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Exercise during neoadjuvant treatment: is high-intensity interval training (HIIT) a smart choice?

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Abstract

This work investigated the efficacy of High-Intensity Interval Training (HIIT) on cardiorespiratory fitness in patients with cancer undergoing prehabilitation. Further, we explored the potential molecular mechanism underlying HIIT and tumor cells. The HIIT protocols trend to increase VO_2peak to a similar fashion of moderate high-volume exercise (+1.6 to 2.6 ml/kg.min), 10-20% compared to baseline levels. One striking difference between protocols is the shorter time commitment favouring HIIT, which may be an allied instrument in the busy neoadjuvant schedule. Thus, HIIT has been emerged as a "smart" exercise alternative in the prehabilitation repertory. In cancer cells, preliminary studies showed that immunosurveillance and pro-inflammatory activation arrived as a potential anticancer effect underlying HIIT protocols. HIIT did not alter *PGC1-α* expression (P=0.09), a key player in exercise-induced mitochondrial biogenesis and a driving force towards oxidative metabolism. However, understanding the interplay between HIIT and tumor physiology has just begun. HIIT is likely to settle as an alternative in cancer prehabilitation and future investigations should focus on stratify who are the "best" candidates.

Introduction

Exercise oncology guidelines generally recommend 30 to 60 min of moderate-intensity exercise on most days of the week [1,2]. Despite overwhelming literature regarding exercise benefits across all stages of cancer treatment, most adults fail to achieve the minimum dose necessary. Common important barriers include lack of time, fatigue, transportation, and lack of information [3,4]. Therefore, exercise prescription innovations represent a potentially valuable approach in cancer care.

The prehabilitation encompasses, among others, an exercise rehabilitation program between diagnosis and surgical treatment. This period is usually combined with neoadjuvant chemo-radiotherapy, which leads to additional surgery and survival benefits, whereas come to a cost of functional capacity when patients most need. Just five weeks of Neoadjuvant Chemo-radiotherapy significantly compromised VO_2peak (-2.5 ml/kg.min, 95% CI -1.33 to -3.71) in patients with rectal cancer [5]. Of interest, authors showed that one arm following interval-exercise protocol for 6 weeks improved VO_2peak (+2.65 ml/kg.min, 95% CI 1.19 to 4.10) The goals of prehabilitation are enhancing physical capacity, reduce surgical morbidity and accelerate post-surgical recovery in patients with cancer [6]. Given the short perioperative period, sometimes less than a month, novel strategies have been postulating to maximize adherence of patients with cancer while optimizing physical fitness [7]. High-intensity Interval Training (HIIT) protocols are recognized to improve cardiorespiratory fitness similar to traditional endurance protocols, with only the third part of time commitment [8].

HIIT protocols describe brief episodes (30 seconds to 5 minutes), usually above 80% of VO_2peak, interspersed with rest or activity recovery [9]. The impact of HIIT protocol on the human physiology goes beyond time-efficiency, and novel molecular approaches shed light on the unique molecular adaptations [10]. In patients with breast cancer undergoing adjuvant chemotherapy (Anthracycline and Cyclophosphamide regime), HIIT protocol for 16 weeks counteracted skeletal muscle dysfunction by enhanced mitochondrial turnover and functionality [11]. However, only a few studies investigated HIIT programs during prehabilitation in patients with cancer. Thus, we aimed to explore the relationship between HIIT and cancer patients undergoing neoadjuvant therapy over two critical outcomes: the cardiorespiratory fitness and the tumor-environment interplay.

HIIT on cardiorespiratory fitness during neoadjuvant treatment

For decades, HIIT programs have been utilized in different healthy and athlete populations with positive effects on cardiorespiratory fitness, vascular functional, metabolic factors, and body composition [12]. For clinical populations, HIIT parameters are commonly adjusted to lower loads as a substitute for maximal efforts in healthy individuals [13]. However, only the recent literature attempts to implement HIIT in the cancer setting [14]. To date, a growing body of literature suggests that HIIT can be safely considered as an exercise alternative in patients with cancer [15,16].

