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Breast Cancer Chemotherapy Vascular Toxicity: A Review of Mediating Mechanisms and Exercise as a Potential Therapeutic

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Abstract:- Despite being extremely effective against tumour tissue, breast cancer chemotherapy has a considerable negative impact on the cardiovascular system. Cardiotoxicity has been the main focus of study in this field. Despite the vasculature's essential role in the cardiovascular system and the consequent harmful effects of injury and dysfunction, there is a dearth of research about the effects of such treatment on this structure. This review focuses on the effects of breast cancer chemotherapy on the vascular endothelium. We believe that endothelium malfunction and direct injury are the most plausible mechanisms of endothelial toxicity. These harmful effects have immediate repercussions since they increase the risk of cardiovascular disease. Exercise, however, may be able to lessen some of the vascular toxicity associated with chemotherapy; supporting data is presented Explained is the possible significance of exercise in preventing vascular toxicity, emphasizing the latest exercise therapies in human and animal models. Finally, the importance of exercise for endothelial health, function, repair, inflammation and hyperlipidaemia, angiogenesis, and vascular remodelling is covered in the mediating processes of exercise protection of endothelial health. These are all significant preventative strategies against toxicity caused by chemotherapy, and they are all covered in great length.

Keywords*: . chemotherapy, cardiovascular toxicity, vasculo-oncology, endothelium, exercise cardio-oncology.*

1. Introduction

In 2018, over two million women worldwide were diagnosed with breast cancer, making it the most frequent type of cancer (1). Because of early identification and successful therapies, the 10-year survival rate for breast cancer has increased from 40 to 78% over the past 40 years (1). As with other cancer kinds, there are several forms of breast cancer that differ based on the location of the cancer. Additionally, as the disease progresses, there are various stages of breast cancer that affect the treatment plans that are selected (2). The two main treatment options for early-stage breast cancer are a simple mastectomy or a lumpectomy followed by radiation therapy. Furthermore, the adjuvant analogue epirubicin inhibits topoisomerase, preventing mitosis, and causes oxidative stress by producing reactive oxygen species (ROS), which

damages cells (3). medications that block metabolism, such 5-fluorouracil (5-FU), damage DNA and RNA, and prevent the synthesis of new DNA (3). Alkylating agents—like cyclophosphamide—alkylate the nucleophilic bases found in tumour DNA, causing breakages, crosslinks to develop between and within DNA strands, and an inhibition of DNA replication (3). Finally, taxanes (e.g., docetaxel and paclitaxel) affect microtubule function, which prevents cell division (3). When combined, these pathways trigger the death of tumour cells, which effectively slows the formation of new cancers (3). Because intravenous chemotherapy is systemic, the harmful effects of the medications affect not only the cancer cell but also the cells in the circulatory system (CVS). Cardiovascular disease (CVD) accounts for the majority of deaths among breast cancer survivors (15.9%), and cardiovascular toxicity is linked to clinically significant adverse effects of deaths, with breast cancer coming in second with 15.1% (4), suggesting that the risks to the cardiovascular system could be greater than those resulting from the cancer itself. Compared to the general population, breast cancer survivors have a 1.9-fold increased risk of dying from CVD (5). There is a growing amount of knowledge addressing the pathophysiology of the syndrome, and research into the cardiovascular toxicity of chemotherapy is crucial to improving the quality of life for breast cancer survivors and the likelihood of disease-free survival. Nonetheless, research has mostly focused on the cardiac effects of chemotherapy damage. Notwithstanding the vasculature's pivotal and modulating position in the CVS, the effects of these medications on it are frequently disregarded. Nonetheless, new data is beginning to show how important the Vasculature in the development of CVD after exposure to chemotherapy. As the initial site of contact for any intravenous chemotherapy treatment, the vascular endothelium suffers negative effects from this exposure, which manifest as increased cell death (7) and endothelial dysfunction (3, 6). Nitric oxide (NO), a powerful vasodilator that is essential for controlling normotension and contributing significantly to the preservation of cardiovascular health due to its anti-thrombotic and anti-platelet characteristics, is produced by the endothelium (8). Indeed, one of the mediating pathways for the first cardiotoxicity that results in chronic cardiovascular problems and, eventually, premature death in cancer patients, may be endothelial damage (6). Therefore, it's critical to comprehend the role of the endothelium to offer a mechanical foundation for the start and development of CVD after exposure to chemotherapy. This will clarify whether any interventions or treatments are possible to stop, reverse, or lessen the cardiotoxicity of cancer treatment.

