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The Potential Role of Exercise on the Bioavailability of Cancer Treatments



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Abstract

Recently, exercise in oncology has been proposed as an effective strategy in managing symptoms, reducing psychological distress (i.e. anxiety, depression) and easing the harmful effects of treatments. The studies showing the direct benefits of exercise on cancer are valuable. However, the mechanisms leading to these improvements are still unclear. The practice of exercise may influence the pharmacokinetics of drugs, but the number of studies in this field is limited. It then seems legitimate to hypothesize that exercise plays a role in the bioavailability of cancer drugs. As a matter of fact, no articles have focused on the role of exercise in the bioavailability of cancer drugs. This article shows a poverty of data examining the role of exercise in the bioavailability of cancer drugs. To our knowledge, this is the first published article to examine this issue.

Keywords: Exercise; Bioavailability; Cancer; Drugs; Pharmacokinetics.

Introduction

Cancer is a complex disease characterized by the uncontrolled growth of abnormal cells. This disease is considered to be one of the leading causes of death in the world, with about 8.2 million deaths and 13% of overall mortality [1]. In America, the improvement of clinical care over the past few decades has allowed improving the 5-year relative survival to 69% [2]; this being similar in other continents such as Europe [3]. Some patients with cancer are sometimes obligated to rest excessively, which causes a lack of daily exercise resulting in a decrease in their functional state [4]. Indeed, almost 68% of cancer patients do not comply with exercise recommendations, while this practice is safe for them [5]. However, the literature is explicit about this as it informs that changes in the lifestyle, including exercise, can have a major impact on the risk of different types of cancer [6]. Recently, exercise in oncology has been proposed as an effective strategy in managing symptoms, reducing psychological distress (i.e. anxiety, depression) and easing the harmful effects of treatments [7-9]. The studies showing the direct benefits of exercise on cancer are valuable [10]. However, the mechanisms leading to these improvements are still unclear.

In oncology, the main cancer treatments are surgery, radiation therapy, and systemic therapy or chemotherapy [11]. Most

anticancer therapies are administered intravenously rather than orally due to the immediate and complete bioavailability following intravenous administration [12]. Oral drugs are attractive because of their convenience and ease of administration, but their solubility affects their bioavailability. Indeed, if a drug reports poor solubility, the absorption of the drug in the aqueous gastrointestinal fluids is insufficient [13]. Several anticancer oral drugs have a low therapeutic window and the prescribed dose is close to the maximum dose tolerated by patients [14]. The more effective the bioavailability of a drug, the better the delivery of the drug to the active site, optimizing pharmacokinetics. Pharmacokinetics explain the relationship between the absorption, distribution, metabolism, and excretion of a drug and its metabolites. Organisms respond only to the fraction which is biologically available [15]. Thus, one of the current problems concerns the biological availability of oral anticancer drugs which have a low bioavailability [14]. The practice of exercise may influence the pharmacokinetics of drugs, but the number of studies in this field is limited [16]. It then seems legitimate to hypothesize that exercise plays a role in the bioavailability of cancer drugs. One of the plausible mechanisms for explaining this is that exercise would improve tissue and cell vascularization to optimize the transport of the cancer drug in the body. Some studies have investigated this mechanism

in the murine model [17-19], however, to our knowledge, it does not appear that there have been such studies in cancer patients.

As a matter of fact, no articles have focused on the role of exercise in the bioavailability of cancer drugs. Our first aim is to evaluate the effect of the exercise on the biological availability of cancer drugs. The second aim is to show a poverty of data examining the role of exercise in the bioavailability of cancer drugs by a comprehensive review of the existing literature.

Systematic Review of Exercise effects on the Bioavailability of Cancer Treatments

In order to answer our aims, a systematic literature search was performed by two independent reviewers (MC, DC) in PubMed (MEDLINE) (1946 to January 30, 2019), Web of Science (all databases) (1945 to January 30, 2019), EMBASE (1974 to January 30, 2019), Cochrane Central Register of Controlled Trials (November, 2016 to January 30, 2019), Reviews - Cochrane Database of Systematic Reviews (2005 to January 25, 2019) and Scopus (1970 to January 30, 2019). The search terms for inclusion criteria are a combination of database specific MeSH terms and keywords: “Motor Activity” OR exercise OR “physical activity” OR sport* AND “Biological Availability” OR bioavailabilit* OR “biological availability” AND “Neoplasms” OR cancer* OR tumor*.

When it is possible, in the different database, we add the human filter. Also, the reference lists of all identified studies are scanned manually for additional studies.

We included all studies which investigate exercise and the biological availability of cancer drugs in human subjects without any age restriction (age of children “≤” 18 and age of adults >19). No publication date or language restrictions are applied to the initial search. However, during the first analysis by abstract, the conference abstracts, case reports, reviews, theses, letter to editor or protocol paper are excluded due to the inability to evaluate the risk of bias of the individual study. When the title and the abstract are potentially eligible for inclusion, a full-text is obtained after removal of duplicates. The studies with a design of randomized controlled trials (RCT), nonrandomized controlled trials (NCT) and uncontrolled interventions (i.e. pre and posttests without controls) are included.

