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Original Article

Assessment of diet quality after operative fixation of acute fractures

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Background: Nutrition supplementation has potential to improve clinical outcomes of musculoskeletal trauma. An improved understanding of common nutrition deficiencies present during the healing phase after trauma is needed to choose the appropriate composition of nutrition supplementation. Our objective is to document dietary deficiencies after operative fixation of acute fractures in young adults.
Methods: A prospective observational study enrolled young adults (age 18–55 years) indicated for operative fixation of a pelvic or extremity fracture. Postoperative dietary intake was measured using the Automated Self-Administered 24-h dietary recall (ASA24®). Inadequate dietary intake was determined using Dietary Reference Intake (DRI) values and the Healthy Eating Index 2015 (HEI-2015) score.
Results: Thirty-two subjects completed 122 ASA24® surveys in the 4 weeks after operative fixation. Dietary intake overall was severely inadequate in the early post-operative period; 81% did not meet calorie needs and protein intake was inadequate in 41%. All subjects did not meet DRIs for fiber, vitamin E, or potassium. More than 50% did not meet DRI for magnesium, zinc, folate, vitamins C, A, K, or D. The mean HEI-2015 score was 44.0 (±11.4 SD) across all time points.
Conclusions: In a population of previously healthy, young adults indicated for operative fracture fixation, dietary quality was poor even compared to the average for the US population (44.0 vs 58.7

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HEI-2015). This data provides targets for future clinical investigations of nutrition interventions to improve outcomes in young adults with significant musculoskeletal trauma.

Introduction

Recent investigation in musculoskeletal trauma has been dedicated to defining the impact of malnutrition and nutrition supplementation on clinical outcomes. Much of this previous work has focused on the geriatric fracture population, with little to no investigation in young adults.

Sarcopenia (loss of muscle mass that occurs typically with malnutrition, advanced age, and chronic disease) [1–10] is a marker for malnutrition and a predictor of poor clinical outcomes after pelvis and hip fractures [5,11–17]. Randomized clinical trials report positive impacts of nutrition interventions in the geriatric fracture population [18–22], but there is significant variability in the composition of the dietary supplement used in each of these investigations. Protein, amino acids, vitamin D, and mixed nutrition supplements have been trialed in the geriatric fracture population with variable effectiveness.

Our group is specifically interested in nutrition interventions to reduce the loss of functional muscle mass and injury related complications after high-energy trauma in young adults. As we design clinical trials to investigate the impact of a nutrition supplementation intervention on clinically relevant outcomes, it became apparent we do not have a good understanding of the nutrition deficiencies present during the healing phase after severe musculoskeletal trauma. A thorough understanding of these inadequacies will allow us to design evidence-based interventions targeting specific needs for supplementation in this population. The objective of this investigation was to thoroughly document the prevalence of specific nutrient deficiencies that exist after surgical fixation of acute fracture in young adults with validated 24-h dietary recalls using Dietary Reference Intake (DRI) values reported by the Institute of Medicine and the Healthy Eating Index 2015 (HEI-2015) described by the United States Department of Agriculture (USDA) [23,24].

Methods

Subjects

Adults, aged 18–55 years, presenting to a single Level 1 trauma center between June and November 2019 with acute extremity or pelvis fractures indicated for operative fixation were eligible were for the study. Subjects were excluded if they were incarcerated, pregnant, not placed on an oral diet immediately postoperatively, sustained injuries which prevented accurate completion of 24-h diet recalls (i.e. head injuries), or if they did not have access to a smartphone or computer with internet access after discharge from the hospital. Fifty-four subjects consented to the study. Our institutional review board approved this investigation. All subjects provided written informed consent before enrollment.