Interventions that lessen toxicity are necessary because cardiotoxicity is a significant clinical concern for breast cancer survivors and their physicians. For patients receiving chemotherapy, exercise has been suggested as an efficient adjuvant treatment that is low-risk, low-cost, and low-burden. Exercise interventions, for instance, have been shown to reduce cardiovascular events (9), increase blood pressure reduction (10), improve vascular function (11, 12), prevent atherosclerosis (12), de-strengthen arteries (13, 14, 15), and increase skeletal muscle angiogenesis (16). These outcomes have been observed during adjuvant breast cancer treatment. Similar to studies on the toxicity itself, studies on exercise therapies have also prioritized cardiac advantages over other benefits, even though the vasculature is crucial for halting the development of CVD (6). Thus, the present review will centre on the role of vascular endothelial cells in possible exercise defence against cardiovascular toxicity, emphasizing

existing understanding, plausible protective mechanism routes, and the need for more studies in this area.

Clinical cardiac symptoms of chemotherapy-induced cardiotoxicity

Acute damage from chemotherapy

Depending on the regimen selected, distinct cardiovascular toxicology are associated with different chemotherapy medicines. While some of these impacts happen right away, other cardiovascular risks take longer to manifest. Antimetabolites like 5-FU have immediate effects; throughout chemotherapy cycles, 1–68% of patients experience cardiotoxicity; as a result, 2–13% of afflicted patients pass away during treatment (17). During therapy, cyclophosphamide also has an instantaneous 5% effect on the CV frequency of heart-related issues (18). Reduced left ventricular ejection fraction (LVEF), which frequently appears 1–10 days after the first cycle and has a prevalence of 7–28%, depending on the dose, has also been linked to cyclophosphamide-induced heart failure (17). Around seven months after treatment, exposure to taxanes is linked to a 5% incidence of cardiac problems (19). These issues include a 2-8% incidence of heart failure with a considerably lowered LVEF and a 1.7% incidence of ischaemia.

For patients with node-negative, hormone receptor-positive breast cancer, anti-herceptin2 medications, such as trastuzumab, are provided in conjunction to chemotherapy and endocrine therapy for a duration of five to ten years (2). The common chemotherapy regimens administered for early-stage breast cancer will be the specific focus of this review. This frequently entails a mix of medications, such as taxanes, alkylating agents, anthracyclines, and antimetabolites (3). These medications combine in various ways to eliminate malignant tumors. Anthracycline medications, such as doxorubicin and the long-term damage it causes from chemotherapy

According to reports, anthracycline-treated breast cancer patients have a 5% overall incidence of heart failure (20). Depending on the dosage and medication used, anthracyclines can cause cardiotoxicity at different rates; doxorubicin can cause a toxicity incidence of 3–26%, whereas epirubicin can cause a toxicity incidence of 1-3% (3). The hallmark of anthracycline-induced cardiotoxicity is frequently a markedly decreased LVEF (15). Cardiotoxicity develops during treatment and may never fully recover (20). Five years after treatment, only 11% of patients have full recovery of LVEF, and 71% have partial recovery (LVEF staying less than 50%). benefits of protection from exercise's effects on cancer sufferers' cardiovascular systems

Clinicians think about lowering therapy doses to avoid cardiotoxicity and employing cardiac monitoring to identify the early stages of cardiotoxicity (17). Attenuation of the dose, however, may impair the effectiveness of the treatment. As a result, there is room for additional supplemental treatments to reduce cardiotoxicity. Pharmaceutical therapies have been employed up to this point, such as antihypertensives and neurohormonal blockers (17), but they come with their own set of side effects and raise treatment expenses. Exercise offers hope as a complementary treatment to mitigate cardiovascular toxicity because it is safe, economical, and almost non-destructive for cancer patients (9, 10, 11, 12, 16).

The American Heart Association has suggested creating a model to identify patients who could be cardiotoxic to chemotherapy and to address the developing issue by implementing a thorough cardiac rehabilitation program inside cancer care (21). There is growing evidence supporting the protective effects of exercise on the CVS in cancer survivors, which provides strong support for this notion (9, 10, 11, 12, 16). Following their treatment, cancer patients' Framingham risk scores were 2% for the exercise group and 13% for the usual care group. This difference was associated with an 11% reduction in the estimated 10-year risk of developing cardiovascular disease (CVD) (9). Additionally, an 8-year follow-up study of women treated with chemotherapy for breast cancer found that increased leisure-time physical activity was linked to a lower incidence of CVD (22). Additionally, there is a negative correlation between aerobic fitness and the incidence of chemotherapy-induced cardiac fibrosis (23), as well as higher baseline physical activity is linked to a reduction in the typical LVEF decline (24).

Exercise training can improve aerobic fitness, which supports the idea that exercise may lessen the cardiotoxicity of chemotherapy. It is crucial to remember that these research only show relationships, underscoring the necessity of doing randomized controlled trials on exercise.

