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Review

NUTRITION AND EXERCISE: IMPACT OF LEAN BODY MASS PRESERVATION ON HEAD AND NECK CANCER OUTCOME. A REVIEW

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Abstract:
Rationale: Smoking and alcohol consumption, combined with the tumor location and antineoplastic treatments are the main reasons that put HNC patients at a high risk of malnutrition. Current evidence shows that more than weight loss alone, is the impaired lean body mass (LBM) that may be the main predictor of both mortality and complications in HNC patients. The main goal of the nutritional intervention should be LBM preservation and it seems that exercise can influence LBM preservation and treatment-related recovery, as well as improve functional capacity and modulate adverse side effects. We reviewed the existing literature regarding interventions with both nutrition and exercise designed to preserve LBM in HNC patients, during the course of treatment and/or after its completion. **Methods:** A literature search for relevant papers indexed in MEDLINE and Cochrane Library was conducted, until February 20th, 2020. All papers written in English, focusing on interventions in humans with both nutrition and exercise, designed to preserve LBM, were selected. **Results**: Four articles met the inclusion criteria. The length of interventions varied from 3 to 12 weeks. One included protein and creatine supplementation; one Oral Nutrition Supplements and two nutritional counselling. Exercise interventions varied from progressive resistance training and strength, endurance, and flexibility exercises. **Conclusions**: A multidisciplinary approach with nutrition and exercise is suggested to be the key in the preservation and rehabilitation of LBM. The reviewed studies demonstrate the possibility to plan successful exercise and nutritional interventions for HNC patients, during and after treatment, with high compliance.

Keywords: head-neck cancer, nutrition, exercise, cachexia, body composition, lean body mass, outcome

1. Introduction

Head and neck cancer (HNC) causes approximately 300.000 annual deaths, with a 40% to 50% survival rate.[1] Smoking and alcohol consumption, combined with the tumor location and antineoplastic treatments, are the main reasons by which HNC patients have a high malnutrition risk[2]. About 60% of HNC patients will develop a poor nutritional status between diagnosis and treatment completion, and about 80% will lose weight during treatment. The lost weight represents around 20% of the patients' weight at the time of diagnosis [3], and about 50% of it is muscle mass [4].

Cachexia, in advanced cancer stages, is irreversible by conventional nutritional support. This multifactorial syndrome affects more than 50% of the HNC patients and is associated with a higher surgical risk, a progressive functional deficit, decreased Quality of Life, and worst treatment response[5,6]. Of note that 20% of the cancer-related deaths are caused by cachexia[5]. Current evidence shows that more than weight loss alone is the impaired lean body mass (LBM) that the main predictor of mortality as well as complications in HNC patients. Hence, the main goal of the nutritional intervention should be LBM preservation[7,8], once nutritional interventions have a positive impact on patients' survival and are essential for treatment completion[3]. One other condition associated with increased mortality in cancer patients is sarcopenia, which is characterised by a decrease in muscle mass with or without a decrease in adipose tissue[9].

There is some evidence suggesting that exercise has a positive impact on LBM preservation, treatment-related recovery, as well as on the improvement of functional capacity and management of treatment-related side effects[10, 11].

We reviewed the existing literature regarding interventions designed to preserve LBM in HNC patients that included both nutrition and exercise during treatment and/or after its completion.

2. Materials and Methods

A literature search for relevant papers indexed in MEDLINE and Cochrane Library until February 20th, 2020 was conducted, using the following terms: head and neck neoplasms OR laryngeal neoplasms OR hypopharyngeal neoplasms OR oropharyngeal neoplasms OR Lip neoplasms OR mouth neoplasms OR salivary gland neoplasms OR nasopharyngeal neoplasms OR nose neoplasms OR paranasal sinus neoplasms OR ear neoplasms AND exercise OR rehabilitation program OR physical activity OR prehabilitation AND diet therapy OR nutrition. In accordance with the aim of the present review, selected articles had to meet the inclusion criteria: longitudinal studies, written in English, with interventions in humans including both nutrition and exercise, planned to preserve LBM in HNC patients during the course of treatment or after its completion. Were excluded papers that only considered one of the interventions (nutrition or exercise).

3. Results

A total of 578 articles were identified in the selected databases, using the designated search terms. The articles' full texts were evaluated after a first selection based on the titles and abstracts. Four articles were considered eligible to be reviewed[12-15] **(Table 1)**. All studies included HNC patients, but one also included other cancer types and locations[14]. All reviewed studies used specific exercise training programs in the exercise intervention, including resistance/strength training, and two of them also included other types of exercise. No studies regarding prehabilitation were found.

