

Hypothesis

Lactate can promote metastasis in cancer, what about physical exercise?

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Abstract

Cancer is regarded as one of the most cunning and perilous diseases globally. Numerous studies have emphasized the significance of exercise both prior to cancer diagnosis and after hospital discharge, in conjunction with various treatment approaches. However, the role of exercise during cancer itself remains an unresolved query. Oncology research reveals that three crucial factors for metastasis and tumor progression during cancer are lactate, platelets, and angiogenesis. Interestingly, exercise can also have a noteworthy impact on stimulating these three factors. In this brief review, our aim is to shed light on the potential appropriateness of exercise during cancer.

Key Words: Cancer, Physical exercise, Metastasis, Lactate

Introduction

Although cancer treatments have been identified, cancer is still the number one cause of death worldwide (Kroemer et al., 2024). In the meantime, sports oncology studies have reported in their results that physical activity can lead to the management of the severity of the disease for cancer patients, reducing tumor volume and increasing the number of tumor-specific immune cells (Smith-Turchyn & Mukherjee, 2024). However, with a deeper look at oncology results, the importance of lactate in tumor growth has been noticed (Dunn et al., 2002). On the other hand, exercise physiology has highlighted the importance of lactate released due to exercise. However, an important hypothesis is raised whether physical activity during cancer can affect the released lactate and what will be the fate of lactate with the tumor. This study will seek to answer this question.

Hypothesis

Under physiological conditions, the heart, brain, and skeletal muscles use lactate as a fuel source. It can also be converted to glucose in the liver by the Cori cycle and serve as an alternative source of energy (Gladden, 2004). On the other hand, Tumor cells must produce sufficient ATP and biosynthetic precursors to sustain the demands of cell proliferation. Otto Warburg showed that tumor cells take up large amounts of glucose and produce large amounts of lactate even in the presence of oxygen (K. G. de la Cruz-López et al., 2019). Lactate has also been shown to promote local tumor invasion and the formation of metastatic disease (Ahmadi Hekmatikar et al., 2019; Z. Pennington et al., 2019). Many studies support that lactate can lead to tumor aggressiveness and increased metastasis (Brizel et al., 2001; Zach Pennington et al., 2019; Rizwan et al., 2013). However, the mechanism of how lactate can lead to the aggressiveness of the tumor environment still needs to be clarified. However, it seems that lactate can lead to an increase in angiogenesis and a decrease in the immune system's function, which can be one of the main justifications for the importance of lactate in cancer (Ding et al., 2017; Hunt et al., 2008).

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Looking back at the history of physical exercise and its connection to cancer, numerous studies have indicated that engaging in physical exercise can have a significant impact on enhancing brain function, boosting the immune system, improving physiological aspects such as muscle strength, and even affecting tumor size in cancer patients (Clemente-Suárez et al., 2023; SEVERSON et al., 1989; Westerlind, 2003). These studies cautiously suggest that physical exercise at low to moderate intensity can be beneficial for individuals with breast cancer. However, recent hypotheses and more in-depth investigations into the relationship between physical exercise and tumors have introduced new concerns. One of the proven hypotheses related to exercise is that exercise can lead to an increase in lactate in the body (Brooks, 1986; Hubbard, 1973). Among different exercises, high-intensity interval training results in the greatest increase in lactate (Juel et al., 2004; Tomlin & Wenger, 2001; Weltman et al., 1977). Although resistance and aerobic exercises with low to moderate intensity have little effect on increasing lactate, but most of the acidosis can be caused by high-intensity interval training, which is prohibited for these patients (Dominguez et al., 2018; Gentil et al., 2006; Martins-Costa et al., 2016; Tayebi et al., 2020). One of the clear indicators of cancerous tumors is unequal oxygen supply, which can lead to hypoxic and normoxic areas in the tumor (Liu et al., 2022). Finally, these conditions can lead to the acidity of the tumor environment (Liu et al., 2022). It seems that the significant increase of lactate in cancerous tumors is because of the high activity of the glycolysis cycle (Harjes, 2017), and this process was identified by Otto Warburg in 1927 as the Warburg effect (Pérez-Tomás & Pérez-Guillén, 2020). Therefore, despite the misconceptions about lactate (lactate is a waste molecule), it seems that lactate can play a role in cancer progression in favor of cancer cells (Karen G de la Cruz-López et al., 2019; Karen G. de la Cruz-López et al., 2019; Liu et al., 2022; Sharma et al., 2022). Therefore, the evidence strongly supports that lactate is the main fuel to meet the anabolic needs of cancer cells and can be the key factor in cancer growth (Apostolova & Pearce, 2022; Ishihara et al., 2022; Li et al., 2022; Sharma et al., 2022). Considering these complex physiological conditions, the question arises whether or not an exercise in cancer patients can be appropriate. However, the effects of lactate by physical activity and its relationship with tumor are in many debates (Ceci et al., 2024; Wang & Zhou, 2021).