Similar to research on the cardiotoxicity of chemotherapy, studies on physical activity and exercise have mostly examined the effects on the heart. But exercise during chemotherapy has also been shown to improve vascular function and health (9, 10, 11, 12). The next sections will cover the significance of the vasculature's participation in treatment toxicity, the possibility that exercise can mitigate this, as well as mechanistic relationships

Vascular impairment as a precursor to cardiotoxicity

Early identification and development of chemotherapy toxicity may be influenced by damage and malfunction of the vascular endothelium. A non-invasive method of measuring NO-mediated endothelium-dependent dilatation, flow-mediated dilation (FMD) evaluates the vasodilatory response to an abrupt resumption of blood flow following a period of venous occlusion (8). Vasodilation is caused by the release of NO, a strong vasodilator, which is stimulated by an increase in blood flow that increases shear stress across the endothelium (8). The ability of the endothelium to release NO is predicted by the relative change in arterial diameter (8). In patients with breast cancer, a 2.7% drop in FMD is associated with a 37% higher chance of LVEF decline three months after chemotherapy (25). Moreover, arterial stiffness has been identified as a critical indicator of the risk of CVD recently.

profile of patients receiving comparable anti-cancer medication (26). A non-invasive bioassay for arterial stiffness, pulse wave velocity (PWV) is a significant predictor of cardiovascular disease and mortality in women with breast cancer (27). By measuring the time it takes for a pulse wave to move from the carotid to the femoral arteries in relation to the distance traveled, PWV is defined as the speed at which the blood pressure pulse propagates through the circulatory system. Following the third round of chemotherapy, a 27% rise in PWV reliably indicates a decline in LVEF following the end of chemotherapy (28). Cardiotoxicity is also predicted by vascular remodelling, where a 7% decrease in LVEF is linked to a 4% rise in arterial stiffness (29). This suggests that modifications also take place in the vasculature.

changes heart function and, as a result, may serve as early screening instruments to estimate the risk of cardiotoxicity. This is significant because toxicity can be reversed in the early stages, but if LVEF is impacted, it cannot be restored (15). The management of late-stage cardiovascular disease (CVD) and heart failure is inferior to early detection and intervention. Measurements of vascular health, such as arterial stiffness, PWV, and FMD, have the potential to identify cardiotoxicity early and enable successful intervention, but they are not routinely included in clinical treatment. Chemotherapy-induced vascular damage/dysfunction and possible exercise protection

Significant cellular damage is present in the vasculature, which could be a factor in the harmful effects of chemotherapy on the entire cardiovascular system. The first organ to be exposed to intravenous treatment is the endothelium And this exposure damages it (3, 6, 7, 30). There is evidence linking vascular injury and dysfunction as an early stage for the initiation and progression of CVD, and chemotherapy-induced endothelium damage may be a major factor in the development of cardiotoxicity (6, 31). Consequently, this provides a chance to evaluate vascular health as a marker of early cardiotoxicity, enabling early intervention or reduction of treatment. Similar to heart risks, physical activity can lessen the vascular toxicity of chemotherapy. Exercise has a rich history of advantages include decreased blood pressure (10), decreased risk of cardiovascular events overall (9), enhanced endothelial function (11–12), prevented formation of atherosclerosis (12), de-stiffening of arteries (13–15), and increased angiogenesis (16). We'll go over the possible vascular-mediated systems that could protect against exercise with regard to reducing the cardiovascular damage brought on by chemotherapy.

Chemotherapy's deleterious effects on the endothelium show up as vascular dysfunction and may be a factor in myocardial ischaemia, which is more common in patients treated with 5-FU and has an incidence of more than 20% (32). According to ST-segment alterations, angina brought on by myocardial ischaemia is the most prevalent sign of this cardiotoxicity (32). This ischemia frequently happens without the coronary arteries being blocked, but rather with increased vasoconstriction, which is suggestive of vasospasm brought on by vascular endothelial dysfunction. It is also likely that this ischemia has negative effects on the vascular smooth muscle, which lowers the oxygen supply to the heart tissue (31, 32). Exposure to taxanes (3) and cyclophosphamide (33) can also result in myocardial ischemia. While coronary vasospasm is less common (<5%) than what is seen with 5-FU, it is also the cyclophosphamide's cardiotoxicity mechanism has been hypothesized (33). Owing to this hypothesised fundamental mechanism, studies on the toxicity of cyclophosphamide, taxane, and 5-FU ought to concentrate on vascular pathophysiology in order to clarify possible methods of reducing myocardial ischaemia and raising the likelihood of surviving without illness.