Diet assessment

Dietary intake was measured using the Automated Self-Administered 24-h dietary recall (ASA24®), 2018 version, developed by the National Cancer Institute. The ASA24® is an automated, web-based tool that enables self-administered 24-h dietary recalls [25,26]. Through a series of promoted steps, participants list all the foods, beverages, and dietary supplements consumed in the past 24 h, defined as midnight to midnight the previous day. Participants then answer detailed questions about the foods and beverages reported, including food type, preparation, additions. For each 24-h diet recall, the

ASA24® software generates total intake values for macronutrients, micronutrients, and food groups. Details of the automated system have been described previously [25]. Previous studies have validated the ASA24® as a dietary assessment tool, demonstrating its ability to provide accurate estimates of dietary intake when compared to true consumption, recovery biomarkers, as well as interviewer-administered 24-h recalls [27,28].

Participants were asked to complete a total of 9 ASA24® recalls. The goal of the assessments was to obtain an estimate of normal intake in the month following surgical fixation by averaging intake from postoperative weeks 1, 2, and 4. The diet recalls were scheduled for nonconsecutive days and included 2 weekdays and 1 weekend day each week, consistent with best practices in diet recall methodology [29]. During hospital admission, the subjects were enrolled and oriented to the ASA24® website (https://asa24.nci.nih.gov/). While admitted to the hospital, participants were provided with an iPad® to complete ASA24® recalls. Following discharge, prompts to complete recalls were sent via email. A reminder email and phone call were sent if a requested recall was not completed within 24 h. All completed recalls received within 32 days of surgical fixation were included.

Dietary guidelines

Macro- and micronutrient intake were evaluated using Dietary Reference Intakes (DRIs).24 DRIs refer to a set of reference values reported by the Food and Nutrition Board, Institute of Medicine of the National Academies, which provide quantitative estimates of nutrient intakes for planning and assessing diets for healthy people [30]. Each nutrient has either an Estimated Average Requirement (EAR) and a Recommended Dietary Allowance (RDA), or an Adequate Intake (AI). Estimated Average Requirement (EAR) is defined as an average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular biological sex and age group [31]. Recommended Dietary Allowance (RDA) is defined as two standard deviations above the EAR, resulting in a nutrient intake value that exceeds requirements for nearly all (97–98%) individuals in a particular biological sex and age group [31]. Adequate Intake (AI) is defined as a recommended average daily nutrient intake level based on observed or experimentally determined approximations of nutrient intake by a group, or groups, of apparently healthy people that are assumed to be adequate – used when an EAR cannot be determined [31]. In diet assessment methodology, the proportion of individuals with intakes below the EAR represent the prevalence of inadequate intake for that nutrient [24,30]. In contrast, individuals with usual intakes of a nutrient that are above the RDA are assumed to have adequate intake [24,30]. With regard to protein, well-accepted guidelines recommend a higher intake of protein for critically ill individuals, including the postoperative trauma patient population [32,33]. In accordance with current clinical practice guidelines for postoperative trauma patients, a weight-based equation of 1.2 g protein per kg body weight was also used to assess protein intake [33].

Overall diet quality was assessed using the Healthy Eating Index 2015 (HEI-2015). The HEI-2015 measures adherence to the 2015–2020 Dietary Guidelines for Americans [34]. It is a validated measure of diet quality, evaluating food groups based on densities (i.e. amounts per 1000 kcal consumed) rather than absolute intakes [23,35]. The HEI-2015 is a sum of 13 component scores and ranges from 0 to 100. The component scores are based on 9 adequacy food groups (foods recommended to eat more of) and 4 moderation food groups (foods recommended to limit), with scores ranging from 0 to 5 or 0 to 10 depending on the component [23]. A higher score indicates a diet that better aligns with dietary recommendations. Therefore, a high adequacy component score reflects high consumption because these foods are encouraged, but a high moderation component score reflects low consumption because lower intakes of these foods are more desirable [23,36]. Guidelines for food group consumption were drawn from the US-Style Healthy Eating Pattern, as reported by the USDA's 2015–2020 Dietary Guidelines for Americans [34].

