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ORIGINAL RESEARCH

Investigation of the Impact of a Low-Carbohydrate Diet on The Chronic Pain Experience Among Adults with an Acquired Limb Loss: A Pilot Study

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Purpose: Acquired limb loss can be a traumatic experience that is often accompanied by chronic pain (ie, phantom limb pain (PLP) and/or residual limb pain (RLP)) and can cause a reduction in emotional well-being and overall quality of life. Although, there are available treatments for PLP/RLP, few provide long-term relief. Therefore, the purpose of this study was to investigate the potential benefits of diet on reported pain and quality of life measures among adults with acquired limb loss.

Methods: Seven adults with acquired limb loss (M = 50.57, SD ± 13.63 years of age) were enrolled in a 6-week low-carbohydrate diet (LCD) intervention. Baseline, 3-week, and 6-week measures of pain sensitivity (BPI, NPQ), cognitive flexibility (CFS), depression (CES-D, PROMIS-57), anxiety (PROMIS-57), pain resilience (PRS), and overall quality of life (SF-36) were obtained using validated questionnaires.

Results: On average, all participants had appreciable levels of depression (M = 18.71, SD ± 6.16) and anxiety (M = 19.71, SD ± 5.94), yet relatively high levels of pain resilience (M = 44.42, SD ± 6.70) at baseline. After 6 weeks, participants showed improvements in self-reported measures of pain severity, emotional well-being, and other psychosocial measures of interest, including depression and anxiety.

Conclusion: These results suggest that an LCD might have an influence on multiple chronic pain-related factors among adults living with an amputation. Furthermore, adults living with chronic PLP/RLP may report high resilience, although high levels of depression and anxiety are also reported.

Keywords: low-carbohydrate diet, LCD, acquired limb loss, resilience, chronic pain

Introduction

Chronic pain that occurs as a result of a missing limb can be classified as phantom limb pain (PLP) and/or residual limb pain (RLP). PLP is characterized as a feeling of pain or discomfort in a limb that is missing or no longer present, whereas RLP is characterized as pain or discomfort at the site of a missing limb.[1] PLP and RLP often co-occur, but not always.[2] It was estimated that about 1.6 million Americans were living with limb loss in 2005, and this number is expected to increase every year.[3] Most amputations occur below the knee,[4] but above the knee amputations and various upper limb amputations may also be present.[5,6] PLP/RLP can stem from changes in nociception and neuronal circuitry, causing chronic neuropathy or neuropathic pain.[7] Although there are treatments to reduce PLP/RLP (eg, medications, surgery, virtual reality, mirror therapy), not all are effective,[8] perhaps due to the somewhat unclear mechanisms whereby PLP/RLP elicits pain. Therefore, other alternative treatment approaches should be explored to determine levels of effectiveness.

One potential mechanism to reduce or help manage PLP/RLP is the utilization of diet and nutrition. The effect of diet and nutrition on chronic pain has been well documented.[9–22] Energy-rich and nutrient-poor diets (eg, Standard American Diet and Total Western Diet) have been shown to increase oxidative stress, elevate cytokines, and activate the inflammasome, ultimately leading to chronic inflammation and contributing to chronic pain states and diseases.[23–25] On the other hand, anti-inflammatory diets (eg, low-carbohydrate diet [LCD] and Mediterranean diet) have been shown to reverse the negative outcomes often associated with energy-rich, nutrient poor diets (ie, reduced inflammation,

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oxidative stress, disability, and chronic pain).[26,27] Previous work in our lab has also shown that an LCD, but not a low-fat diet, significantly reduced functional pain responses, improved self-reported symptoms of chronic pain, decreased oxidative stress, and decreased adipokine leptin levels for adults living with knee osteoarthritis (KOA).[16] Diets have also been shown to be related to multiple psychological factors that can contribute to overall quality of life and emotional well-being for people living with chronic pain. For example, diet has been shown to be associated with an enhancement of positive adaptive factors like psychological resilience,[28,29] an improvement in cognitive functioning,[30,31] depression,[27,32] and anxiety,[33] and contribute to overall quality of life.[27] These data suggest that the positive psychological benefits provided with diets that are nutrient-rich and anti-inflammatory may also play a protective role within the chronic pain experience.