Exercise's potential to attenuate toxicity and the function endothelial damage plays in it

Chemotherapy treatment can cause hypertension, which is especially well-documented in response to cyclophosphamide (3, 31). In animal models, this medication is responsible for 43% of cases of severe pulmonary hypertension (3). Acute endothelial damage is linked to cyclophosphamide-induced hypertension, which in turn disturbs the signaling cascade

necessary for controlling NO-mediated vasodilation and blood pressure regulation (31). An enlarged myocardial may also result from endothelial injury, as shown in patients receiving cyclophosphamide treatment (34). Exposure to cyclophosphamide causes direct endothelial damage, which leads to the leakage of erythrocytes and plasma proteins. This causes wall thickening due to interstitial oedema and haemorrhage, which can lower left ventricular diastolic function and manifest as cardiomyopathy (34). Endothelium damage in the coronary arteries causes harmful compounds to flow out, directly harming cardiomyocytes (33). This could provide additional chemotherapeutic medications a way to enter the heart and increase cardiotoxicity. Increased intracellular oxidative stress levels have been connected to the mechanism behind endothelial injury produced by anthracyclines and docetaxel, which triggers apoptotic signaling pathways (3, 29). This takes place inside the endothelium, which causes more vascular dysfunction and damage. Anthracyclines increase the permeability of arterial endothelial cells by approximately ten times, leading to significant decreases in ATP and antioxidants from the endothelium (36), further inducing metabolic dysfunction, oxidative stress, and apoptosis. Oxidative stress also causes increased permeability of the endothelium by negatively affecting endothelial junction proteins (35). All things considered, receiving chemotherapy makes one more vulnerable to vascular injury. and malfunction, with the primary cause for cardiotoxicity being described as cellular death within the CVS (31). Damage to RNA and DNA, inhibition of topoisomerase, elevation of oxidative stress, and binding and stabilization of tubulin are some of the mechanisms of action (3). In the end, these processes result in the suppression of cell division and the start of cellular apoptosis (3). These acts cause apoptosis throughout the entire CVS since they are non-specific. summarizes the possible mechanisms via which chemotherapy causes cellular death. The damage's vascular manifestations have a knock-on effect on one another and the general condition of the heart, and there , there is currently evidence indicating that vascular dysfunction and damage is a precursor to the development of CVD (31). For instance, coronary artery disease typically results from a build-up of of atherosclerotic plaques, caused by inflammation and vascular injury (37). Vascular narrowing causes hypertension, which raises the heart's stress level because of pressure overload (37). Reduced blood flow to the myocardium due to restricted coronary arteries can cause myocardial infarction (MI) depending on how severe the reduction in blood flow is. Chemotherapy exposure raises the risk of atherosclerosis, myocardial ischaemia, and hypertension, which increases the likelihood that the embolism may break off from its localized site and cause MI (33). When a myocardial has an abrupt stoppage of blood flow, it undergoes apoptosis and necrosis, which modifies cardiac electrical stimulation. In the event that the patient survives an acute MI, the heart makes an effort to heal by growing more cardiomyocytes. This causes hypertrophy and pathological remodelling, together with fibrous tissue development (38), resulting in cardiac dysfunction and mechanical stiffness that cause heart failure and a never-ending chain of negative consequences for the cardiovascular system. the mechanisms by which vascular and cardiomyocyte damage brought on by chemotherapy may result in heart failure.

It has been observed that exercise training decreases apoptosis in cardiomyocytes exposed to doxorubicin (39), most likely as a result of increased antioxidant levels and decreased ROS levels (40). Therefore, reducing oxidative stress and apoptosis is one possible way to exercise protection against endothelial damage. Since both oxidative stress and endothelial apoptosis

contribute to the toxicity of chemotherapy, reduced oxidative stress and apoptosis may protect against CVD risk (2, 28, 30).

The possibility for attenuation and the role of endothelial function (eNOS) in toxicity with physical activity

The harmful effects of these medications on endothelial nitric oxide synthase (eNOS), a crucial vasodilator and anti-thrombotic enzyme, are perhaps one of the most important side effects of chemotherapy. It has been observed that chemotherapy medications decrease eNOS bioavailability and/or activation in the endothelium (3, 6, 30, 41), a finding that is probably related to oxidative stress (41). Overall, as observed with chemotherapy, impairments in the endothelium vasodilatory pathway are probably to blame for the ensuing vasospasm and constriction (6, 30). Due to the anti-thrombotic properties of NO, reduction in its production is also likely to contribute to the higher incidence of venous thromboembolism in chemotherapy patients (42). It's interesting to note that cyclophosphamide has been linked to higher eNOS concentration and microcirculatory relaxation, but this is probably a compensating reason for the significant amounts of endothelial damage brought on by exposure to cyclophosphamide (7). According to FMD, anthracycline treatment also causes disruption of NO regulation (12). Because of the endothelium damage caused by anthracycline, there is a 7% decrease in FMD from pre- to post-treatment (12). This suggests that NO bioavailability is decreasing, raising the risk of CVD (25). Reduced endothelial-dependent vasodilation is therapeutically significant because it may be a mediating factor in the 5% incidence of heart failure associated with anthracycline treatment (20) and because FMD inversely corresponds with LVEF decline in breast cancer patients treated with chemotherapy (25).

