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FULL COMMUNICATION

Whey Protein Supplementation Improves Nutritional Status, Glutathione Levels, and Immune Function in Cancer Patients: A Randomized, Double-Blind Controlled Trial

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ABSTRACT Clinical side effects from medical therapy play an important role in causing malnutrition among cancer patients. Whey protein isolates (WPIs) have the potential to improve the nutritional status of cancer patients. The present study determined the effects of whey protein supplementation on nutritional status, glutathione (GSH) levels, immunity, and inflammatory markers in cancer patients in Thailand. A total of 42 cancer patients (41–63 years old) who received intravenous chemotherapy were randomized in a double-blind controlled trial at the National Cancer Institute in Thailand. Patients received 40 g of WPI plus zinc and selenium (intervention group, $n = 23$) or a maltodextrin oral snack (control group, $n = 19$) every day during the daytime for 12 weeks. Nutritional status, GSH levels, immunity, and inflammatory markers were assessed at baseline, 6, and 12 weeks. Whey protein supplementation significantly increased albumin (2.9%) and immunoglobulin G (4.8%) levels compared to the control group at week 12. Controls showed a significantly lower percent change in GSH levels (6.0%), whereas there was a significant time-dependent increase in the intervention group (11.7%). Whey protein supplementation improved nutrition status scores in the intervention group compared to the control. These data indicate that whey protein supplementation can increase GSH levels and improve nutritional status and immunity in cancer patients undergoing chemotherapy. These results will facilitate implementation of malnutrition risk prevention strategies and improve protein status, including immune function, during chemotherapy.

KEYWORDS: • ***albumin*** • ***cancer*** • ***glutathione*** • ***immunity*** • ***whey protein***

INTRODUCTION

CANCER IS A LEADING CAUSE OF DEATH in Thailand. The number of cancer cases has increased from 94.8 to 112.8 per 100,000 people from 2011 to 2015.[1] Importantly, cancer treatments are known to cause serious malnutrition issues.[2] Gastrointestinal symptoms experienced by cancer patients, such as loss of appetite, nausea, vomiting, bloating, constipation, and diarrhea, are related to inadequate energy and protein intake, which is the main cause of malnutrition.[2–4] Thus, nutritional therapy should be applied together with medication to alleviate chemotherapy-related malnutrition, and a high energy and protein diet is recommended for cancer patients by the American Society for Parenteral and Enteral Nutrition.[5]

Whey protein isolate (WPI) is an alternative oral nutrition supplement (ONS) that is suitable for cancer patients due to its lactose- and fat-free composition, high quality of protein with excellent amino acid profiles, and high digestability.[6] The benefits of WPI have been shown to include immune system support,[7] improved muscle strength and synthesis, and improved metabolism.[6,7] In terms of immune support, WPI may increase GSH function because cysteine-enriched supplementation can lessen oxidative radical formation and prevent infection.[8]

Trace elements, such as zinc (Zn) and selenium (Se), are key nutrients related to cell membrane protection. Zn is a cofactor of glutathione peroxidase and superoxide dismutase enzymes, both of which have the ability to scavenge free radicals and eliminate oxidants, such as hydrogen peroxide.[7,9] Furthermore, Se can interact with vitamin E and provide antiaging properties by acting as a cellular booster.[10] Thus, WPI enriched with Zn and Se improves cell-mediated immunity and antioxidant capacity, which would be beneficial for cancer patients undergoing chemotherapy.

However, there is a limited amount of research, especially human trials, on the beneficial effect of WPI supplements in cancer patients. Therefore, the purpose of the present study was to determine the effect of supplementation with WPI enriched with Zn and Se on the nutritional status, GSH level, immunity, and inflammatory status in cancer patients who are undergoing chemotherapy in Thailand.

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MATERIALS AND METHODS

Patients and treatments

Forty-eight[11] cancer patients (20–65 years old) receiving intravenous chemotherapy at the National Cancer Institute of Thailand were included in this randomized, double-blind controlled trial. All patients provided written informed consent before study inclusion and agreed to follow the study protocol. All participants were diagnosed by an oncologist as cancer patients without metastatic diseases and able to communicate in Thai. In addition, all patients received their first or second cycle of intravenous chemotherapy without complications and did not plan to have surgery, radiation therapy, or concurrent therapy. Patients were ineligible to take part if they were pregnant or lactating, had underlying kidney or liver diseases, cardiovascular problems, or progression of metastases. Patients who were unable to drink the ONS and/or used herbal medicine or dietary adjuvants, especially those containing whey protein, were also excluded.