Given the effect of diet on pain, inflammation, and psychological contributors to chronic pain, diets should be explored as a means to reduce PLP/RLP. Moreover, due to the complex nature of PLP/RLP and the debilitating symptoms associated with living with an amputation, other non-invasive methods to reduce this pain-specific condition should be explored. Therefore, the objective of this study was to examine the potential impact of an LCD on outcomes related to chronic pain, cognitive flexibility, depression, anxiety, psychological resilience, and overall quality of life among adults living with an amputation. In our case, an LCD was chosen as a more accessible diet option for our participant population in addition to having fewer common allergens as part of the diet, as opposed to the Mediterranean diet that tends to rely on fish/seafood, nuts, and seeds.

Materials and Methods

The data presented are part of a pilot clinical trial where adults with an acquired limb loss along with PLP and/or RLP were enrolled in an LCD intervention (clinicaltrials.gov, NCT 05460845). Participants were recruited with flyers in the local area and from nearby clinics. A telephone screening interview was conducted to evaluate each potential participant's current amputation status, history of amputation, other comorbid pain conditions, current and past treatments and/or medication use, and potential metabolic conditions. Inclusion criteria included: 1) amputation ≥6 months prior to enrollment; 2) PLP and/or RLP for ≥6 months; 3) pain that is at least ≥40/100 for at least 4/7 days/week ("0" referring to "no pain at all", whereas "100" referred to "the most pain imaginable"); 4) age between 18 and 65 years of age; 5) average daily consumption of >100g carbohydrates; 6) understanding of verbal and written English; and 7) body mass index (BMI) between 25 and 40 kg/m^2. Exclusion criteria included 1) unwillingness to follow prescribed diet; 2) recent weight change (>4 kg in past month); 3) being currently on a diet; 4) having a history of eating disorders, or other psychiatric disorders requiring hospitalization in the past 6 months; 5) digestive diseases; 6) difficulty chewing or swallowing; 7) reliance on others for meal preparation; 8) uncontrolled cardiovascular or pulmonary disease; 9) history of renal failure; 10) uncontrolled metabolic conditions (eg, Type I Diabetes, Type II Diabetes, metabolic syndrome); 11) use of daily opioid pain medications; 12) use of medications known to alter metabolism or digestion (eg, proton-pump inhibitors); 13) use of anti-hypertensive medications that affect glucose tolerance; 14) use of tobacco; and 15) participation in extreme exercise. For the most part, inclusion criteria were chosen to confirm impactful pain due to limb loss, whereas exclusion criteria were chosen based on factors that may affect diet adherence (ie, eating disorders, reliance on others, chewing/swallowing difficulties) and data interpretation (ie, excessive recent weight loss, already on a diet, metabolic medications). Eligible participants were scheduled for a baseline visit where they provided informed consent after a full description of the experimental protocols. Subsequently, they completed questionnaires on resilience, chronic pain and disability, cognitive flexibility, and overall quality of life at different time points throughout the study.

All tests were conducted at the University of Alabama at Birmingham testing facilities. All enrolled participants provided informed consent, and all procedures were performed in accordance with the University of Alabama at Birmingham (UAB) Institutional Review Board, the Office for Human Research Protections and complied with the Declaration of Helsinki.

Dietary Intervention

Eligible participants were recruited and enrolled into a 6-week LCD intervention. As this was a pilot study, we were interested in differences over time and not between groups. Participants first provided one week of baseline normal

dietary habits via paper food logs. Food logs consisted of the time, place, meal, types of food, and amount of food consumed each day. Once assigned to the diet, participants were provided meals and snacks that reduced their total carbohydrate intake to ≤40 g/day. Total carbohydrates refer to the amount of carbohydrates in the foods, not the amount of carbohydrates that can be digested and used by the body (net). Meals were combination of premade meals and recipes, with no restriction on fats nor protein (ie, meats and eggs). Fruits (natural sources of carbohydrates) were restricted to ≤1 cup of fresh blueberries each day, and vegetables were permitted in limited quantities of 2 cups/day of leafy greens and/or 1 cup/day non-starchy vegetables (amounts, respectively). Participants were also instructed on the types and quantities of beverages that were permitted to accompany the LCD. Beverages such as water, herbal teas, and drip coffee without sugar and with limited skim milk were permitted. Overall, this intervention provided participants with a detailed list of ingredients and recipes, along with a detailed list of instructions for daily food consumption. Additionally, all food items were delivered to each participant's residence, weekly. Participants were also instructed to record their eating during the intervention on the provided paper food logs. All steps were primarily taken to reduce any potential burden and improve diet adherence. A general timeline of the study overview and participant matriculation can be seen in Figure 1.