Patients with breast cancer experienced a 4% rise in FMD following an exercise intervention during chemotherapy, which may indicate improved endothelial function and eNOS production (12). Because eNOS possesses anti-atherogenic qualities that lower the chance of atherosclerosis development, this is encouraging for lowering the risk of cardiovascular events. These outcomes are repeated in investigations on exercise training conducted without treatment, and it has been discovered that shear stress mediates FMD benefits (43). A non-significant rise in FMD was seen in the exercise group from pre- to post-doxorubicin-cyclophosphamide chemotherapy after 12 weeks of thrice weekly cycling (60–100% VO2Peak, 30–45 min), but there was no change in the usual care controls (11). An 8-week, thrice-weekly high-intensity interval training (HIIT) cycling strategy combined with anthracycline chemotherapy produced more encouraging effects; following the intervention, brachial FMD increased by 4% with exercise, while FMD in the usual care group decreased by 7% (12). It's a a clinically significant finding: in patients with breast cancer, a 2.7% rise in FMD is associated with a 37% lower risk of LVEF decline three months after chemotherapy.

While there are already some, however few, human research on exercise training prior to and during breast cancer treatment, it is important to note some preliminary findings from mouse models. Increased endothelium-dependent vasodilation in rats was linked to eight, but not four, weeks of exercise training (5 days/week, 30 min jogging 20–25 m/min) before exposure to chemotherapy (44), indicating that exercise-induced protective effects on the vasculature are dose-dependent. During doxorubicin treatment, exercise training (6 weeks, 5 days/week, 30

minutes jogging at 50–60% maximal velocity) was linked to a decrease in mortality as well as an improvement in endothelium-independent but not endothelium-dependent vasodilation rats exhibiting heart failure brought on by doxorubicin (45). This implies that exercise restores vascular function, although the process may involve better vascular smooth muscle characteristics and/or enhanced vascular structure rather than higher NO bioavailability. The differences in the mechanistic conclusions of Hayward et al. (2004) and Matsuura et al. (2010) point to the need for additional research.

Vasoconstrictors' function in toxicity and their ability to be modulated by exercise

Exercise-induced protection against vascular toxicity may also be mediated by downregulating vasoconstrictive factors, including the powerful vasoconstrictor endothelin-1. Chemotherapy treatment raises endothelin-1 activity, which causes a phenotype favouring vasoconstriction and hypertension. This is probably the mechanism by which 5-FU-induced vasospasm is postulated (3). Furthermore, endothelin-1 suppresses the activity of eNOS It is most likely a mediator of the eNOS downregulation shown in 5-FU (6). Anthracycline exposure also causes an increase in vasoconstriction (6), while endothelin-1 expression has not been studied in relation to anthracycline exposure. However, the increase in vasoconstriction causes hypertension, which raises the risk of cardiovascular events and plaque rupture due to increased vessel pressure, as well as an increase in pre-load and strain on the myocardium, which aggravates any cardiac dysfunction and, if untreated, results in heart failure Taxanes have been shown to lower endothelin-1 expression in breast cancer patients compared to other chemotherapy medications, which may increase overall survival (46). Conversely, research on older women without cancer who engaged in exercise has demonstrated that linked to better blood pressure profiles and a decrease in vasoconstrictive variables (47). In healthy older women, exercise reduced plasma endothelin-1 content from 2.9 ± 0.2 to 2.2 ± 0.2 pg/mL. Systolic blood pressure declined from 127 ± 4 to 112 ± 3 mmHg, and diastolic blood pressure decreased from 79 ± 2 to 65 ± 2 mmHg (47). In general, it seems that exercise encourages a pro-vasodilatory phenotype, which then lowers the risk of hypertension and enhances cardiovascular health in general.

Exercise may lessen the arterial stiffness brought on by treatment.