Statistical analysis

Descriptive characteristics of study subjects and their injuries were reported as summary statistics. Macronutrients, vitamins, and minerals were analyzed as absolute intakes, while food groups were analyzed as cup and ounce equivalents. To estimate each subject's usual daily intake in the month following surgical fixation, intake data from all recalls completed by the subject were averaged to calculate a mean observed intake. Subjects' mean observed intake for each nutrient and food group was then summarized using categorical divisions of success versus failure to achieve dietary guidelines for a subject's particular biological sex and age group [24,33,34]. Finally, the proportion of individuals with inadequate nutrient intake was assessed using the EAR cut-point method [30,31]. Resting energy expenditure for each subject was predicted using the Harris–Benedict Equation [37]. Using data from the ASA24®, HEI-2015 overall and component scores were calculated for each subject. Linear mixed model analysis was used to determine the effect of time on caloric intake and HEI-2015 score. Analyses were completed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) [38].

Results

Thirty-two of the 54 subjects enrolled completed at least one dietary recall. Demographics and injury characteristics are summarized in Table 1. The subjects were typically young and healthy with isolated extremity trauma. Lower extremity trauma was more common than upper extremity. Subjects typically underwent definitive surgical fixation in a single operative setting, but 11 subjects underwent staged definitive fixation of injuries.

Macronutrient and micronutrient intake

Thirty-two subjects completed a total of 122 ASA24® dietary recalls. There was variability in the number of days completed across participants (≥9 days n = 4; 7 days n = 1; 6 days n = 1; 5 days n = 4;

Table 1
Demographics and injury characteristics of adults, aged 18–55 years, indicated for operative fixation of acute extremity or pelvis fractures (n = 32). Data are presented as % (n) for qualitative variables, and mean ± SD or median (min–max) for quantitative variables

Variable		
Age (years)		36.7 ± 12.1
Biological sex	Female	53.1 (17)
	Male	46.9 (15)
Race	White	87.5 (28)
	Black/African American	3.1 (1)
	Asian	3.1 (1)
	Other	6.3 (2)
Ethnicity	Hispanic	6.3 (2)
	Non-Hispanic	93.8 (30)
Body mass index (kg/m^2)		29.5 ± 8.0
Primary payer	Private	56.3 (18)
	Medicaid	37.5 (12)
	Other	6.3 (2)
Charlson Comorbidity Index	0	71.9 (23)
	1	21.9 (7)
	2	6.3 (2)
Discharge location	Home	78.1 (25)
	Acute Rehab	18.8 (6)
	SNF	3.1 (1)
Length of hospital stay (days)		3.5 (1–39)
Fracture location	Lower ext.	84.4 (27)
	Upper ext.	9.4 (3)
	Lower + upper ext.	6.3 (2)
Open injury	No	59.4 (19)
	Yes	40.6 (13)
Polytrauma	No	59.4 (19)
	Yes	40.6 (13)
Surgeries (#)	1	65.6 (21)
	2	21.9 (7)
	≥3	12.5 (4)

4 days n = 4; 3 days n = 3; 2 days n = 9; 1 day n = 6). Ninety of 122 surveys were completed between days 0–14 postoperatively.

Daily caloric intake among subjects averaged 1624.8 ± 664.8 kcal with a range of 453–3134 kcal. Nineteen subjects (59.4%) reported a mean daily caloric intake below their predicted resting energy expenditure. Results from the linear mixed model showed that time had no significant effect on caloric intake postoperatively ($p = 0.94$).

The mean intake of macronutrients and the proportion of subjects with average intakes below the EAR are presented in Table 2. All subjects (n = 32) reported inadequate intakes for fiber. Thirteen subjects reported inadequate intake of protein, based on recommendations for healthy individuals (EAR). When protein intake was compared to the predicted needs for the postoperative trauma patient population, most subjects in this study (n = 24) reported intakes below this recommendation. Table 3 summarizes the mean intake of micronutrients and the proportion of subjects with average intakes below the EAR. Intake of vitamin E was inadequate among all subjects (n = 32). Greater than 50% of subjects reported inadequate intakes for magnesium (n = 26), zinc (n = 16), folate (n = 20), as well as vitamins C (n = 22), A (n = 24), and D (n = 27). More than half of subjects reported intakes above the RDA for selenium (n = 28), niacin (n = 19), as well as vitamins B-6 (n = 17) and B-12 (n = 29).