Measures

Anthropometric measures (ie, body weight, height, waist circumference) were not obtained during this study due to the variable mobility level of the participants.

Psychosocial Questionnaires

Measures of cognitive flexibility, depression, anxiety, and psychological resilience were obtained at baseline, 3-week, and 6-week of the intervention using the following questionnaires in paper form: 1) Pain Resilience Scale (PRS) to examine total resilience, and components therein (ie, behavioral perseverance and cognitive-affective positivity);[34] 2) Center for Epidemiologic Studies Depression Scale (CES-D) to examine levels of depression;[35] 3) Patient-Reported Outcomes measurement Information System 57 item (PROMIS-57) to examine certain aspects such as anxiety and depression;[36] 4) Multidimensional Psychological Flexibility Inventory (MPFI) to examine psychological flexibility and inflexibility;[37] and 6) Cognitive Flexibility Scale (CFS) to examine cognitive flexibility.[38]

Pain Questionnaires

Measures of pain severity and interference, overall chronic pain disability and functioning, and overall quality of life were also obtained at baseline, 3-week, and 6-week using the following questionnaires in paper form: 1) Brief Pain Inventory (BPI) Short Form to examine pain severity and interference;[39] 2) Neuropathic Pain Questionnaire (NPQ) to assess presence of neuropathic pain-like symptoms;[40] and 3) Short Form 36 (SF-36) to examine overall quality of life (ie, measures of physical function, emotional well-being, social functioning, role limitations due to some physical problem or emotional problem, energy/fatigue, general health and pain).[41]

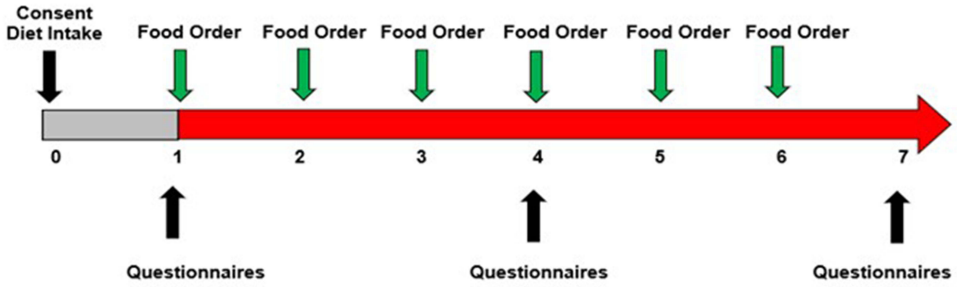

Figure 1 The general timeline of participant matriculation. Participants completed a one-week run in period (gray, baseline) before diet initiation (red), followed by 6 weeks of the LCD. Food orders were placed and delivered weekly (green arrows). Numbers below the arrow represent time in the study – one week of baseline and 6 weeks of the LCD.

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Table 1 Participant Demographics, Including Recorded Site of Amputation

Factor	Variable	Overall	
		N	%
Race	Black	5	71.4
	White	2	28.6
Gender	Man	5	71.4
	Woman	2	28.6
Site of Amputation	Bilateral Leg-Below Knee	2	28.6
	Left Leg-Below Knee	1	14.3
	Right Leg-Below Knee	3	42.9
	Right Arm-Below Elbow	1	14.3
		Mean	**SD**
Age (years)		50.6	13.6

Abbreviation: SD, standard deviation.

Statistical Analysis

All variables were analyzed using repeated measures ANOVA, and the Greenhouse-Geisser correction was used when violations of sphericity were detected (SPSS version 24.0, IBM). In all cases, a p-value of <0.05 was considered significant.

Results

Seven adult participants with amputations (M = 50.57, SD ± 13.63 years of age) were enrolled into the LCD intervention and all completed the study protocol. Most participants were male (62.5%), identified as Black (62.5%), and had a lower limb amputation (85.8%). Two had bilateral lower limb loss (28.6%) (Table 1).