Another important factor in vascular dysfunction caused by anti-cancer therapy is arterial stiffness (26). As a compensatory strategy to endothelial injury, chemotherapy treatment causes the resistance vessels to remodel, changing their shape to a bigger lumen and indicating substantial endothelial injury lower the blood pressure (7). Nevertheless, remodelling results in blood vessel stiffening and decreased compliance, which is linked to higher levels of oxidative stress from taxane treatment (29) and lower levels of NO-dependent vasodilation from doxorubicin exposure (48). Additionally, elastin breakdown and the production of advanced glycation end products, which are mediated by TNFA-dependent vascular inflammation, cause structural remodelling that leads to arterial stiffness during chemotherapy (49). Variations in vascular compliance are linked to declines in cardiac function because they cause a hypertensive state, which increases cardiac afterload and stress and causes major

cardiac harm. From pre- to post-treatment, LVEF decreased by 7% (29). This suggests that alterations in vascular anatomy coincide with declines in heart function.

It's interesting to note that exercise can minimize arterial stiffness; people who exercise regularly throughout their lives tend to have lower arterial stiffness in comparison to peers who are age-matched and sedentary (14, 15). Exercise has the ability to lessen TNFA-induced arterial stiffness (49), since it is linked to decreased levels of circulating inflammatory cytokines IL6, IL10, IL1B, and TNFA (50). Mechanistic linkages for this exercise benefit have been established in vivo animal models; for example, mice that voluntary wheel ran showed enhanced PWV, which was ascribed to decreased oxidative stress, mechanical stiffness, and the buildup of collagen-I and advanced glycation end products (13). Exercise with chemotherapy may have this effect, but no research has looked into this as of yet. However, given that exercise training lowers the risk of hypertension and the ensuing organ damage, it may have a contributing influence to the lowering of cardiotoxicity during chemotherapy (51).

17% (cyclophosphamide) was higher than the 1.5%–10% range for all other chemotherapy regimens (42). Current theories about the consequences suggest that participant characteristics and high treatment dosage may be to blame for this very high occurrence (42). As increased pressure can result in plaque rupture, it is important to take into account that the increased prevalence of hypertension associated with cyclophosphamide will be a contributing factor to thromboembolism. Stroke (31) and MI (26) are caused by thrombosis, which is also associated with cyclophosphamide and 5-FU alone (3). Because of the endothelial cell damage caused by the mechanisms of action of these medications, there is a considerable danger to the integrity and health of the vasculature, which increases vulnerability to pro-thrombotic phenotypes. To enhance, the problem of thrombotic risk must be addressed survival and quality of life in patients receiving chemotherapy treatments.

The dysfunctional change that chemotherapy causes in endothelial cells toward a pro-thrombotic shape may be reversed by exercise. Exercise may have a preventive impact against atherosclerosis risk, as evidenced by an 8-week exercise intervention that stopped the typical rise in carotid intima-media thickness that occurs after chemotherapy (12). Adhesion molecule expression in the endothelium is low at rest and is elevated in response to stimuli like inflammation and abnormal blood flow. Increased production of adhesion molecules is a sign of endothelial activation and is significant for the risk of thrombosis (52). Atherosclerosis begins when leukocytes roll and adhere to the active endothelium; this process is mediated by E-selectin, vascular cell adhesion molecule 1 (VCAM1), and intracellular adhesion molecule 1 (ICAM1) (52). The ICAM1 expression is particularly significant since it is linked to both overall and disease-free survival (52). Exposure to taxanes (52) and anthracyclines (53) results in an upregulation of ICAM1, which is thought to be the mechanism of action behind the vascular toxicity of cyclophosphamide (3). Since eNOS suppresses the expression of endothelial adhesion molecules, the upregulation of adhesion molecules is probably a result of the downregulation of eNOS brought on by chemotherapy exposure (54), which raises the risk of atherosclerosis formation. However, more research is necessary to confirm this impact in chemotherapy medications as there is currently insufficient evidence supporting it. Exercise may lower the expression of adhesion molecules, a key modulator of vascular risk, by raising eNOS expression and activation. As of right now, no research has looked at this activity in

clinical populations without cancer has been reported to lower circulating plasma levels of endothelial-derived adhesion molecule expression, notably E-selectin and ICAM1 (55). This suggests that exercise plays a mediating role in the expression of these molecules in cancer patients. Shear stress is considered to be one of the possible causes of the downregulation of adhesion molecules on endothelial cells. Laminar blood flow across the vascular endothelium is increased during exercise, and investigations conducted in vitro have revealed that increased shear stress decreases the expression of VCAM1 and E-selectin while, surprisingly, boosting ICAM1 (56). This calls for more research as it points to a different mechanism causing the downregulation of ICAM1 brought on by exercise.