Considering these complex physiological conditions, the question arises whether or not an exercise in cancer patients can be appropriate (Koelwyn et al., 2020; McTiernan, 2008; Mok et al., 2022). Several studies have investigated the effect of exercise during cancer with different mechanisms that have reported the positive effect of exercise to improve psychological or immunological effects (Koelwyn et al., 2020; McTiernan, 2008; Mok et al., 2022). However, the special concentration of exercise,

lactate and its relationship with tumor growth has yet to be specifically investigated. Physiologically, exercise with any intensity can increase lactate in the body (Stallknecht et al., 1998). One of the factors that can have a significant effect on increasing lactate is the intensity of training (Stallknecht et al., 1998). According to Brooks et al., lactate is the largest myokine in terms of concentration and dynamic range and the most diverse in terms of metabolic and physiological regulation (Brooks et al., 2022). In the past, lactate was believed to be produced in anaerobic conditions. However, in recent years, the theory has been proposed that lactate is also produced in completely aerobic conditions (Brooks, 2018). Therefore, it seems that both aerobic and anaerobic training will have an effect on increasing lactate (Brooks, 2018). As the intensity of training increases, the ratio of NAD⁺ to NADH increases, and as a result, fat oxidation decreases and focuses on the glycolysis cycle and increases lactate (A factor that can be harmful to cancer (Apostolova & Pearce, 2022; Karen G de la Cruz-López et al., 2019; Karen G. de la Cruz-López et al., 2019; Ishihara et al., 2022; Li et al., 2022; Liu et al., 2022; Sharma et al., 2022; Ahmadi Hekmatikar et al., 2019; Brooks, 2018; Suzuki et al., 2022; Tayebi et al., 2020). Also, common research supports the hypothesis that lactate increase during exercise can lead to angiogenesis and is one of the key factors of this process (Certo et al., 2022; Kon et al., 2022; Morland et al., 2017). It seems that lactate can 1) through its effect on factors such as vascular endothelial growth factor and 2) as an important cardiac fuel and metaboreflex regulation leading to greater cardiac output for angiogenesis (Brooks, 2018). On the other hand, considering that there is hyperlactatemia in cancer and the long history of cancerous tumors to absorb lactate, researchers are looking to prevent lactate transport in tumors by blocking MCTs (Brooks, 2018; Rami et al., 2023; Sonveaux et al., 2008). Accordingly, the development of therapies that limit lactate exchange and signaling within and between cancer cells should be a priority in cancer research, contrary to the physiological effects of exercise (San-Millán & Brooks, 2017). For example, sports physiologists stated in their conclusion that aerobic exercises with an intensity of 40 to 65% and anaerobic exercises (with a high intensity of 70 to 95%) can lead to an increase in MCT1 and MCT4 (Ahmadi et al., 2021; Coles et al., 2004; Otonkoski et al., 2007; Rahmani et al., 2021; Suzuki et al., 2022; Takimoto et al., 2013).