At baseline, prior to any dietary intervention, participants reported an average pain resilience score of 44.42 (SD ± 6.70) on the PRS (Figure 2). Still, participants also reported moderately high levels of depression (M = 18.71, SD ± 6.16) and high levels of anxiety (M = 19.71, SD ± 5.94) on the PROMIS-57 (Figure 3A), and moderate levels of depression (M = 19.14, SD ± 6.79) on the CES-D at baseline (Figure 3B). On the PROMIS-57, a raw score of 19 on the depression subscale corresponds to a T-score of 57.7 (mild depression), whereas a raw score of 20 on the anxiety subscale corresponds to a T-score of 58.4 (above average). On the CES-D, scores above 16 are considered at risk for clinical depression. However,

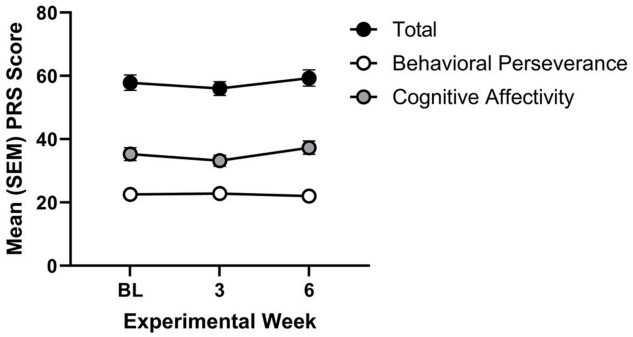

Figure 2 Mean (SEM) pain resilience scale (PRS) total score (black) and behavioral perseverance (white) and cognitive affectivity (grey) (ie, components therein) at baseline (BL), week 3 (W3) and week 6 (W6) of the intervention.