Patients were enrolled and randomly assigned using a computer program to the intervention or control group. The intervention group ($n=24$) received 40 g of supplement containing WPI[12] with Zn (2.64 mg/day) and Se (0.76 mg/day), while the control group ($n=24$) was provided with 40 g of placebo (maltodextrin) as a daytime snack. The compositions of supplement are presented in Table 1. The intervention and control groups received the same amount of calories (160 calories) in their snacks, which were provided once a day for 12 weeks, and both types of ONS were similar in texture, color, flavor, and odor. Neither daily overall caloric intake nor protein intake was controlled because we wished to have patients continue their daily lifestyle and dietary patterns. The daily energy intake at baseline for the control and intervention groups was 1144 and 1075 kcal/day, respectively, and after implementation was 1118 and 1265 kcal/day, respectively; baseline protein intake for control and intervention groups was 53 and 48 g/day, respectively, and 63 g (1.06 g/average body weight/day) and 100 g (1.6 g/average body weight/day), respectively, after implementation. Research assistants visited participants to explain the details of this project and measure participant weight, percent body fat, and muscle mass. Ethical approval for the present study was granted by the Ethics Review Committee for Human Research of the National Cancer Institute of Thailand (135_2015RC_OUT465), and the present study was conducted in accordance with the Declaration of Helsinki on human subjects.

Table 1. The Compositions of Supplement

Composition	*Content*
WPI	40 g
β-lactoglobulin	27.68 g
α-lactalbumin	5.68 g
IgG	0.84 g
Bovine serum albumin	1.32 g
Glycomacropeptide	0.64 g
Leucine	5.72 g
Isoleucine	2.52 g
Valine	2.24 g
Zn	2.64 mg
Se	0.76 mg

IgG, immunoglobulin G; Se, selenium; WPI, whey protein isolate; Zn, zinc.

Biochemical analyses

Blood samples were collected by registered nurses at the beginning of the trial (baseline), week 6, and at the end of the trial (week 12) for the determination of complete blood count, kidney function (blood urea nitrogen and creatinine), liver function (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), protein status (albumin), oxidative stress (GSH), inflammation (high sensitivity C-reactive protein), and immune biomarkers (immunoglobulin G [IgG] and $CD4^+$). Albumin levels were measured using the modified bromocresol purple method,[13] and GSH was measured by reduction of 5,5′-dithiobis-(2-nitrobenzoic acid) method.[14] High sensitivity C-reactive protein was determined by latex immunoturbidimetry assay,[15] IgG was measured by enzyme-linked immunosorbent assay,[16] and $CD4^+$ was determined by flow cytometry.[17] Biochemical assessments were carried out at N Health Asia Lab (Bangkok, Thailand), a medical laboratory with ISO15189:2007 certification. To assess clinical symptoms and quality of life, the Subjective Global Assessment (SGA)[18] was modified to document participant weight patterns within the last 3 months, dietary type, dietary changes, gastrointestinal symptoms, functional capacity, edema, and wasting of subcutaneous fat and muscle. The SGA was graded as follows: grade A, well nourished or low risk of malnutrition (8 points); grade B, suspected or moderate malnutrition (9–16 points); and grade C, severe malnutrition (>16 points). The Thai version of the EORTC QLQ-C30 (version 3)[19] was used to assess participant quality of life. Compliance was checked by asking participants to return supplement packaging and reminding them through telephone every week before their visit to the National Cancer Institute. All patient visits were set on the same day as their physician appointment.

Statistical analyses

SPSS version 18.0 for Windows was used for statistical analyses. Data that followed a normal distribution are expressed as means ± standard deviations. An independent Student's *t*-test was used to evaluate the differences in normally distributed variables between intervention and control groups. The Wilcoxon signed-rank test was used to assess pre- versus post-trial measures within groups. A $P<.05$ was considered statistically significant.