Finally, the hypothesis that lactate could be suitable for cancer patients during cancer seems to be a false hypothesis given the strong results that were found. Both directly, as an energy source, and indirectly, as a gluconeogenic precursor, lactate plays a major role in the bioenergetics and self-sufficiency of cancer cells. Exercise both acutely and chronically has positive physiological effects that cannot be suitable for cancer patients. On the other hand, the tumor environment is such that lactate is one of its key fuels for aggressiveness and growth. On the other

hand, lactate itself induces angiogenesis. Physiological changes that occur as a result of exercise can lead to an increase in lactate, angiogenesis, and an increase in lactate transporters, which can benefit the tumor. Physiological changes that occur as a result of exercise can lead to an increase in lactate, angiogenesis, and an increase in lactate transporters, which can benefit the tumor. However, the role of exercise in increasing lactate is prominent; although these effects in regular exercise lead to adaptation and lactate reduction, this does not seem to be a good idea for cancer patients.

Our previous publications have reported the importance of exercise for cancer patients (Ahmadi Hekmatikar, 2023; Ahmadi Hekmatikar et al., 2023; Lavín-Pérez et al., 2023). This hypothesis raises concerns from multiple angles, which can be explored in future research specifically addressing these concerns in order to answer the crucial question of whether physical activity is advantageous in the context of cancer. From one perspective, the hypothesis presented in this study emphasizes the notion that physical activity can enhance angiogenesis, an aspect that has been extensively emphasized in the field of sports physiology. However, the study also demons-

What is already known on this subject?

Exercise during cancer

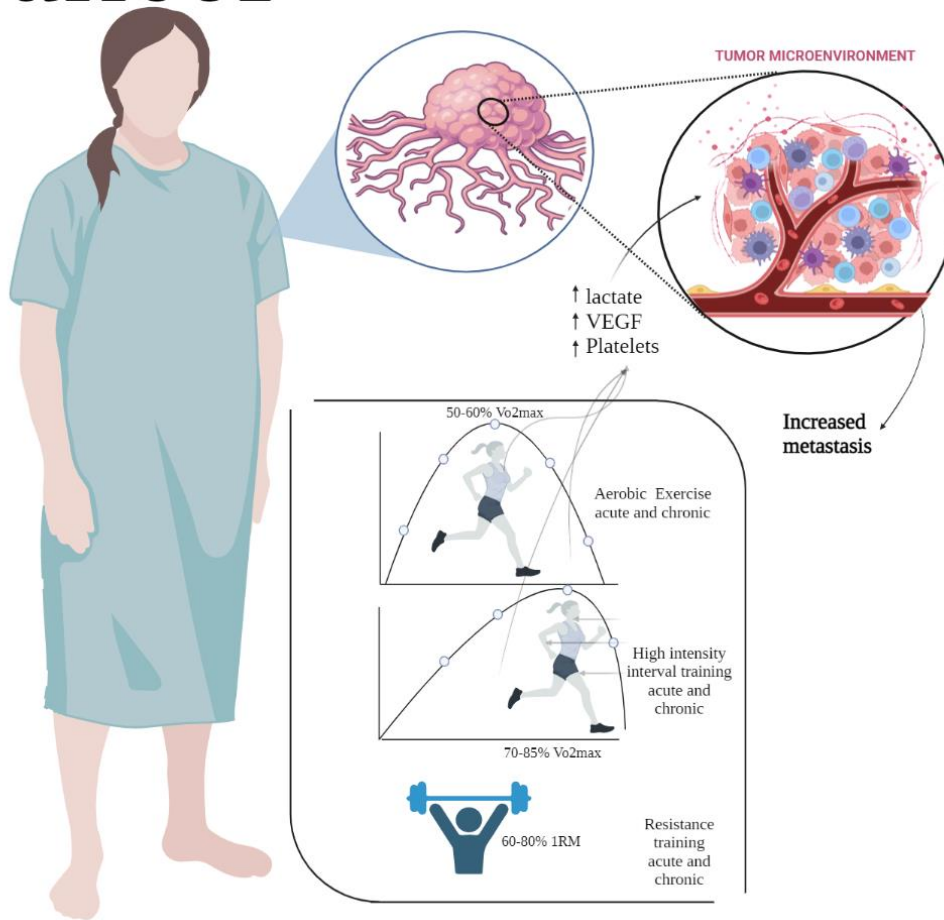
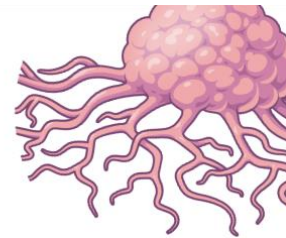