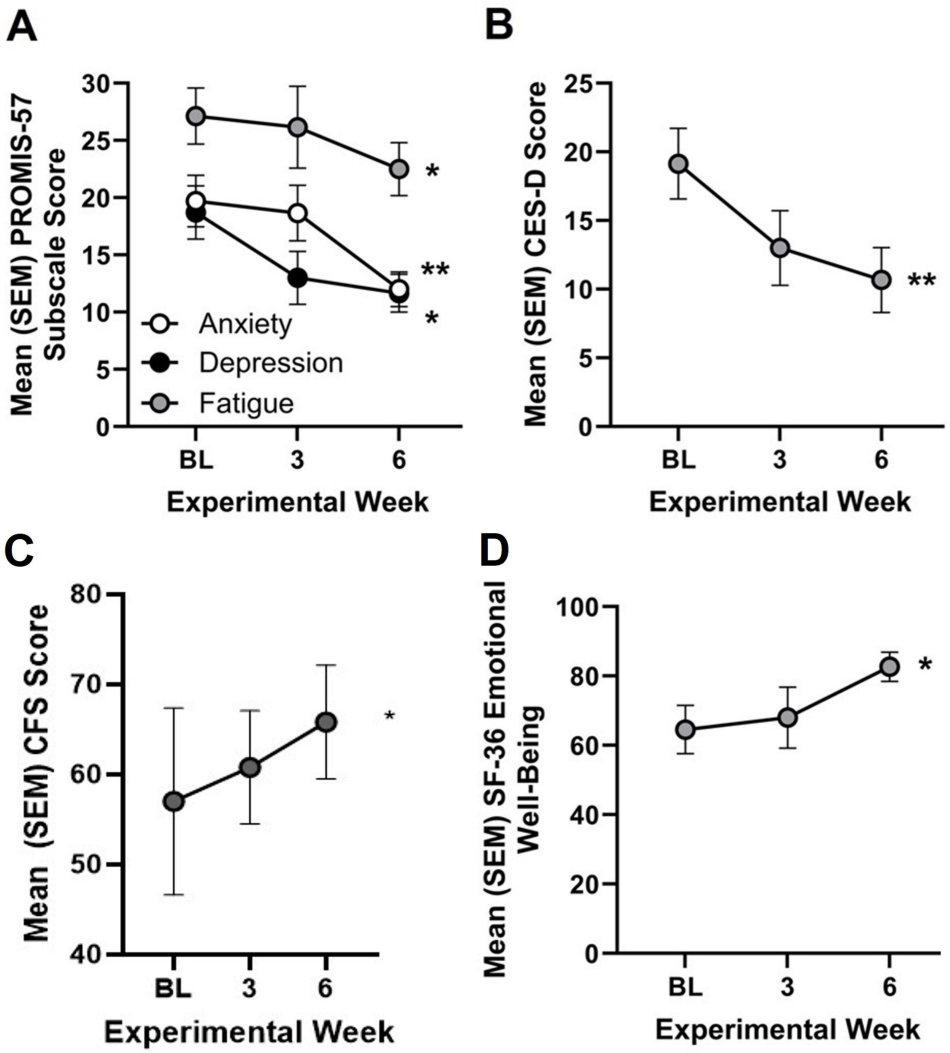

Figure 3 Psychosocial questionnaire responses at baseline (BL), week 3 (W3) and week 6 (W6) of the intervention. (**A**) Mean (SEM) Patient-Reported Outcomes Measurement Information System 57 (PROMIS-57) subscale scores for anxiety (white), depression (black), and fatigue (grey) across time. (**B**) Mean (SEM) Center for Epidemiological Studies Depression (CES-D) scores for depression across time. (**C**) Mean (SEM) Cognitive Flexibility Scale (CFS) scores over time. (**D**) Mean (SEM) Short Form 36 (SF-36) subscale score for emotional well-being across time. *p<0.05, **p<0.01.

depression levels ($F(2, 10) = 6.00$, $p \leq 0.05$), anxiety levels ($F(2, 10) = 7.750$, $p \leq 0.01$), and levels of fatigue ($F(2, 10) = 4.629$, $p \leq 0.05$) on the PROMIS-57 and depression levels ($F(2, 10) = 8.774$, $p \leq 0.01$) assessed on the CES-D were significantly decreased over the 6-week LCD intervention (Figure 3A and B). On the other hand, there were no significant differences among any other variables measured by the PROMIS-57, such as physical function, sleep, social activity, and pain interference. Similarly, total pain resilience, and its components therein on the PRS did not significantly change over the intervention. There was also no significant change in psychological flexibility or psychological inflexibility on the MPFI. Yet, there was a significant increase in cognitive flexibility ($F(2, 8) = 8.289$, $p < 0.05$) on the CFS (Figure 3C). Participants also reported significant increases in emotional well-being ($F(2, 10) = 5.519$, $p < 0.05$) on the SF-36, but no changes on any other subscales (Figure 3D).

With respect to the pain experienced by the participants, pain severity ($F(2, 10) = 7.007$, $p \leq 0.05$), but not pain interference in the BPI were significantly reduced during the intervention (Figure 4A). In addition, there was a significant change over time ($F(2, 12) = 3.882$, $p < 0.05$) on the NPQ, perhaps suggesting less neuropathic pain over time (Figure 4B).

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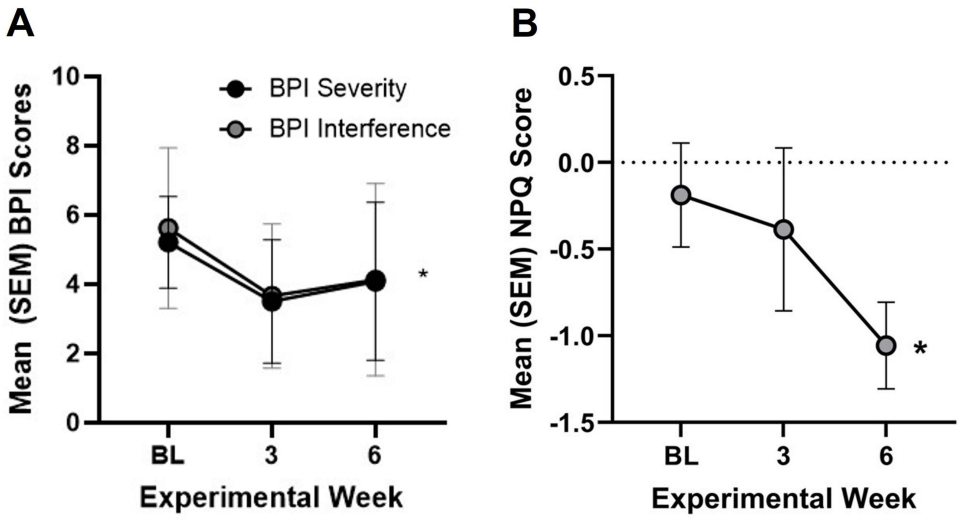

Figure 4 Pain questionnaire responses at baseline (BL), week 3 (W3) and week 6 (W6) of the intervention. (**A**) Mean (SEM) Brief Pain Inventory (BPI) scores for pain severity (black) and pain interference (grey) across time. (**B**) Mean (SEM) Neuropathic Pain Questionnaire (NPQ) scores for neuropathic pain across time. Dotted line represents the discriminant function such that scores below 0 represent non-neuropathic pain and scores at or above 0 represent neuropathic pain. *p<0.05.