RESULTS

General characteristics are presented in Table 2. The dropout rate was ~12.5% due to cancer progression ($n=3$) and being unable to drink the ONS ($n=3$); thus, a total of 42 patients completed the study. Both groups included males and females, and the average age was 51.5 years in the control group and 54.1 years in the intervention group. There were no significant differences in age, weight, percent weight change, body mass index, muscle mass, percent body fat, complete

Table 2. General Characteristics and Blood Chemistry of Participants

General characteristics and biochemical parameters	*Control* (n = *19*)			*Whey protein* (n = *23*)			P
	Baseline	*6 week*	*12 week*	*Baseline*	*6 week*	*12 week*	
Age (year)	51.5 ± 9.6	—	—	54.1 ± 9.3	—	—	.38
Sex, *n* (%)							
Male	3 (15.8)	—	—	7 (30.4)	—	—	
Female	16 (84.2)	—	—	16 (69.6)	—	—	
Type of cancer, *n* (%)							
Breast	13 (68.4)	—	—	13 (56.5)	—	—	
Colon	4 (21.1)	—	—	5 (21.7)	—	—	
Lung	0	—	—	2 (8.7)	—	—	
Rectum	0	—	—	1 (4.3)	—	—	
Stomach	0	—	—	1 (4.3)	—	—	
Cholangiocarcinoma	1 (5.3)	—	—	1 (4.3)	—	—	
Pancreatic	1 (5.3)	—	—	0	—	—	
Lymphoma	0	—	—	0	—	—	
Weight (kg)	58.4 ± 10.8[a]	59.1 ± 10.7[a]	59.0 ± 10.5[a]	62.3 ± 13.5[a]	63.5 ± 12.6[a]	63.0 ± 12.3[a]	.32
Weight change (%)	—	1.3 ± 5.2[a]	1.2 ± 6.4[a]	—	1.1 ± 2.2[a]	1.2 ± 2.9[a]	
Body mass index (kg/m^2)	23.6 ± 3.7[a]	23.6 ± 3.9[a]	23.6 ± 4.0[a]	24.9 ± 5.7[a]	24.5 ± 5.3[a]	24.6 ± 5.3[a]	.38
Muscle (kg)	38.3 ± 6.2[a]	38.9 ± 7.1[a]	38.7 ± 6.2[a]	39.6 ± 6.9[a]	40.0 ± 7.2[a]	40.1 ± 7.1[a]	.53
Body fat (%)	30.1 ± 8.9[a]	30.2 ± 10.5[a]	29.6 ± 9.6[a]	31.0 ± 12.2[a]	29.0 ± 11.9[a]	29.2 ± 12.4[a]	.78
Hb (g/dL)	11.8 ± 1.4[a]	11.8 ± 1.1[a]	12.0 ± 1.0[a]	11.3 ± 1.4[a]	11.0 ± 1.3[a]	10.9 ± 1.6[a]	.26
Hct (%)	35.9 ± 3.7[a]	36.3 ± 3.5[a]	37.0 ± 3.5[a]	35.0 ± 4.0[a]	33.8 ± 3.9[a]	34.1 ± 4.6[a]	.46
RBC ($\times 10^6$/mm^3)	4.5 ± 0.6[a]	4.5 ± 0.6[a]	4.4 ± 0.6[a]	4.4 ± 0.7[a]	4.4 ± 0.6[a]	4.2 ± 0.7[a]	.95
WBC ($\times 10^3$/mm^3)	7.3 ± 1.5[a]	6.6 ± 2.4[a]	6.8 ± 3.0[a]	6.9 ± 2.2[a]	7.0 ± 2.6[a]	6.8 ± 2.9[a]	.57
Plt ($\times 10^3$/mm^3)	282.1 ± 70.5[a]	306.6 ± 96.0[a]	290.3 ± 82.7[a]	267.2 ± 74.6[a]	325.8 ± 98.6[b]	307.7 ± 94.1[a,b]	.52
BUN (mg/dL)	9.0 ± 2.7[a]	10.1 ± 3.2[a]	11.0 ± 3.1[b]	11.2 ± 3.9[a]	13.5 ± 5.1[a]	12.7 ± 5.2[a]	.40
Cr (mg/dL)	0.7 ± 0.2[a]	0.7 ± 0.2[a]	0.7 ± 0.2[a]	0.8 ± 0.3[a]	0.7 ± 0.2[a]	0.7 ± 0.2[a]	.12
AST (U/L)	32.4 ± 34.9[a]	29.1 ± 14.8[a]	40.1 ± 42.5[a]	42.8 ± 47.0[a]	28.0 ± 12.1[a]	30.0 ± 13.8[a]	.44
ALT (U/L)	26.4 ± 43.4[a]	26.1 ± 17.8[a]	31.5 ± 23.0[a]	27.3 ± 21.6[a]	22.7 ± 10.5[a]	25.1 ± 19.2[a]	.93
ALP (U/L)	92.9 ± 82.3[a]	86.1 ± 45.3[a]	99.3 ± 69.7[a]	106.7 ± 96.7[a]	102.9 ± 59.9[a]	117.3 ± 118.6[a]	.63

Values are means ± SD.