The ability to control inflammation and cholesterol flux is another possible defense against thrombotic risk (50). Given the vascular damage caused by chemotherapy, the anti-inflammatory qualities of the endothelium are reduced (31), and it has also been discovered that chemotherapy raises triglycerides, total cholesterol, and low-density lipoprotein—all of which are linked to an increased risk of cardiovascular disease (57). This is probably going to contribute to the development and/or progression of atherosclerosis due to the build-up of inflammatory and fatty molecules in the vasculature, together with the downregulation of eNOS (3, 6, 30) and the upregulation of adhesion molecules (52, 53). Exercise both before and after chemotherapy is linked to improved lipid profiles with higher levels of high-density lipoprotein and lower levels of total cholesterol (9), as well as a decrease in the inflammatory cytokines IL6, IL10, IL1B, and TNFA (50). As exercise training lowers the risk of atherosclerotic development, it may have a contributing influence to the lowering of cardiotoxicity during chemotherapy. This could act as a counteraction to the toxicity of anti-neoplastic treatments.

Work out encourages angiogenesis in skeletal muscle

Exercise during chemotherapy treatment enhances both macrovascular health and muscle angiogenesis (16). Chemotherapy decreased capillary density by 10%, according to skeletal muscle biopsies (16). This lower skeletal muscle perfusion could be a factor in the muscular atrophy and dysfunction that chemotherapy-treated cancer patients frequently experience. Nonetheless, capillary density was enhanced by 30% with 16 weeks of twice-weekly HIIT cycling combined with 20 minutes of continuous cycling or resistance exercise training in addition to chemotherapy, which lessened the vascular toxicity (16). Circulating levels of vascular endothelial growth factor (VEGF), a pro-angiogenic signaling molecule that is directly linked to hypertension and stroke risk, are decreased with exposure to docetaxel and cyclophosphamide (3, 31). Effective angiogenesis requires VEGF because it promotes the development of new blood vessels in hypoxic areas and aids in the restoration of damaged vessels, which is a crucial step in preventing vascular disease. Reduced eNOS activation has been linked to docetaxel-induced disruption of the VEGF pathway (3). Consequently, VEGF plays a crucial role in angiogenesis as well as NO synthesis, vasodilation that follows, and anti-thrombotic qualities that shield the vascular. It has been demonstrated that targeting VEGF is a therapeutic approach to prevent endothelial damage mediated by doxorubicin (58), possibly by modulating the increase of vascular mitochondrial ROS induced by doxorubicin (41). There has been no discernible impact of exercise during chemotherapy on levels of circulating VEGF, despite the possibility that exercise-induced increases in circulating VEGF could decrease

chemotherapy-induced cardiotoxicity (11). But there has only been one study that looks into this of its food and oxygen sources, ultimately causing the tumor to die. But in other situations, like in mice receiving chemotherapy, physical activity enhanced the density of tumor microvessels, the maturity and perfusion of the vessels, and the reduction of intratumoral hypoxia. These factors were linked to a significant decrease in tumor growth and an increase in tumor apoptosis (59). As a result, increasing angiogenesis within tumors may actually increase the effectiveness of chemotherapy since it will improve the path by which the medications will enter the tumor (60). Exercise is important because it causes the vasculature surrounding the tumor to normalize because it creates shear stress-induced angiogenesis, as opposed to angiogenesis, a characteristic of cancer that results in "leaky" and disorganized pathological arteries that decrease treatment efficaciousness and raise the risk of of spread (60). Therefore, by increasing the number of capillaries, exercise may provide protection against vascular toxicity be advantageous for the chemotherapy's own efficacy.

Physical activity increases vascular regeneration ability.

There has to be evidence regarding the effects of chemotherapy on endothelium healing in order to deepen our understanding of exercise-induced endothelial protection. Since endothelial injury without repair is frequently the first step toward the development of pathological vascular states, endothelial repair is a crucial function of the endothelium to guard against dysfunction and plaque formation (5, 30). Endothelial cells' ability to migrate across the site of injury was found to be impaired in a wound healing assay when exposed to 5-FU and epirubicin (6); Boyden's chamber assay also demonstrated that 5-FU and epirubicin decreased migration, likely as a result of cell cycle arrest and downregulation of NO, which is involved in the migration process signaling chain (6). Endothelial progenitor cells (EPCs) are involved in mechanisms that preserve the integrity of the endothelium layer through reparative actions (61). The effect of chemotherapy on EPCs is not well-supported by data, therefore this could be a topic for further investigation. On the other hand, docetaxel has been demonstrated to lower circulating EPC levels, most likely as a result of increased apoptosis and inflammatory mediators (62). This highlights the issue of anti-neoplastic medicines on the CVS and is linked to both CVD and death (62). This raises the risk of developing CVD along with the previously discussed disruption of the VEGF signalling pathway by docetaxel (3), which results in an endothelium with a decreased ability to heal vascular damage. Beneficially, exercise has been shown to raise circulating EPCs in breast cancer patients and factors angiogenic (11). Acute exercise has been shown to mobilize EPCs, and regular exercise has been found to increase resting EPC numbers in both healthy and heart failure populations. These findings provide additional evidence for the potential benefits of effects on EPCs and are likely responsible for the exercise-induced improvements in endothelial function (61). Therefore, exercise may prevent vascular toxicity by promoting repair, maybe by upregulating EPCs and pro-angiogenic factors. Fortunately, enhanced vascular networks don't seem to have an impact on the effectiveness of treatment.