Discussion

In our pilot study of adults with an acquired limb loss, the LCD provided multiple positive benefits related specifically to chronic pain, mental health, fatigue, and overall emotional well-being. More specifically, there was a significant reduction in self-reports of pain severity, a reduction in reported neuropathic pain, a decrease in depression and anxiety, a decrease in levels of fatigue, and an increase in emotional well-being during the LCD intervention. LCDs have been shown to provide significant benefits related to chronic pain and inflammation;[16,42,43] thus, it was not surprising to observe significant differences related to pain. Similarly, ketogenic diets (related to LCDs) have also been shown to be associated with increased emotional well-being,[44] whereas poor-quality diets (eg, Standard American Diet or Total Western Diet) have been shown to be associated with the presence of depression and anxiety disorders.[45] In addition, high psychological and emotional well-being is associated with an overall better quality of life.[46,47] These data suggest that an LCD diet can provide positive benefits not only for pain but also for mental health and quality of life. The positive benefits related to the LCD among our sample suggest anti-inflammatory diets (ie, an LCD) may be utilized as a pain-specific treatment approach to help manage chronic pain and psychological factors that can further affect the chronic pain experience.

There was no significant difference in pain resilience (or components therein) over time. It may be possible that initial levels of high resilience could have influenced the degree of change in any resilience factors. If participants already had high resilience, then an LCD might not be sufficient to increase those scores (ie, a ceiling effect). Although several psychosocial factors were analyzed in this study, it is likely that there may still be other psychosocial factors (not measured in this study) that could have contributed to the initial presence of high resilience. One study examining the effects of positive emotion and activity restriction on resilience and pain interference among traumatic acquired upper limb loss found that greater resilience was significantly associated with greater positive emotion and less activity restriction.[48] Furthermore, these relationships were associated with less depression and post-traumatic stress disorder (PTSD). This finding suggests that psychological resilience can be related to levels of emotional well-being and mental health that can be common among people living with an acquired limb loss. However, resilience specifically related to the experience and expression of chronic pain (ie, pain resilience) might be more complex.

Similar to previous reports demonstrating an association between improved cognitive flexibility and ketogenic diets,[49–51] we observed similar effects in our study whereby reported levels of cognitive flexibility significantly increased over time. However, the LCD did not affect psychological flexibility/inflexibility measures. Cognitive flexibility refers to the ability to control cognitive processes in order to adapt to new and/or unexpected situations.[52] Whereas psychological flexibility/inflexibility refers to the ability to interact with the environment by maintaining or changing behavior based on personal

values.[53] Although similar, these two concepts are measured differently where one is considered to be an active process (requiring effort) or change in behavior, while the other is not.[54] It could be possible the differences in mobility limitations or functioning (due to a missing limb) could have differential impacts on brain pathway connections as result of re-learning to maneuver in different environments and settings under multiple conditions. Specifically, it is possible that adults living with an amputation may be able to adapt to their new situation or environment, but might be limited in their interactions with the environment as a result of an acquired limb loss.

We also did not observe any significant effects among other contributors to quality of life for adults living with chronic pain (outside of emotional well-being, fatigue, depression, and anxiety). Although there were decreases in levels of fatigue with the LCD, there were no significant changes in measures of sleep or energy. Our participants reported experiencing lower fatigue during/after engaging in everyday tasks, chores, or physical demands post intervention, although quality of sleep or levels of energy remained the same. The level of sleep or the quality of sleep and the amount of energy an individual has can be influenced by a magnitude of other factors (eg, stress, genetics, light or sleep environments, caffeine, medications, etc.), outside of diet. Therefore, those other factors could have a more significant effect on sleep, sleep quality, or levels of energy than our intervention.

The LCD also did not have a significant effect on physical function, social functioning, social activity, role limitations due to physical or emotional problems, energy, general health, pain, sleep, or pain interference (various measures of the PROMIS-57 and SF-36). This could be due to the nature of the specific chronic pain condition examined among our sample or the length of the LCD intervention. Perhaps, a longer study would have seen more robust effects on these secondary measures. On the other hand, we did observe reductions in pain severity and neuropathic pain on targeted questionnaires (BPI and NPQ). Considering that we did not observe these effects in pain interference in the BPI, it could be possible that even if the sensation of pain is reduced or less severe, the pain may still have an impact on daily life or general activities. Additionally, the discrepancies in pain severity, pain, and general health may perhaps be due to the more directed nature of the questions on the BPI and NPQ, as opposed to more general questions used in the PROMIS-57 or SF-36. Regardless, there were other effects on the various subscales of both questionnaires (ie, fatigue, anxiety, depression, and emotional well-being).