Two independent researchers (MC and DC) review the articles for eligibility and validity. Data extraction is performed by one investigator (MC); when data are lacking in the original article, the authors of the review contact the original author to obtain additional data. To assess scientific evidence for each study, this review is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

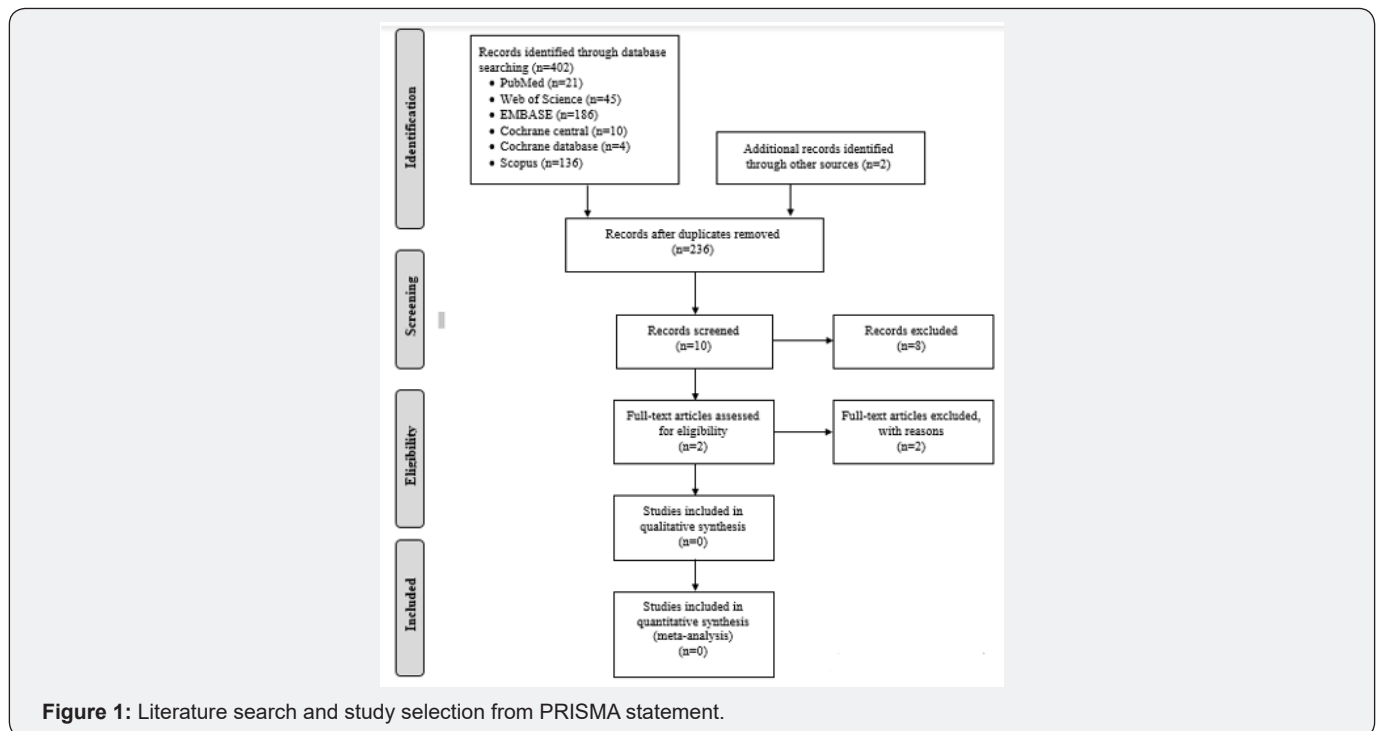


Figure 1: Literature search and study selection from PRISMA statement.

A flow-chart showing the different phases of the review according to the PRISMA schema is depicted in Figure 1. The electronic database search generated 236 potential articles that are screened for eligibility. After the first analysis by title and abstract, 10 abstracts are assessed. Among these abstracts, 8 do not meet our inclusion and exclusion criteria. A total of 2 studies are identified as eligible and valid for a full-text review. These 2 articles do not fit our criteria and are excluded.

The potential role of Exercise in the Bioavailability of Cancer Drugs

The aim of this research is to examine the potential role of exercise in the bioavailability of cancer drugs. Our study shows a poverty of data examining the role of exercise in the bioavailability of cancer drugs. To our knowledge, this is the first published article to examine this issue.

The interaction of exercise and the bioavailability of cancer drugs is legitimate. Indeed, exercise produces many positive physiological changes in the human body. It is shown that exercise increases muscular blood flow [21] and is positively correlated with the increased content of red blood cells [22]. In exercise physiology, the main role of red blood cells is the transport of oxygen by hemoglobin [23]. However, in the human organism, the red blood cells can also have a role in the transport of drugs [24]. In cancer patients, many suffer from anemia, since, they do not have enough healthy red blood cells in their organism [25]. This is accentuated by chemotherapy treatments [26]. Thus, in cancer, the involvement of exercise in the transport of drugs is very interesting. Indeed, exercise promotes the increase of red cell mass and plasma blood allowing the increase of blood volume [27]. The implication of exercise in the transport of red blood cells in cancer drugs is very important. Especially since the cellular absorption of cytotoxic drugs (i.e. chemotherapeutics) is recognized in the destruction of tumors [28].

This study shows that there is a significant lack of data on the bioavailability of cancer drugs in exercise. The diagnosis and the stage of cancer are two important characteristics that play in role in how the body responds to bioavailability [29]. Also, individual characteristics and type of exercises practiced also play a role in the response of the human body [29]. The literature observes a possible effect of exercise in improving the bioavailability of drugs. The authors of this article hypothesize that exercise could promote the bioavailability of cancer drugs through better vascularization of the cancer cell, thus allowing greater circulation of red blood cells carrying the cancer drugs. Further oncology studies are required to better understand how exercise can have a potential role in bioavailability of cancer drugs.

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