Diet quality

The mean intake of food groups and comparison with the Healthy US-Style Eating Pattern are presented in Table 4. Overall, subjects' diets lacked sufficient amounts of beneficial foods to meet guidelines for healthy Americans. No subjects reported meeting whole grain and vegetable guidelines, and most reported intake below guidelines for fruit (n = 29) and protein foods (n = 23). Many subjects also reported consuming excessive amounts of added sugar (n = 12) and saturated fat (n = 13). The mean total HEI-2015 score among subjects was 44.0 ± 7.54 out of a maximum score of 100, with a range of 27.5–57.6, indicating overall poor dietary quality. The intake of our sample was even less than the general U.S. population (mean HEI-2015 score of 58.7), which has been associated with poor health outcomes [39,40]. The mean HEI-2015 component scores are presented in Fig. 1. Time had a significant effect on total HEI-score postoperatively, with the score decreasing with days postoperative (Estimate ± SE: −0.228 ± 0.104, $t = -2.19$, $p = 0.031$).

Discussion

This is the first study to evaluate postoperative dietary intake and quality in young adults (ages 18–55 years) after orthopedic trauma. In this series, diet quality in the 4 weeks after operative fracture fixation was overall insufficient. Most subjects reported intake of calories, protein, and several key micronutrients that did not meet recommendations. Diet quality based on the HEI-2015 was significantly lower than the average for the US population. These results have significant implications after orthopedic trauma because adequate nutrition is essential to supporting soft tissue healing and bone

Table 2
Macronutrient intake and comparison with Dietary Reference Intakes of young adults (n = 32) in the four weeks after acute extremity or pelvis fracture fixation.

Nutrient	EAR	Mean	SD	Min–max	Below EAR % (n)
Carbohydrate (g)	*100*	*181.5*	±88.8	34.2–450.7	12.5 (4)
Protein (g/kg)	*0.66*	*0.86*	±0.4	0.2–2.1	40.6 (13)
Fat (g)	–	*66.4*	±31.0	17.5–138.4	
Fiber (g)					100.0 (32)
Males	*38*	*9.5*	4.9	4.1–22.0	
Females	*25*	*10.2*	5.6	2.4–21.2	

EAR = Estimated Average Requirement based on Institute of Medicine's recommendations.
SD = standard deviation.

Table 3
Micronutrient intake and comparison with Dietary Reference Intakes of young adults with acute extremity or pelvis fracture indicated for operative fixation (n = 32) in the four weeks after surgery.

