohydrate carnivore diet comprising nutrient dense foods, with the goal of getting at least 1 g/kg/day of proteins and double the fat. No restrictions were placed on the type of meat consumed. The patient was given the choice of consuming eggs, chicken, mutton, buffalo meat, pork, fatty fish, and prawns. No seed oils were to be used for cooking. Rather, the food had to be cooked in ghee, butter, tallow, or virgin coconut oil. Eggs could be prepared in any way that the patient preferred. Other meats could be minced, in-bone, boneless, ribs, chops, etc. He was advised to track his daily macronutrient intake using a mobile application. No portion control was advised; rather, he was asked to eat ad libitum until satiety. Daily FBS and blood pressure charts were logged onto a shared Excel sheet daily, which was then monitored by us and his sons. Aside from monthly HbA1c assessments, regular follow-up examinations with his primary physician were maintained. The patient also incorporated intermittent fasting and was advised to respond to hunger signals. During this period, he also attempted 24-hour fasts.

From mid-January to April 2024, the patient's average FBS was 100 mg/dL, ranging from 76 to 136 mg/dL. Throughout the whole of April 2024, he had an average FBS of 96 mg/dL, ranging from 76 mg/dL to 110 mg/dL. His average blood pressure from March through April 2024 (blood pressure records from home were not available for previous months) was 125/87 mmHg.

His HbA1c fell from 6.9% from the end of January 2024 to 5.4% by the end of April 2024. His fasting insulin also remained low, ranging from 4.21 to 2.48 mIU/L. His average serum creatinine from February to July 2024 was 1.99 mg/dL, whereas his average serum urea was 76.78 mg/dL. His eGFR by Epidemiology Collaboration (EPI) increased from 28.34 to 40 mL/min/1.73 m^2 (Table 2). In the March of 2024, the patient tapered medications based on self-monitored glucose and blood pressure logs under remote physician supervision. In May 2024, the patient's primary physician (endocrinologist) discontinued all oral hypoglycemic and anti-hypertensive medications, suggesting that the patient had achieved remission from DM and hypertension and did not require further medications for the same.

Unfortunately, ultrasound examination on January 13 suggested an enlarged left kidney with a subtle increase in bilateral renal parenchymal echogenicity along with a large well circumscribed heterogenous, mass lesion involving the lower pole of the posterior cortex of the left kidney with areas of necrosis within the mass. This finding was suggestive of a renal cell carcinoma, which was subsequently confirmed with a positron emission tomography on January 16, with metastasis to the left psoas muscle; right paratracheal, precarinal, pretracheal, right hilar, and left hilar lymph nodes, and both lung fields.

He then underwent palliative immunotherapy in January 2024 with pembrolizumab and radical nephrectomy in June 2024. Thereafter, he underwent radiation therapy for spinal metastasis and was started on a sequence of treatments, including axitinib, everolimus combined with lenvatinib, denosumab (Xgeva), sunitinib (Sutent), and bevacizumab, which continued until March

Table 1. Laboratory values and medications before sought help from our institution

Date	FBS (mg/dL)	PP (mg/dL)	HbA1c (%)	TG/HDL ratio	Medication
May 2004	157	150	7.0	2.90	Metformin Repaglinide Rosuvastatin
June 2008	240	282	9.0	4.62	Metformin Glimepiride Ramipril Aspirin+atorvastatin
August 2008	NA	NA	9.3	7.44	Metformin Glimepiride Aspirin+atorvastatin
January 2011	180	NA	11.3	3.64	Metformin Glimepiride Saxagliptin Rosuvastatin Ramipril
March 2011	NA	NA	8.7	NA	Metformin Glimepiride Saxagliptin Rosuvastatin Ramipril
January 2013	NA	NA	8.9	Check	Metformin Glimepiride Saxagliptin Rosuvastatin Ramipril
April 2014	NA	293	8.7	1.40	Glimepiride Metformin+sitagliptin Pioglitazone Ramipril Rosuvastatin
May 2018	135	NA	7.5	1.55	Glimepiride Metformin+sitagliptin Pioglitazone Ramipril Rosuvastatin
June 2021	134	NA	12.2	NA	Metformin Empagliflozin+linagliptin Gliclazide Cilnidipine Ramipril Rosuvastatin
July 2021	NA	NA	10.7	5.66	Hydrochlorothiazide+ramipril Metformin Empagliflozin+linagliptin Gliclazide Cilnidipine Rosuvastatin
September 2021	NA	NA	6.9	NA	Hydrochlorothiazide+ramipril Metformin Empagliflozin+linagliptin Gliclazide Cilnidipine Rosuvastatin
December 2023	130	180	8.0	1.88	Hydrochlorothiazide+ramipril Metformin Empagliflozin+linagliptin Gliclazide Cilnidipine Rosuvastatin

FBS, fasting blood sugar; PP, postprandial; HbA1c, hemoglobin A1c; TG, triglyceride; HDL, high-density lipoprotein; NA, not available.