Practice imitating

It's interesting to note that in individuals who are "at risk" for CVD, exercise mimics have been suggested as preventative measures. Under the notion of exercise mimetics, a polypill

containing many chemicals that are anti-thrombotic, lower blood pressure, decrease blood lipids, mute autonomic responses, and lower blood glucose concentration may provide CVD protection in a manner similar to exercise (63). According to human research, taking a polypill (amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg, and simvastatin 40 mg) for a short period of time can cut the risk of CVD by about 80% (63). Considering the obstacles to physical activity in cancer patients, this could be a different approach to treating or avoiding vascular dysfunction while using chemotherapy medications (64). Nevertheless, cancer patients have found success with exercise therapies receiving chemotherapy (8, 9, 10, 11, 12) and may, thus, be a more comprehensive and affordable therapeutic approach.

Research gaps: an appeal for intervention

It is important to identify the various research gaps that exist in the areas of cardiovascular toxicity and possible exercise protection. Up until recently, research on the cardiotoxicity of chemotherapy was the main focus; however, at this time, study is also looking at the vascular effects of cancer treatment. Despite preliminary findings, little study has been done on the vasculature, with the majority of in-person studies concentrating on the health of vascular endothelial cells after chemotherapy treatment. To validate and deepen our understanding of the mechanisms behind the endothelium's involvement in the onset and progression of chemotherapy-induced cardiovascular disease, more study is needed. Despite the methods this review suggests They are highly likely to be involved in the cardiotoxicity of chemotherapy, although their exact role in cancer treatment is yet unclear. Thus, more research is required to validate the underlying processes of vascular toxicity. Furthermore, despite the fact that chemotherapy causes cardiotoxicity as well and is frequently used in patient care, the majority of evidence for cardiotoxicity comes from studies looking into doxorubicin; in contrast, relatively few studies look into the effects of chemotherapy on breast cancer (3).

More research gaps are evident when scrutinizing the literature that has investigated exercise protection against toxicity. There are only a small number of studies investigating vascular outcomes with exercise interventions during chemotherapy, and there are even fewer studies proposing underlying mechanisms for this. Furthermore, most exercise studies have investigated anthracyclines despite the multiplicity of chemotherapy drugs utilized in breast cancer care. A full review of the mechanisms by which exercise may improve vascular function in the specific setting of anthracycline chemotherapy is discussed in depth elsewhere (65). Despite gaps in the literature, these studies show promise for the potential inclusion of exercise therapy during cancer treatment. Future randomized controlled trials of exercise in those undergoing chemotherapy should assess vascular health and function outcomes including blood pressure, FMD, circulating endothelial cells, EPCs and PWV to fully determine the vascular benefits of exercise in this population. As yet, the majority of evidence for exercise protective mechanisms comes from non-chemotherapy-treated populations, and hence, assumptions regarding interdisciplinary consistency have been drawn. Despite the likelihood that these studies are still applicable to cancer treatment, there is a strong requirement for conformational studies regarding the mechanisms of exercise protection against vascular damage and dysfunction with chemotherapy.

Conclusion

Chemotherapy exposure is associated with cardiovascular toxicity, which is linked to CVD development and mortality, and is the number one cause of death in breast cancer patients (4). This is highly likely to be due to, in part, the toxic effects of chemotherapy drugs on the vasculature. The underlying pathology involves vascular dysfunction which results in ischaemia, hypertension, and thrombosis which can lead to cardiovascular events including arrythmias, heart failure, and MI. This is likely due to increased activation and apoptosis of vascular cells inducing a significant shift in the endothelial health from an anti-thrombotic, anti-coagulative, vasodilatory phenotype to a phenotype which promotes vasoconstriction, atherosclerosis, and thrombosis. Focusing on attenuation of vascular endothelial damage could provide a much-needed alleviation of cardiotoxicity. Exercise shows promise as an adjunct therapy to reduce vascular toxicity, by improving or maintaining endothelial function, reducing inflammation and hyperlipidaemia, as well as promoting endothelial repair. The emerging evidence outlined provides promise for exercise as a potential therapeutic, but there are still several research gaps. Future research should include studies elucidating potential mechanisms behind endothelial protection of exercise in this patient population, and large exercise trials in breast cancer patients are required to ensure exercise effects are applicable and feasible for breast cancer survivors.

Conflict of interest : None

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