Nutrient	EAR	RDA	Mean	SD	Min–max	Below EAR % (n)	Above RDA % (n)
Calcium (mg)	800	1000	868.1	±390.5	133.8–1973.4	46.9 (15)	25.0 (8)
Magnesium (mg)						81.3 (26)	6.3 (2)
Males	330	400	216.7	±57.8	133.0–335.4		
Females	255	310	207.6	±103.8	58.2–407.3		
Sodium (mg)	1500[a]	–	2898.0	±1049.8	866.3–5197.9		
Zinc (mg)						50.0 (16)	40.6 (13)
Males	9.4	11	10.5	±4.0	5.1–18.3		
Females	6.8	8	8.2	±3.6	1.8–16.1		
Copper (mg)	0.7	0.9	0.9	±0.4	0.2–1.6	40.6 (13)	40.6 (13)
Selenium (μg)	45	55	92.8	±38.5	24.4–187.1	9.4 (3)	87.5 (28)
Thiamine (mg)						25.0 (8)	40.6 (13)
Males	1.0	1.2	1.3	±0.6	0.5–2.5		
Females	0.9	1.1	1.3	±0.6	0.2–2.6		
Riboflavin (mg)						9.4 (3)	21.9 (7)
Males	1.1	1.3	1.9	±0.7	1.1–3.4		
Females	0.9	1.1	1.6	±0.8	0.3–3.1		
Niacin (mg)						15.6 (5)	59.4 (19)
Males	12	16	18.7	±9.1	5.6–35.1		
Females	11	14	18.5	±8.0	6.1–38.6		
Vitamin B-6 (mg)	1.1	1.3	1.6	±0.7	0.5–3.1	21.9 (7)	53.1 (17)
Folate (μg)	320	400	280.2	±133.8	52.1–591.7	62.5 (20)	18.8 (6)
Vitamin B-12 (μg)	2	2.4	5.6	±4.2	1.4–21.4	3.1 (1)	90.6 (29)
Vitamin C (mg)						68.8 (22)	21.9 (7)
Males	75	90	89.1	±90.1	2.3–297.6		
Females	60	75	70.7	±106.6	5.0–420.4		
Vitamin A (μg)						75.0 (24)	15.6 (5)
Males	625	900	588.4	±286.2	216.0–1206.9		
Females	500	700	392.5	±248.2	98.6–995.0		
Vitamin E (mg)	12	15	5.3	±2.6	1.2–11.0	100.0 (32)	0.0 (0)
Vitamin D (μg)	10	15	5.9	±6.4	0.0–24.1	84.4 (27)	12.5 (4)
Phosphorus (mg)	580	700	1234.3	±448.3	322.0–2237.1	6.3 (2)	87.5 (28)
Potassium (mg)	4700[a]	–	2114.4	±759.0	622.6–3871.3		
Vitamin K (μg)							
Males	120[a]	–	47.8	±38.6	10.1–146.0		
Females	90[a]	–	87.5	±105.2	7.3–459.9		

EAR = Estimated Average Requirement based on Institute of medicine's recommendations.
SD = standard deviation.
RDA = Recommended Dietary Allowance based on Institute of Medicine.
[a] AI, adequate intake, is reported when EAR is not yet determined by the Institute of Medicine.

Table 4
Mean food group consumption and comparison with US-Style Healthy Eating Pattern of young adults (n = 32) in the four weeks after acute extremity or pelvis fracture fixation.

Food group	Recommended daily amount[a]	Mean	SD	Failure to achieve recommendation
				% (n)
Whole grains (oz.)	3.0–5.0 oz	0.44	±0.54	100% (32)
Vegetables	2.5–3.5 cup	1.05	±0.65	100% (32)
Fruits	1.5–2.5 cup	0.91	±1.15	90.6% (29)
Dairy	3.0 cup	2.0	±1.45	87.5% (28)
Protein foods	5.0–7.0 oz	5.23	±3.11	71.9% (23)
Saturated fats	≥22–31 g	24.1	±15.6	40.6% (13)
Added sugar	≥50–70 g	61.05	±59.75	37.5% (12)

SD: standard deviation.
[a] Recommended Daily Amount based on the 2015–2020 Dietary Guidelines for Americans' US-Healthy Eating Pattern.