P = Comparison of means between the 2 groups at baseline; significant differences at $P < .05$.

Means in a row with superscript letters without a common letter differ within group, $P < .05$.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; RBC, red blood cell; WBC, white blood cell.

blood count, or kidney (blood urea nitrogen or creatinine) or liver (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase) function between the two groups at baseline. All patients who completed the study were able to follow the study protocol and consume their assigned ONS as planned. Notably, platelet levels significantly increased in a time-dependent manner in the intervention group compared to the control group.

Protein status, GSH level, and immune function are presented in Table 3. Albumin levels significantly increased at week 12 in the intervention group by 2.9%. GSH (biomarker of oxidative stress) was significantly decreased when consistent with cancer chemotherapy. Nevertheless, GSH levels significantly improved after WPI supplementation at week 6 by 6.0% and at week 12 by 11.7% in the intervention group, compared with the control. Regarding immune function, IgG levels significantly decreased after participants received chemotherapy in the control group. There was a significant increase in the percentage of IgG at weeks 6 (0.5%) and 12 (4.8%) in the intervention group, compared to the control, whereas high sensitivity C-reactive protein and $CD4^+$ were not significantly different.

The outcome of nutritional status and quality of life measurements are shown in Table 4. The SGA score in the control group was not significantly different from the intervention group, but it was significantly lower at weeks 6 and 12 in the intervention group. At the end of the study (week 12), SGA scores were significantly different between the two groups. While there was no significant change in the control group, the SGA grade significantly improved in the intervention group at week 12. Health status and quality of life scores showed the same pattern; they did not significantly change in the control group, while scores for both of these indicators significantly increased in the intervention group.

DISCUSSION

WPI supplementation with Zn and Se improved the protein status, GSH level, and immune function of cancer patients undergoing chemotherapy by significantly increasing albumin, GSH, and IgG levels after 12 weeks of intervention. Previous studies support the role that whey protein plays in improving albumin levels and immune function. The WPI used herein was enriched with β-lactoglobulin, α-lactalbumin,

Table 3. Biomarkers of Protein Status, Oxidative Stress, Inflammation, and Immune Function

	Control (n = *19*)			*Whey protein* (n = *23*)			
Biomarkers	*Baseline*	*6 week*	*12 week*	*Baseline*	*6 week*	*12 week*	P
Albumin (g/dL)	4.3 ± 0.3[a]	4.3 ± 0.2[a]	4.3 ± 0.4[a]	4.1 ± 0.4[a]	4.2 ± 0.4[a]	4.4 ± 0.3[b]	.07
Albumin change (%)	—	0.6 ± 1.7	−0.6 ± 0.7	—	0.2 ± 1.8	2.9 ± 1.5*	
GSH (μmol/L)	20.7 ± 4[a]	19.4 ± 3.5[a, b]	18.5 ± 3.7[b]	22.8 ± 4.4[a]	23.9 ± 3.7[b]	25.0 ± 3.4[b]	.12
GSH change (%)	—	−4.7 ± 14.2	−9.6 ± 13.3	—	6.0 ± 6.7*	11.7 ± 12.6*	
hs-CRP (mg/L)	4.6 ± 6[a]	5.1 ± 9.4[a]	6.8 ± 15.3[a]	7.0 ± 9.5[a]	6.5 ± 6.6[a]	5.4 ± 6.4[a]	.29
hs-CRP change (%)	—	51.9 ± 122.8	14.5 ± 103.3	—	48.5 ± 114.6	23.8 ± 108.4	
IgG (mg/dL)	1439.6 ± 344.1[a]	1152.7 ± 329.5[b]	1277 ± 8241.5[a,b]	1591.3 ± 333.4[a]	1581.1 ± 301.5[a]	1658.0 ± 408.8[a]	.17
IgG change (%)	—	−13.8 ± 11.3	−9.5 ± 20.4	—	0.5 ± 14.1*	4.8 ± 18.1*	
$CD4^+$ (%)	38.0 ± 7.1[a]	37.1 ± 9.9[a]	36.0 ± 9.2[a]	39.6 ± 10.0[a]	37.3 ± 9.9[a]	38.9 ± 10.8[a]	.58
$CD4^+$ change (%)	—	−2 ± 20	−5.3 ± 18.7	—	−3.7 ± 186	−1.0 ± 13.5	

Values are means ± SD.
P = Comparison of means between the 2 groups at baseline; significant differences at $P < .05$.
Means in a row with superscript letters without a common letter differ within group, $P < .05$.
*Significant differences between groups at $P < .05$.
GSH, glutathione; hs-CRP, high sensitivity C-reactive protein.