Table 1. Studies that met the inclusion criteria

Authors	Patient population	Exercise Intervention	Nutritional Intervention	Results
Lonbro et al., 2012	21 HNC (7 placebo group)	Resistance Training	Supplementation: 30g protein + 5g creatine	Higher LBM, strength and functional performance improvement.
Eades et al., 2011	27 HNC	Strength, endurance and flexibility	Nutritional counselling	Strength and functional performance improvement.
Gagnon et al., 2013	131 Palliative (stage III or IV): 15% HNC	Strength, endurance and flexibility	Nutritional counselling	Funcional performance improvement.
Sandemael et al., 2017	29 HNC	Resistance Training	ONS	Lower loss of LBM at 6th week and lower weight loss (IDT)

HNC - Head and neck cancer, IDT - Intervention during treatment, LBM - Lean Body Mass, ONS - Oral nutritional supplements.

3.1. Nutrition Interventions

In Lonbro et al., 2012 trial, participants were randomized between a placebo group (that ingested placebo in the seven days pre-trial - 4x5g maltodextrin - and in every training session) and an intervention group (that ingested both creatine (5g) and protein powder (30g) supplementation in the seven days pre-trial - 4x5g creatine - and in every training session). To assess the macronutrients and energy intake during the intervention period, the participants were asked to do a four-day diet registration (3 weekdays and one weekend day). Compliance with the supplementation was reported by pre-trial questionnaires as well as at 12 weeks of exercise intervention[12].

Sandemael et al., 2017, instructed the participants to include a minimum of one 350 kilocalories oral nutritional supplement (ONS). Adherence to the intervention was assessed through weekly recalls. The group that started the intervention after the treatment beginning could attend nutrition counseling and cooking classes[15].

Gagnon et al., 2013 and Eades et al., 2011, both included nutrition counseling with ONS when needed[13,14]. The counseling sessions took place between 3 [13] and 5 [14] times during the intervention.

3.2. Exercise Interventions

Sandemael et al., 2017, randomized patients into two groups, one assigned to a resistance training beginning in the first six weeks of treatment, consisting in 2 weekly resistance training sessions with the duration of 30 minutes, starting with a 5-minute warmup of treadmill walking or stationary cycling and including two lower body exercises (leg extension and seated hamstring curl) and two upper body exercises (chest press and standing row). The exercises were repeated 6 to 12 times and the number of sets ranged from 3 to 4 sets. The other group was assigned to a three-week resistance training program, beginning 2 to 4 weeks after the end of treatment. Patients attended three planed sessions per week for 45 minutes and additional training sessions, which took place in a rehabilitation center located 150km from the hospital. The exercise sessions consisted of 3 lower body exercises (seated leg press, leg extension, and seated hamstring curl) and three upper body exercises (chest press, pulldown, and seated row).The exercises were repeated 6 to 12 times and the number of sets ranged from 3 to 4 sets. Functional status, including strength and cardiorespiratory fitness, was not evaluated. The authors considered different interventions between the two groups of participants (with regards to training modalities, duration of intervention, and place), mentioning that it is a pilot trial preceding a future larger multicenter trial[15].

Gagnon et al., 2013, included semiweekly sessions with a physical therapist and a home exercise plan, beginning after treatment completion from 10 to 12 weeks. For the physical functioning evaluation, the 6-Minute Walk Test (6MWT) and the 5-Metre Walk Test (5MWT) were used. In the 6MWT, it was measured the walked distance in 6 minutes and no encouragement was given. At each minute, the patients were informed of the walked distance. The maximal gait speed was assessed with the 5MWT in which patients walked as quickly as possible over 10 meters. To minimize the effects of acceleration and deceleration, it was measured the distance at 5 meters.

Eades et al., 2011, included an individually planned rehabilitation program of 8 weeks, with semiweekly exercise sessions with a physiotherapist and a home exercise plan. The exercise sessions included endurance (walking or biking), strength (lower and upper extremity free weights), and flexibility. The 6MWT was used to assess functional status. The median attendance was ten sessions (range, from 5 to 23).

Lonbro et al., 2012, planned 30 training sessions over 12 weeks. It included a total-body training program with seven exercises that included leg press, knee extension, hamstring curls, chest press, sit-ups, back extension, and lateral pulldown. There were three instruction sessions in the first two weeks and an average of 5 supervised sessions in the following ten weeks. The other sessions had no supervision. Exercise compliance was assessed through patient registrations.

There appears to be some evidence favouring exercise interventions after treatment completion, as compared to exercise interventions during treatment; however, these are still preliminary data and need further research[16]. The superiority of multicomponent lifestyle interventions that include both physical activity and exercise, either during or after treatment completion, have not been confirmed[15].