Table 2. Blood test results while on the carnivore diet

Date	HbA1c (%)	FBS (mg/dL)	Urea (mg/dL)	Creatinine (mg/dL)	Fasting insulin (mIU/L)	eGFR by EPI (mL/min/1.73 m^2)
January 29, 2024	6.9	100	77.00	2.36	NA	28.34
February 4, 2024	6.3	94	64.91	2.08	4.21	34.00
March 22, 2024	5.1	114	86.14	1.83	3.74	40.00
April 15, 2024	5.4	97	74.15	1.86	2.48	39.00
July 10, 2024	5.5	92	81.73	1.82	NA	40.00

HbA1c, hemoglobin A1c; FBS, fasting blood sugar; eGFR, estimated glomerular filtration rate; EPI, Epidemiology Collaboration; NA, record not available.

2025. The patient suffered an intestinal obstruction with perforation in March 2025 due to intestinal metastasis and succumbed to the complications. The patient continued with the carnivore diet and maintained remission of his DM and hypertension until his demise.

DISCUSSION

No reports from India have shown remission from DM and hypertension using the carnivore diet. Type 2 DM has been well known as a disease associated with carbohydrate overconsumption [8,9]. The diabetic diet our patient was advised to consume was very high in carbohydrates and was obviously counterproductive. This case highlights the inefficacy of standard diabetic diets in reversing DM. The patient suffered from various complications of DM throughout the years, such as early onset retinopathy, cataract, kidney disease, and renal cell carcinoma.

Ketogenic and very low carbohydrate (< 50 g of carbohydrates/day) diets have been shown to be effective in reversing DM [10]. In fact, the Prospective Urban Rural Epidemiology study highlighted a significant association between high carbohydrate intake and mortality, whereas higher intake of fats was associated with lower mortality [11]. Unwin et al. [12] found that patients with DM who selected a low carbohydrate diet achieved a 77% remission rate in < 1 year. Moreover, a randomized study by Saslow et al. [13] reported greater HbA1c reductions in the very low carbohydrate group compared to the moderate carbohydrate, calorie restricted, low fat groups. Furthermore, Kelly et al. [6] recommended early deprescription of DM medications, such as insulin, sulphonylureas, and sodium-glucose cotransporter inhibitors. In line with this recommendation, our patient was similarly tapered off his medications in approximately 3 months.

Ketogenic diets have been shown to ameliorate schizophrenia, reverse metabolic dysfunction-associated liver disease, reduce behaviors related to autism, promote pleitrophic effects to positively influence the cardiovascular systems, provide therapeutic benefits against cancer, and treat epilepsy [7,14-18].

Carnivore diets, however, have yet to be extensively studied. Norwitz et al. [19] reported a series involving 10 patients with inflammatory bowel disease who showed a positive clinical response to mostly carnivore diets. In another series, patients suffering from anorexia not responding to standard treatment achieved 1 to 5 years of remission, weight gain, reduced anxiety, and improved mental well-being while on an animal-based ketogenic diet [20]. Another study involving 2,029 respondents consuming a carnivore diet (> 85% animal products daily) for 14 months reported reductions in median HbA1c, body mass index, and diabetes medication use [21]. A recent meta-analysis of randomized trials reported that carbohydrate restricted diets significantly improved glycemic control, decreased hepatic stress, and increased renal function particularly in females, obese people, and those suffering from type 2 DM. In fact, replacing carbohydrates with a combination of fats and protein yielded even better outcomes [22].

The success of any diet or lifestyle change depends on adherence and consistency. Our patient showed consistent efforts to stay on the carnivore diet. Reversing diabetes and hypertension for 20 years only added to his motivation. Research suggests that the carnivore diet may induce some B vitamin and vitamin C deficiencies, but the requirements for the same is reduced for people who are on this diet [23]. Another interesting finding in our case was the lack of a drastic deterioration in kidney function while on a high fat and protein diet, which contradicts beliefs that higher protein diets decrease renal function.