One systematic review and meta-analysis of HIIT protocols during all stages of cancer treatment highlighted significant improvements on VO_2 peak compared to usual care, while findings showed no superior effect than moderate endurance training [15]. These data are consistent with data from healthy middle-aged adults [17]. Regarding prehabilitation stages, a consensus of the effects of HIIT on

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Table 1. Effects of High-Intensity Interval Training (HIIT) on cardiorepiratory fitness in patients with cancer undergoing neoadjuvant treatment. NSCLC – non-small cell lung carcinoma; CRC – colorectal cancer; FITT principle = F (frequency), I (Intensity), T (time), T (Type); 6MWT – six-minute walk test; AT – anaerobic Threshold, NAT – neoadjuvant treatment

Study	Population	HIIT Protocol	Control	Main fitness findings
Hwang C, *et al.* [19]	NSCLC, n=24	F =24 sessions (3 times x week) I=80% VO_{2peak} and recovery 60% VO_{2peak} T=2-5 minutes length T=treadmill or cycle ergometer	Unsupervised general exercise orientations	The intervention arm improved VO_{2peak} in 1.6 ml/kg.min (10.5%). Control group had VO_{2peak} unchanged
West MA, *et al.* [5]	Rectal	F=18 sessions (3 times x week) I=50% difference VO_{2peak} and VO_2 at θ_L, recovery = 80% of VO_{2peak} at θ_L T=2 min sprint and 2 min recovery (28-32 min total) T=cycle ergometer	Usual care	Exercise group re-established fitness levels compared to baseline (before NAT). Exercise intervention improved VO_{2peak} in 2.6 ml/kg.min following NAT. Control group had worsened VO_2 over the whole study.
Licker M, *et al.* [21]	NSCLC, n=151	F = 2-3 times x week, 26 days total I=80 – 100% peak watts rate T=2 sets of 10min (15 sec sprint + 15sec recovery) T=cycle ergometer	Not specified	Intervention group improved VO_{2peak} in 2.5 ml/kg.min (14.5%) and 6MWT in 66m (15%). Both parameters declined in UC group, VO_{2peak} (-8%) and 6MWT (-0.5%)
Karenovics W, *et al.* [21]	NSCLC, n=151	F = 2-3 times x week, 26 days total I=80 – 100% peak watts rate T=2 sets of 10min (15 sec sprint + 15sec recovery) T = cycle ergometer	Not specified	Following rehabilitation, intervention group increased VO_{2peak} (+17.7%), whereas control group declined (- 6.3%). 1 year follow up showed 10-20% declined in VO_{2peak} regardless of intervention
Boereboom CL, *et al.* [18]	CRC, n=18	F=3-4 times x week for 19 (± 7 days) I=100 – 120% max Watts at baseline T=5 x 1 minute + 90 sec rest. T=cycle ergometer	Not Applied	Fitness parameters VO_{2peak} and AT did not change.

cardiorespiratory fitness remains unclear. The (Table 1) summarized five studies using HIIT during neoadjuvant stages and their findings on fitness achievements [5,18-21]. Three studies (60%) were conducted in patients with non-small cell lung cancer. The length of programs ranged from 19 days to 8 weeks. The intensity was settled between 80% of VO_2peak to 120% of peak watts rate, depending on the baseline protocol (cardiopulmonary exercise test or rump up protocols). Cycle ergometer was the preferred exercise modality. HIIT appeared to reverse fitness deconditioning observed in cancer patients undergoing neoadjuvant treatment. Moreover, there was a trend that HIIT programs improved VO_2peak for + 1.6 to 2.6 ml/kg.min, 10-20% compared to baseline. This magnitude was similar to observe in patients scheduled to abdominal cancer surgery and performed Moderate Continuous Intensity Training during the prehabilitation (VO_2 peak +1.8 to 2.6 ml/kg.min) [22]. Some authors defined the minimum clinically important difference in VO_2 of lactate threshold of 2.0 ml/kg.min for patients undergoing abdominal surgery [20]. Although this threshold is not clear in cancer patients, the HIIT protocol seems to achieve this goal emerging as an effective intervention.

Despite no clear dominance of HIIT over moderate continuous training on aerobic fitness, the HIIT may act trough specific biological mechanisms. While moderate-continuous training enhanced body capacity to transport, extract and eliminate oxygen [23], some data indicated that even a few sessions of HIIT facilitate oxidative phenotype towards a more mitochondria-centric adaptation to oxidative metabolism [10]. It is well documented that PPARg coactivator-1 alpha (PGC1α) activation leads to mitochondrial biogenesis, fatty acid oxidation, and GLUT-4 expression in skeletal muscle [24]. However, these physiologic adaptations remain poorly investigated in other tissues or in the malignant microenvironment. Given that forces favouring oxidative metabolism may be critical to impair tumor development [25], the next section will explore the biological interplay between HIIT and tumors.