The study by Gagnon et al., included 131 patients with advanced cancer (stages III and IV), with different cancer types, 38% during chemotherapy (CT). The average age of the patients that completed the program was 63 years (63.4 +- 11.2 years) and the three most prevalent cancers were colorectal (16%), HNC (15%), hematologic cancers who had not received a bone marrow transplant and breast cancer (10%)[14]. The intervention had a duration of 10 to 12 weeks, and patients attended a median number of 7 exercise sessions (interquartile range: 4-11). Patients showed a decline in symptoms severity, an improvement of 41m (95% confidence interval: 29m to 52m) in the 6MWT and an improvement in the average maximal gait speed by 0.15m/s (95% confidence interval: 0.09 m/s to 0.21 m/s) from baseline to the end of the program. The majority of the patients (77%) had a variation of less than 2kg in their weight or gained more than 2kg during the program. Although a significant improvement in functional performance was found, because body composition was not reported, it was not possible to assess the effect of this intervention on LBM. Further it was not possible to disclose if the improvement can be attributed to increases in muscle mass or to enhanced neural drive, or muscle quality or to any other possible adaptation to exercise.

Sandemael et al., 2017, included 29 HNC patients randomized into two groups, one (EN-DUR) with 18 patients and intervention planned for the first six weeks of radiotherapy (RT) / chemoradiotherapy (CRT) and another (EN-AF) with 11 patients, beginning the intervention 2 to 4 weeks after RT/CRT treatment. Both interventions had a duration of 3 weeks. Body composition was assessed by computed tomography scan (CT scan) at the 3rd lumbar vertebra, before the intervention and at 6th and 14th weeks. The average age of the participants was 62 years (62.1 +- 2.2 years) in the EN-DUR group and 64 years (64.3 +- 2.0 years) in the EN-AF group. The ONS adherence was 52% in the EN-DUR group and 40% in the EN-AF group and the overall exercise adherence was 74% and 49%, respectively. No significant difference in weight change from baseline until the 14th week was noted between groups. The total loss of body weight in the EN-DUR group was -5.9 kg (SD, 4.38; P <.001) and in the EN-AF group -6.6 kg (SD, 8.03; P = .040). From baseline until the 6th week there was a 2.3 cm^2/m^2 (P = .063) difference in muscle mass between groups and from the 6th week to the 14th week a difference of -1.7 cm^2/m^2 (P = .095), but from baseline until the 14th week no difference was found between the groups and the total muscle mass reduction was -2.6 cm^2/m^2 (SD, 2.26; P = .002)[15].

Lonbro et al., 2012, included 21 patients after RT /CRT; seven were included in the placebo group (PLA) and 14 in the intervention group (PCOR). The intervention had a duration of 12 weeks. Body composition was assessed using dual-energy X-ray absorptiometry (DEXA)[12]. The average age of the patients who completed the program was 56 years in the PCOR group and 60 years in the PLA group. Although both the PLA and the PCOR group showed an increase in LBM, the PCOR group showed a higher increase during the 12-week program (5,0 +- 3,8% vs. 2,8 +- 2,5%). A superior training effect was noted in LBM in HPV-positive patients, and no difference was noted between treatment modalities (CRT or RT). Fat mass decreased non-significantly in both groups, and the authors reported significant improvements in functional performance tests after the resistance training in both groups.

Eades et al., 2011, included 27 patients, and 82% of them after CRT completion. The intervention had a duration of 8 weeks, and body composition was not evaluated [13]. The majority of patients were male, with an average age of 55 years (54,9 +- 9,2 years). At week 8 the patients showed a reduction in symptoms like pain and weakness (strong reduction), shortness of breath, anorexia, insomnia, and depression (moderate reduction) and a significant improvement in the quality of life. There was an improvement by 59m (95% confidence interval: 27m to 91m) in the 6MWT. Six patients lost more than 1kg, and 21 patients had a variation of less than 1kg in their weight or gained more than 1kg during the program.

Weight and weight loss were assessed in the four studies[12-15].

4. Discussion

Although the interventions included in this review are heterogeneous, positive results preserving or increasing LBM without adverse effects were still identified in the studies that included body composition evaluations. Therefore, resistance training appears to promote muscle protein synthesis, and this effect can potentially be improved when used along with amino acids supplementation[17] in accordance with what has been observed in the general population [18]. Exercise interventions seem to have also a positive effect on aerobic capacity and functional status in this specific population[19].

Lonbro et al., 2012, reported an increase of 2.8kg +- 2.5% ($p<0.07$) in LBM and also an improvement in the functional status in the group of patients that only used resistance training (without supplements), demonstrating that resistance training on its own can improve LBM[12]. The same research group, using the same set of exercises, evaluated 24 healthy individuals to compare the results with the ones of the 55 HNC patients. It was possible to demonstrate that HNC patients after RT treatment show less LBM, strength, and functional status, but the reduction can be reversed with resistance training[8].