Unique aspects

India has a largely carbohydrate-consuming population. In their recent INDIAB survey, Anjana et al. [24] reported that most Indians consuming 64% of their daily calories from carbohydrates, with 83% of the participants having at least one metabolic risk factor. To the best of our knowledge this has been the first case from India reporting complete remission of longstanding DM and hypertension using a high fat and moderate protein carnivore diet. No major renal impairments occurred while on this diet. In fact,

we noticed an improvement in the patient's eGFR. This finding is consistent with studies reporting that high intake of dietary protein had no detrimental effects on eGFR [22,25,26]. The remission of DM and hypertension in our patient was maintained despite concurrent management of the renal cell carcinoma, suggesting that the diet positively affected metabolic parameters but not cancer progression.

We acknowledge that the long-term safety profile of the diet remains unknown. Given that this report involves a single case, no generalizations can be established. As such, further studies are needed to clarify whether a nutrient dense carnivore diet can be a potent and safe strategy for the remission of DM. Overall, we believe that physicians and nutritionists alike should be more prudent when treating patients with DM and recommend the complete elimination of carbohydrates.

ARTICLE INFORMATION

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Authors' contributions
All the work was done by Ankur Verma.

Conflicts of interest
None.

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None.

Data availability
Data of this research are available from the corresponding author upon reasonable request.

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Instructions for authors

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Recently revised on January 1, 2026

CLINICAL NUTRITION RESEARCH

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Clinical Nutrition Research (CNR), launched in 2012, is the official, open-access, peer-reviewed journal of the Korean Society of Clinical Nutrition. CNR is dedicated to advancing human health and nutrition by disseminating high-quality research that supports clinical application and promotes education in nutrition care. The journal features original articles, reviews, case reports, and research notes related to the field of clinical nutrition, human nutrition, and public health nutrition. It is published quarterly on the last day of January, April, July, and October.

Manuscripts should adhere to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, issued by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/), unless otherwise specified.

1. ARTICLE PROCESSING CHARGE

There are no author submission fees or other publication-related charges. All costs for the publication process are supported by the Korean Society of Clinical Nutrition.

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It is available at https://e-cnr.org/policy/ethics.php.

3. PUBLISHING POLICIES

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4. COPYRIGHT AND OPEN ACCESS

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5. MANUSCRIPT PREPARATION

A. General requirements

· Language: Manuscripts must be written in English.
· Template-based submission: Authors must use the official journal template for all submissions. All formatting requirements are pre-applied to the template file, which can be downloaded from the journal website (https://e-cnr.org/authors/authors.php).
· Cover letter: The cover letter must confirm that all authors approved the final manuscript, that the work is original and not under review elsewhere, and disclose any potential conflicts of interest. It should include the corresponding author's contact information and authorship statements when co-first or co-corresponding authors are listed. Authors must also suggest at least three qualified reviewers. A completed checklist must accompany the cover letter.
· Submission materials: Include a cover letter, the manuscript components (including the title page, abstract, main text, references, and table/figure legends), tables, and figures.
· Anonymization: Submit the title page and manuscript as separate files. The manuscript must be anonymized for double-blind peer review; do not include authors' names or affiliations.
· Units: Use Arabic numerals for amounts and include a space between the number and unit, except when the number is expressed as % or °.
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gy), and the Celsius scale (°C) should be used for temperature.

- Abbreviations: When the term is mentioned for the first time, it should be spelled out completely first, then followed by the abbreviation in parentheses. Thereafter, only the abbreviation should be used. Commonly used abbreviations need not be defined.
- Use of generative artificial intelligence (AI)-assisted technologies: CNR has adopted policies, as specified by the ICMJE, regarding the use of generative AI platforms assisted technologies in the preparation of materials intended for publication in the journal as outlined below:
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- Information not explicitly covered in these criteria must be followed by the decisions of the editorial board.

B. Reporting guidelines

For specific study designs, such as randomized controlled trials, diagnostic accuracy studies, meta-analyses, observational studies, and non-randomized studies, authors should follow the relevant reporting guidelines. Recommended sources include the EQUATOR Network (https://www.equator-network.org/) and the National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html). CNR requires compliance with the reporting guidelines summarized in **Table 1** for the listed article types.

Table 1. Reporting guidelines for specific study designs

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	https://www.equator-network.org/reporting-guidelines/consort/
TREND	Non-randomized controlled studies	https://www.cdc.gov/hivpartners/php/trend-statement/index.html
STROBE	Observational studies	https://www.equator-network.org/reporting-guidelines/strobe/
STARD	Diagnostic/prognostic studies	https://www.equator-network.org/reporting-guidelines/stard/
PRISMA	Systematic reviews and meta-analyses	https://www.equator-network.org/reporting-guidelines/prisma/
CARE	Case reports	https://www.equator-network.org/reporting-guidelines/care/

C. Article type

CNR publishes four categories of publications: original articles, reviews, case reports, and research notes. Other publication types are negotiable with editorial office.