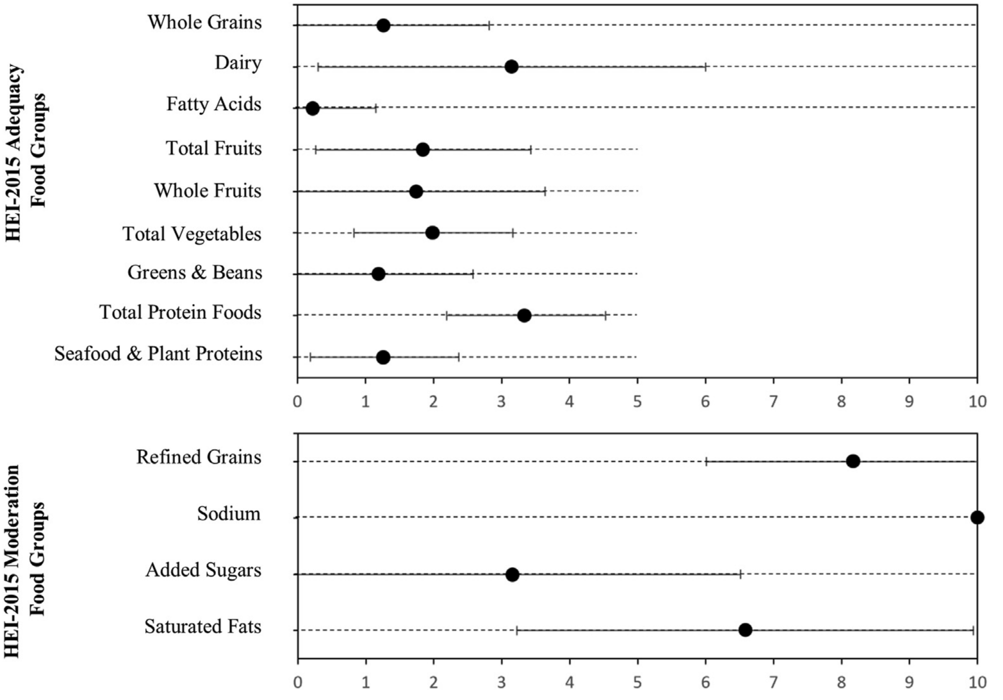

Figure 1. Healthy Eating Index (HEI)-2015 mean component scores in young adults (n = 32) in the four weeks after acute extremity or pelvis fracture fixation.

regeneration. These comparisons likely underestimate the nutrition deficiencies after trauma as wound and fracture healing increases metabolic demand. Future investigations in young adults with acute operative extremity and pelvis fractures should supplement overall calorie, protein, fiber, and multiple micronutrients rather than targeting a single macro or micronutrient to optimize outcomes.

The typical diet of otherwise healthy young adults in the United States has significant baseline deficiencies [41,42]. When patients present with acute musculoskeletal trauma, these pre-existing deficiencies may negatively impact wound and fracture healing. After injury and subsequent surgical treatment, the increased metabolic demand required for healing is likely unmet by a diet that may be negatively impacted by pain, immobility, medications, and financial limitations [43,44]. Consistent with the idea that diet is suppressed in the four weeks after musculoskeletal trauma, the average daily energy intake in our sample (1624.8 ± 664.8 kcal) was lower than the general US population's mean intake (2155 ± 1295 kcal) [45]. Additionally, HEI-2015 component scores suggest that poor diet quality in this population was attributable to a failure to consume adequate amounts of beneficial foods.

The mean BMI was 29.1 kg/m^2 (categorized as overweight) in our series. Other work found that obese individuals have a higher incidence of micronutrient inadequacy compared to normal weight individuals [46]. Unfortunately, this study was not powered to determine a difference in diet quality based on BMI, but this should be an aim of future work in musculoskeletal trauma.

One of the most interesting findings is that caloric intake did not change postoperatively, but total HEI-2015 score actually decreased, indicating that diet quality decreased over time. This finding could be evidence of increased consumption of processed foods that are energy-dense, but nutrient-poor in the weeks following musculoskeletal trauma. Intake of nutrient-poor food is a negative predictor for the consumption of unprocessed, nutrient-dense foods. Unprocessed, nutrient-dense foods such as fruits, vegetables, whole grains, plant, and animal proteins are the primary source of vitamins and minerals in a non-supplemented diet [47]. These vitamins and minerals are essential for wound healing, promoting cell proliferation and collagen synthesis [48]. During the critical period for wound healing evaluated in this study, none of the subjects met USDA recommendations for servings of vegetables and whole grains, and many (90.6%) did not meet USDA recommendations for fruit servings. Additionally, 75% of individuals in this sample did not meet protein requirements, which is likely the most important macronutrient for healing and maintaining lean body mass [32]. Results from this study demonstrate a widespread imbalance in the intake of energy and nutrients, which puts subjects at risk for developing malnutrition following surgical treatment. Malnutrition has been repeatedly associated with more complication and prolonged hospitalization, including increased risk for infections and surgical failure [43,44]. Together, these data suggest that nutrition supplementation has significant potential to optimize healing and functional recovery after musculoskeletal trauma. We need to improve our understanding of the specific deficiencies so that targeted, evidence-based interventions can be designed.