Research shows that poor mental health (ie, depression, anxiety, and PTSD) is associated with increased sensations of PLP.[55] One study examining quality of life and levels of depression among adults with lower limb amputations found that about 78% of those with acquired limb loss had some level of depression and a lower overall quality of life.[56] In addition, high levels of depression were associated with lower levels of quality of life. This finding suggests that psychological and emotional well-being may be lower in people living with an acquired limb loss and can further contribute to a reduction in overall quality of life. Another study examining emotional factors related to an amputation found that about 66% of adults with PLP had mild to severe level anxiety, and this was more prevalent among adults between 18 and 38 years of age.[57] This suggests that anxiety levels can also be significantly high among young adults with PLP and could potentially contribute to a reduction in quality of life or a decline in mental health over time. Together, the studies above emphasize the vulnerability of those with acquired limb loss and how there should be an increased focus on attention to improve overall quality of life and emotional well-being for this group, if not reduce the associated chronic pain altogether. In that respect, the positive effects of our LCD on depression, anxiety, fatigue, emotional well-being, chronic pain, and overall quality of life are important initial steps.

Study Limitations

Some potential study limitations include: 1) adherence; 2) regional or geographical restrictions; 3) sample size; 4) lack of a control group; and 5) weight measures. Participants were not in a controlled environment during the 6-week intervention and biological measures of blood collection were not taken. Therefore, it could be possible that some participants deviated from the diet during the intervention and did not report these deviations. Nonetheless, we observed significant reductions in chronic pain self-reports among our sample. Thus, any potential adherence deviations from the diet may not have had a significant impact on the overall chronic pain benefits provided by the LCD. The limited measures of adherence that we obtained did not suggest significant differences across individuals. Also, because this study was taken place in Birmingham, AL, it is possible that predisposed dietary patterns (ie, Standard American Diets and Southern dietary patterns) could have influenced adherence to (or ease of) the diet, although there were no reports of adherence concerns or problems. In addition, this study included a very small sample size of 7

individuals. Although this was a pilot study, we are limited in the claims we can infer about the general population. However, more research should be conducted with a larger sample size, and over a longer period of time to determine if the observed trends above are consistent and generalizable to this population. We did not compare to a control group to measure the effects related to the intervention. Therefore, we can only imply that our observations are a result of the dietary intervention and not due to natural fluctuations or changes over time or participation in a study. Finally, due to diversity in mobility and the use of assistive mobility devices (ie, wheelchairs, walkers, crutches), we were not equipped to accurately measure body weight throughout the study and do not know whether participants lost significant weight or not. Anecdotally, a number of participants noted that the fit of their prosthetics changed during the LCD intervention, suggesting weight loss.

Conclusions

Our findings highlight that an LCD can have significant effects on chronic pain and various factors affecting quality of life in adults living with an acquired limb loss. Yet, there are limited studies examining the effect of a diet intervention on chronic pain and quality of life in this population. From the collection of data above, we have demonstrated the potential of an LCD to improve or positively affect patient reported levels of pain severity, neuropathic pain, fatigue, social functioning, and overall emotional well-being among adults living with an acquired limb loss in just 6 weeks. Our results indicate that an LCD may be utilized as a treatment to not only improve reports of chronic pain but also provide critical psychological benefits (related to depression and anxiety) that can also be associated with all chronic pain experiences, including PLP/RLP. Anti-inflammatory diets in combination with other therapies (eg, physical medicine and physical therapies) may provide significant relief for individuals living with an acquired limb loss and suffering from chronic pain. Therefore, more research should be conducted across a much larger sample to further investigate the positive effects of an LCD on chronic pain conditions, like PLP and RLP.

Data Sharing Statement

The authors will make deidentified data available that includes summary scores and basic demographics upon request. Study questionnaires are publicly available from the sources. Data will be available for at least 2 years from study publication and can be requested from the corresponding author following this period of time.

Ethics

The UAB Institutional Review Board approved all procedures and protocols outlined above.

Acknowledgments

This article reports the original results of a dietary healthcare intervention registered at clinicaltrials.gov (NCT 05460845, registered on 2022-07-13).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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