IgG, bovine serum albumin, glycomacropeptide, and branched-chain amino acids leucine, isoleucine, and valine. Leucine has been shown to be a protein-synthesis indicator by stimulating translation and initiation pathways, which could prevent muscle loss during malnutrition.[20] Moreover, the high concentration of cysteine and methionine in WPI, together with Zn and Se enrichment, could have also enhanced immune function through intracellular linkages to form GSH,[21] thereby increasing its levels as seen herein. Regarding protein status, serum albumin levels are a key marker of malnutrition status. In the current study, serum albumin levels significantly increased in a time-dependent manner in the intervention group. According to American Society for Parenteral and Enteral Nutrition guidelines for chemotherapy patients, adequate protein intake (1.6 g/body weight/day) can improve malnutrition problems. Moreover, low levels of serum albumin are associated with worse recovery during chemotherapy, and cancer patients with hypoalbuminemia have a poor prognosis of mortality.[22]

In addition, 10–15% of the WPI used is composed of a form of IgG, which has a potential immune modulatory effect in humans.[23] Chemotherapeutic drugs can deplete platelet levels by permanently damaging bone marrow cells (site of platelet production)[24]; our study showed a similar decrease in platelet levels in the control group. Vitamins C, D, and K have been shown to increase platelet levels through an immunomodulatory function.[25] A low platelet level can delay the cycle of medical treatment, lead to further disease progression, and result in spontaneous bleeding.[26] While supplementation with WPI significantly increased platelet levels herein, the mechanism by which this occurred is unclear. One possibility could be that WPI improves vitamin B_{12} and folate absorption, which in turn increase platelet count.[27–29]

Two major strengths of the present study are its randomized, double-blind controlled design and the number of participants, which were much greater than in previous studies.[7,11,29] Even though the type of cancer in each patient was not stratified herein due to time limitations and ability to include cases, the present research was conducted under the care and consideration of physicians and certified dietitians. In the future, comparisons of WPI supplementation on specific cancer types should be evaluated.

Table 4. Nutrition Status and Quality of Life

	Control (n = *19*)			*Whey protein* (n = *23*)			
Assessment	*Baseline*	*6 week*	*12 week*	*Baseline*	*6 week*	*12 week*	P
SGA score	9.2 ± 1.4[a]	9.1 ± 1.2[a]	9.0 ± 1.2[a]	10.0 ± 2.3[a]	8.5 ± 0.9[b]	8.4 ± 0.9[bc,*]	.27
SGA grade, *n* (%)							
Grade A	7 (36.8)	8 (42.1)	8 (42.1)	7 (30.4)	16 (69.6)	19 (82.6)*	
Grade B	12 (63.2)	11 (57.9)	11 (57.9)	16 (69.6)	7 (30.4)	4 (17.4)*	
Grade C	0	0	0	0	0	0	
Health status score	4.7 ± 0.9[a]	—	4.9 ± 1.1[a]	4.5 ± 1.2[a]	—	5.2 ± 1.0[b]	.73
Quality of life score	4.9 ± 1.3[a]	—	5.1 ± 0.9[a]	4.8 ± 1.7[a]	—	5.5 ± 1.1[b]	.94

Values are means ± SD.
P = Comparison of means between the 2 groups at baseline; significant differences at $P < .05$.
Means in a row with superscript letters without a common letter differ within group, $P < .05$.
*Significant differences between groups at $P < .05$.
SGA, Subjective Global Assessment.

Based on the current results, we suspect that there are several mechanisms by which WPI supplementation with additional Zn and Se improves the protein status, GSH levels, and immune function, thereby increasing the overall nutritional status of cancer patients receiving chemotherapy. Thus, WPI supplementation and enrichment with essential minerals, such as Zn and Se, may be an alternative route for improving and supporting nutritional status and quality of life in cancer patients undergoing chemotherapy. However, further studies stratifying particular cancer and chemotherapeutic drug types should be conducted to confirm the comprehensive benefit of this dietary strategy.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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