HIIT effects on tumor development

Tumor metabolism is a hallmark of cancer [26]. The metabolic flexibility of tumors is coordinated by mitochondria functionality and provides cancer cells either, an opportunity to survive under energy stress, intense oxidative and metabolic hassle, or die for apoptosis and autophagy [27-29]. It is rationale hypothesized that chronic HIIT protocols may challenge tumor cells towards more oxidative metabolism reducing tumor capacity to shift between aerobic and anaerobic metabolism undergoing stressful conditions. Among several mediators of mitochondria metabolism, the PGC1-α is one of the main controllers. PGC1-α is target by different kinases activated under stress conditions, including exercise, cold, oxidative stress, and even cancer therapy itself [30]. Given that exercise intensity is one of the key factors influencing PGC1-α phosphorylation, investigations of HIIT-induced PGC1-α is warranted in other tissues rather than skeletal muscle cells.

The overexpression of PGC1-α shows a dual role in cancer cells [31]. While facilitates cancer cells survival through the oxidative metabolic shift and therapeutic resistance in breast cancer, PGC1α can act as a tumor suppressor in melanoma and prostate cancer triggering apoptosis pathways [32]. The discrepancy may be related to the kind of stressor-induced (energy, metabolic or oxidative stress), whether or not tumorigenesis is dependent of PI3K-Akt signalling [33], or the stage of tumorigenesis. The signalling pathway of PGC1-α activation is complex and goes beyond the scope of this work. For an entire view of PGC1-α pathway, as well their role in cancer metabolism, please see [31].

Currently, a few studies have directly investigated HIIT-induced PGC1-α in tumor cells. A recent study submitted patients with colorectal cancer to acute or chronic HIIT sessions (4 weeks, 85-95% at Heart Rate peak) and assessed serum-conditioned responses *in vitro*. The samples collected right after the HIIT session reduced colorectal cancer cells viability, whereas resting serum showed no effect [34]. One preclinical study showed that 16 days of HIIT protocol (running, 5 sets of 3 min at 18m/min + 4 min at 25m/min) reduced tumor growth by 52% and prolong mice survival [35]. The HIIT antitumor response was associated with higher gene expression of *CD274* (PD-L1) and *VEGFA*, genes enrolled with immune/inflammation axis and angiogenesis. However, *PGC1a* expression in tumor cells was unchanged (P=0.09). Therefore, a mechanism towards HIIT-induced PGC1-α in tumor cells is uncertain, while immunosurveillance and pro-inflammatory mechanism emerges as novel players in the HIIT-tumor relationship [36,37].

Future Directions and Conclusions

HIIT appears to be an attractive exercise option in modern society and in the busy oncology schedule. As expecting more debates of exercise in cancer setting, the intensity parameter will be a decisive discussion of personalized therapy. The HIIT literature shows similar cardiorespiratory improvements to the traditional continuous-moderate exercise. However, the biological mechanisms differ between two protocols. HIIT protocols are stronger candidate favouring oxidative metabolism and mitochondrial biogenesis towards PGC1-α. However, limited data support this hypothesis in tumor cells. Rather, continuous-moderate training trend to focus on lipid and glucose metabolism. More studies are warranted to sustain the HIIT influence on immune and inflammatory axis as primarily antitumor interplay.

Future directions of HIIT literature in the prehabilitation setting should explore the "best" candidates to the exercise programme. From molecular perspective, tumors with high glycolytic phenotype in line with the establishment of the epithelial-to-mesenchymal transition and deficiency in immune surveillance appear as theoretical candidates. From physiological perspectives, the major benefits of HIIT are for patients demanding rapidly improvements in cardiorespiratory fitness while preserve muscle mass. Despite promising in some chronic diseases, HIIT protocol is likely to settle as "an additional" tool for exercise repertory. Current exercise professionals should be aware of how, when and for whom HIIT may be applied to cancer survivors.

Conflict of Interest

Authors declare none.

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