Sandemael et al., 2017, reported a smaller LBM decrease despite the significant weight loss until the 6th week (-1,7 cm^2/m^2 vs. -4,0 cm^2/m^2) in the group, which initiated the intervention during antineoplastic treatment with no further significant losses until the 14th week. The group which initiated the intervention after cancer treatment, did not show an increase in the LBM after its beginning[15].

Eades et al., 2011 and Gagnon et al. 2013, did not evaluate the participants' body composition, but identified significant improvements in the functional parameters, with increases in the 6MWT of 59m and 41m respectively[13,14] and, improvement of 0,15m/s in the maximal gait speed at the end of the intervention[14].

The majority of the interventions included in this review started after treatment completion, with good attendance rate. However, Sandemael et al., 2017, reported a higher attendance rate in the group that started the exercise plan during treatment (74%) than in the group that started after treatment completion (49%)[15]. Factors like the time chosen to initiate the exercise sessions, its flexibility[12,13], as well as the symptom control and patient preference[4], seem to be crucial for the successful outcome of the intervention[12,13]. These results are still not consensual as in an exploratory randomized trial, Capozzi et al., 2016, identified a higher attendance rate in the group that started the exercise plan after treatment completion[16].

It seems that supervised interventions (e.g., Lonbro et al., 2012) are more effective in preserving or enhancing LBM and functional performance as compared to interventions that include a home-based or unsupervised component. This is in line with a previous meta-analysis showing higher effectiveness of supervised interventions on quality of life and physical function, over unsupervised interventions, in cancer patients[21].

The benefits of the exercise for HNC patients go beyond the increase in LBM and the strength improvement as better sleep and improvement in quality of life have also been reported[16,20]. Nutritional intervention guidelines for cancer patients highlight the importance of nutritional intervention as well as the use of ONS when necessary[7,22] as it is fundamental to counter the imbalance created by both the low caloric intake and the disease hypermetabolism[17].

Although it seems that the conventional nutritional support is insufficient to reverse cachexia and that weight gain does not always represent LBM improvement in HNC patients[17], weight loss seems to be associated with significant LBM decrease, reduction in functional capacity and increased inflammation[7,4].

It seemed possible to reduce or reverse weight loss with the nutritional and exercise interventions planned in the studies in this review. At the end of the program, Eades et al., 2011, and Gagnon et al., 2013, reported that 77% of patients either maintained or gained weight[13,14]. Sandemael et al., 2017, reported a lower mean weight loss in the group of participants that initiated the exercise during treatment (3,9% vs. 5,5%)[15].

In the Lonbro et al., 2012 trial, the intervention group (that ingested 5g of creatine and 30g of protein powder) seemed to show a tendency towards a higher LBM gain when compared with the placebo group. Although these results do not have statistical significance, the authors consider them clinically relevant, and substantiating the use of supplementation. The low power of analysis occurred due to a significant dropout rate in the intervention group. The authors considered that the creatine supplementation could be an additional advantage, once the macronutrients ingestion did not show differences between groups (1,3 g/kg +- 0,4 in the intervention group and 1,4 g/kg +- 0,5 in the placebo group), despite the protein supplementation set at baseline for the intervention group[12].

Dietary supplementation compliance varied between 40%[14] and 76%[12]. It seems that nutritional counseling can improve compliance with ONS intake, with the potential to reduce malnutrition[23,24]. Nutritional counseling sessions have shown to be a useful tool when it comes to weight maintenance and optimization of energy and protein intake in HNC patients[24], and in the studies in which these were included, there was a high patient compliance (93% to 95%) [13,14].

This review has some limitations as only studies in English and published in only two databases (MEDLINE and Cochrane Library) were included. Furthermore, the studies included are heterogeneous and typically have small sample sizes without a control group.

5. Conclusions

Interventions that combine nutrition and exercise seem beneficial for LBM preservation in HNC patients. Published studies are heterogeneous with small sample sizes that hamper result systematization. Nevertheless, it is possible to depict that a multidisciplinary approach has additional benefits in the preservation and rehabilitation of LBM. The studies included in this review show that interventions that include both exercise and nutrition are feasible for HNC patients, during and after treatment with high compliance and positive results.

More studies are necessary to enable the assessment of the best intervention model and the best timing for its initiation, having in mind the early preservation of LBM and functional capacity with good patient compliance. It may be relevant to consider interventions that facilitate the maintenance of the acquired lifestyle habits in the long term, in order for the benefits to be maintained throughout the years.

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