Previous reports of diet quality focused on the geriatric population. Enroth et al. conducted a randomized controlled trial investigating the impact of combined oral and parenteral nutrition supplementation in a geriatric hip fracture population. The dietary intake energy (kcal) content was recorded in the supplement and control groups [19,49]. They found that the control group had only an average of 665 kcal over the first 3 days and 916 kcal from day 1 to day 10 (only 54% in the control group met the predicted caloric need). In comparison, only 40.6% of our young adult population met predicted caloric needs. They also found significantly fewer combined complications, including infection, venous thrombotic events, and mortality in the nutrition supplement group.

Another observational study of older adults with hip fracture found that a single 24-h dietary recall survey showed significant caloric and macro- and micro-nutrient deficiencies [50]. This study used bioelectrical impedance to document skeletal muscle mass. They found that caloric deficiencies, as well as total protein and leucine (amino acid) intake, predicted lower skeletal muscle mass. Our investigation documents similar nutritional deficiencies in a younger trauma population (ages 18–55 years), providing additional evidence that nutrition supplementation for orthopedic trauma patients may be warranted.

Limitations

This was a nonconsecutive, convenience sample of young adults treated with operative fracture fixation. Fifty-four subjects were enrolled in the study, and only 32 completed at least 1 ASA24® survey (59%). The subjects were offered 9 times points in the first 4 weeks after injury, and an average of 4 ASA24® surveys were completed per subject. Efficient data collection is a well-documented challenge of nutrition research. Previous investigations found that approximately a third of enrolled subjects do not complete the ASA24® survey, citing lack of time [51]. They found each survey required a mean of 39 min to complete. We found that each survey required 30–45 min to complete and completion required prompting from our research team. The substantial time required for completion of the diet assessment tool limited enrollment and follow up. Dietary data for this study was collected using self-administered 24-h food recalls. While this is one of the most accurate methods for dietary assessment, all self-reported dietary intakes are subject to recall bias and underreporting [28]. Additionally, the diet assessment tool used in this study only provides a 24-h window of dietary intake, which restricted assessment to the post-injury period and did not allow for collection of baseline data. Future investigation in the trauma population should consider other validated food frequency questionnaires such as the VioScreen® (VioCare®) dietary assessment tool. VioScreen® is a validated tool intended to simplify the estimation of 3-month dietary intake. However, accurate assessment of previous dietary intake will continue to be a challenge of future studies of nutrition interventions [52,53].

We used broad definitions for adequate diet. Nutrient intake was evaluated using DRIs [24], and overall diet quality was assessed using the HEI-2015 [34]. These are the best available normalized assessments for evaluating macro- and micro-nutrient intake. However, the DRIs were designed to apply to the healthy population. Standard DRIs likely underestimate the nutrition requirements for a trauma population due to the increased metabolic demand required for appropriate fracture and wound healing. This study provides baseline data for a population not treated with nutrition intervention.

Conclusion

In this study of previously healthy young adults, diet quality and nutrient intake did not meet recommendations in the 4 weeks following major musculoskeletal trauma. Most subjects consumed inadequate amounts of calories, fiber, essential vitamins (folate, vitamins C, A, E, K, and D), and minerals (potassium, magnesium, and zinc). Diet analysis revealed that most subjects failed to consume adequate daily amounts of beneficial food groups. Results from this study are consistent with a growing body of evidence suggesting that nutrient intake is severely inadequate among orthopedic trauma populations and represents an area for improvement. Deficiencies identified in this study provide targets for future clinical investigations of nutrition interventions to improve outcomes in young adults with significant musculoskeletal trauma.

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Statement of authorship

MW and RG contributed to the conception and design of the research study; AM, BK, and JD contributed to the acquisition and interpretation of the data; NG contributed to the analysis and interpretation of the data; AM and MW contributed to the drafting of the manuscript. All authors contributed to critically revising the manuscript and approved the final manuscript.

Declaration of competing interest

We have no conflicts of interest to disclose.

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