Figure 1. The importance of exercise during cancer. Designed by the author by Biorender software.

-trated that cancer relies on angiogenesis for its growth and spread. Consequently, this study proposes that intensive physical activity might raise concerns for patients with solid tumors.

In the second aspect, the hypothesis of the present study revealed that cancer cells exploit platelets as a protective shield during metastasis, aiding their movement in the bloodstream and evading the immune system. However, it was discovered that exercise can disrupt the attachment of cells to platelets by inducing shear stress, thereby undermining their ability to evade the immune system. This second possibility highlighted by the study suggests that physical activity, particularly focusing on platelets, may have a detrimental impact on patients with solid tumors.

The third perspective of the hypothesis put forth by the present study addresses the dependence of the tumor microenvironment on lactate, which has been shown to play a role in angiogenesis and the suppression of the immune system. Lactate has the potential to enhance tumor aggressiveness. However, physical activity is one of the primary factors contributing to the release of lactate into the bloodstream. Consequently, this raises another significant concern regarding the interplay between lactate, physical activity, and solid tumors.

Lastly, the present study underlined the importance of investigating more specific physiological changes that occur between tumors and physical activity, which may raise concerns regarding physical activity during cancer. However, this study can serve as a guiding beacon for future research endeavors aimed at addressing the following question: Can physical activity be a suitable strategy for cancer patients, considering the impact on lactate, platelets, and angiogenesis resulting from exercise interventions? This hypothesis merely highlights potential avenues for further investigation based on previous studies, providing valuable research ideas for future studies. This study merely stated valuable hypotheses that will require further research to prove.

Cross talk between physical activity and lactate in cancer tumors

Given the highlighted significance of exerkinines in disease processes, Brooks et al (Brooks et al., 2022) have emphasized lactate as one crucial myokine that holds potential to bridge numerous research gaps. Lactate is secreted by muscle tissue, released into the bloodstream, and utilized by various organs such as the heart, lungs, brain, and kidneys. However, physical activity, which promotes lactate release, may inadvertently supply tumor tissues with an abundance of lactate. The intricate interplay between physical activity and muscular physiology serves as the primary determinant of lactate prominence, while also raising co-

-ncerns regarding its impact on tumor tissues as the secondary factor.

What this study adds?

The importance of lactate in tumor growth cannot be ignored. This study added the important question of whether physical activity during cancer could be dangerous for tumor growth by increasing lactate.

Acknowledgements

None.

Funding

None.

Compliance with ethical standards

Conflict of interest The author declare that she has no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

Author contributions

Conceptualization: A.A.H.; Methodology: A.A.H.; Software: None; Validation: A.A.H.; Formal analysis: None; Investigation: A.A.H.; Resources: A.A.H.; Data curation: None.; Writing - original draft: A.A.H. and A.M.; Writing - review & editing: A.A.H. and A.M.; Visualization: A.A.H.; Supervision: A.A.H.; Project administration: A.A.H.; Funding acquisition: None.

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