• Original articles

Organize your manuscript file as follows:

Title page: upload separately

Manuscript file: (1) abstract & keywords, (2) main text, (3) references, (4) tables, (5) figure legends (upload figures in separate files)

Supplementary materials: upload separately

Title page

This section should include the type of manuscript; manuscript title; running title; full names and affiliations of all authors; full name of institutional affiliation, postal address, and email of the corresponding author; ORCID; authors' contributions; any conflict of interest; any financial assistance; data availability; and acknowledgments.

Title: The title should be a single declarative statement that is brief, informative, and focused on the results presented in the manuscript. It should have the first letter of each major word capitalized, including prepositions and conjunctions of four letters or more.

Running title: Less than 50 characters

Author names: Names of authors should be given in full without abbreviation. In the listing of author names, any degree or professional title, such as MD or PhD, should not be included.

Affiliations: Departments and institutions of the authors. If from multiple institutions, use superscript numbers (1, 2, 3, etc.) to indicate specific affiliations.

Corresponding author: Full name, institutional affiliation, postal address, and email address.

Co-first authors and co-corresponding authors may be designated when applicable. Such designations must be explicitly stated on the title page and reflected consistently throughout the manuscript and submission system. When more than two co-first authors or co-corresponding authors are designated, an appropriate authorship statement should be provided.

ORCID: Providing ORCIDs for all authors is recommended (https://orcid.org/).

Authors' contributions: Describe contributions using the Contributor Roles Taxonomy (CRediT; https://credit.niso.org/). Contributors must meet at least one core role (conceptualization, methodology, software, validation, formal analysis, investigation, data curation) and one writing role (original draft preparation, review, and editing). Authors who do not meet these requirements will not qualify for authorship.

Conflicts of interest: Disclose any potential conflicts of interest, including employment, consultancy, ownership, or close relationships with organizations affected by the manuscript.

Funding: Funding for the research should be detailed here. Provision of a FundRef ID is recommended, including the name of the funding agency, country, and (if available) the number of the grant provided by the funding agency. If the funding agency lacks a FundRef ID, please ask that agency to contact the FundRef registry (email: fundref.registry@crossref.org).

Data availability: Include a statement indicating where the data supporting the article's results can be found, with hyperlinks to publicly archived datasets if applicable.

Data sharing: Based on the ICMJE recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf), all manuscripts reporting the results of clinical trials should submit a data sharing statement to fulfill the ICMJE guidelines after February 25, 2019.

Acknowledgments: List individuals who contributed to the work but do not meet authorship criteria, and specify their contributions (e.g., technical assistance, data collection, analysis, or editorial support). Disclose any writing assistance and the entity that funded it.

Supplementary materials: Supplemental material refers to files related to a specific article, provided by the authors for publication alongside their article. These materials typically include additional content that could not be included in the print version, such as appendices or extra tables. All supplemental materials will be available online alongside the full-text article. Include a listing of supplementary materials at the end of the manuscript file, and ensure they are cited consecutively in the text of the manuscript

Abstract & keywords

Abstract: For original articles, provide a structured abstract of less than 250 words with the following headings: Objective, Methods, Results, and Conclusion.

Keywords: Two to five keywords must be prepared at the bottom of the abstract. Using the medical terminology from Index Medicus (MeSH; https://www.nlm.nih.gov/mesh/) is recommended. If there is no appropriate match to a new concept at present, the authors can use their choice of expression.

Main text

The main text of an original article should contain the following subheadings: Introduction, Methods, Results, and Discussion consisting of no more than 5,000 words (excluding the Abstract, References, Table and Figure legends).

Introduction: The background of the study and its objective must be stated clearly in the Introduction. Describe pertinent findings of others and include the specific questions addressed by the investigation.

Methods: Methods should be written in detail, and the statistics used for data analysis must be indicated as well. For a more specific description, refer to the specific reporting guidelines corre-

sponding to the study design (**Table 1**).

Ethics statement: For studies involving human participants or human-derived materials, include the institutional review board (IRB) approval number and a statement of informed consent from all participants. For animal studies, describe adherence to national or institutional research committee guidelines. If an IRB number is not available, consult the editor.

Study design: Specify the study design (e.g., descriptive analysis, randomized controlled trial, cohort study, case-control study, or meta-analysis).

Materials and/or participants: Provide sufficient detail on the materials used to enable reproducibility. For purchased materials, list the source or manufacturer. Describe research participants with relevant characteristics such as age, sex, region, school, country, intervention period, or occupation. Explain the inclusion criteria, reasons for participant selection, and reasons for excluding particular groups. Non-English questionnaires may be submitted as supplementary materials.

Methods: Refer to appropriate reporting guidelines when describing analytic methods. Cite established methods with references and indicate any modifications. Describe novel methods in sufficient detail for replication. If necessary, provide complex statistical analyses in the supplementary materials. Clearly describe the duration of observation, survey, intervention, analysis, or follow-up.

Statistical analysis: Describe the statistical analyses in sufficient detail to allow replication. Specify the software used, including the program name, manufacturer, and version. Report measurement error or uncertainty, such as confidence intervals, in addition to P-values.

Reporting of Sex, Gender, Race, and Ethnicity: Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results: Results must be presented in the same logical sequence of tables and figures in the text. Do not repeat the results in the text when they are explained in detail through the tables and figures. Emphasize or summarize important observations at the end of this section.

Discussion: Discussion should emphasize concisely the novel and important aspects of the study and avoid unrelated references and statements. The summary and conclusion should be brief, written in the context of the research purpose.

References

All references should be listed in the order of citation in the text, with corresponding numbers. The reference limits are 30 for original articles, 50 for review articles, and 15 for case reports and research notes.

- Identify references in the main text by listed Arabic numerals in brackets and numbered in consecutive order, as they appear in the main text. Use "-" when there are more than 3 references to be cited; for example, [4-7].
- List all authors' names for a reference with up to 6 authors; list first 3 authors' names followed by 'et al.' if more than 6 authors.
- Use the abbreviated journal title according to MEDLINE, available at https://www.ncbi.nlm.nih.gov/journals. For example, "Clinical Nutrition Research" should be written as Clin Nutr Res. Other types of references not described below should follow Citing medicine: the NLM style guide for authors, editors, and publishers (https://www.ncbi.nlm.nih.gov/books/NBK7256/).

Journal articles

1. Jung DH, Moon G, Lee CK, et al. Changes in nutritional status through low-lactose processed milk consumption in Korean adults with lactose intolerance. Clin Nutr Res 2025;14:30-40.
2. Gard CN, Freigeh GE, Janssen EM. Allergic manifestations of actinopathies: a review. J Allergy Clin Immunol 2025;156:1456-64.
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Entire book and book chapter

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Abstract or supplement

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Online sources

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Tables and Figures

The total number of tables and figures should not exceed 6 for original and review articles, and 2 each for case reports and research notes.

Tables

Each table should begin on a new page, with the table number and title above the table and explanatory notes below. Table numbers must correspond to the order in which they are cited in the main text. Tables should be self-explanatory, and the data presented should not be duplicated in the main text or figures.

- For footnotes, use lowercase letters followed by a parenthesis in alphabetical order: [a), b) ,c)], etc or asterisks (*) for statistical significance.
- Avoid unnecessary longitudinal lines.
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Figures

- Color and grayscale images should be at least 300 dpi. Line drawings must be high-quality black on white graphics.
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Review articles focus on a specific topic and may include theoretical perspectives, critical summaries, or updates on current knowledge. Reviews are usually invited by the editors and should have a main text of 5,000–8,000 words, excluding the abstract, keywords, references, tables, and figures. The unstructured abstract should not exceed 250 words. The number of references is limited to 50, and the total number of tables and figures should not exceed 6. However, systematic reviews should be accompanied by a structured abstract, and up to 100 references are permitted.

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Research notes should be 2,000–5,000 words in length, excluding abstract, keywords, main text, references, tables, and figures. The abstract should be no more than 250 words. The number of references is limited to 15, and the number of tables and figures should not exceed 2 each.

Table 2 summarizes each publication type's key features and word count limit.

Table 2. Key features and word count limits of publication type[a)]

Type of article	Abstract (words)	Text (words)	References	Tables and figures
Original article	Structured, 250	5,000	30	6 in total
Review article[b)]	Unstructured, 250	5,000–8,000	50	6 in total
Case report	Unstructured, 250	3,000	15	2 (for each)
Research Note	Unstructured, 200	2,000–5,000	15	2 (for each)

[a)]The limits on word count, references, tables, and figures may be exceeded at the discretion of the editor in chief when justified; [b)]Systematic reviews should be accompanied by a structured abstract, and up to 100 references are permitted.

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CLINICAL NUTRITION RESEARCH

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☐ Research has been approved by appropriate human subjects research review boards, which are named in the text of the manuscript.
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