EXERCISE AND CANCER

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Clinical question: Does exercise protect against cancer and how does it protect?

Conclusion: Mouse models show that exercise has a protective effect against cancer. It reduces the extent of tumour growth and has some effect on the incidence of cancer as well.

Background

The health benefit of physical activity and exercise is well known in disease states such as obesity, metabolic syndrome, diabetes and hypertension. Several studies have also shown that cancer survivors engaged in active exercise have improved functional capacity and a better quality of life (Mishra et al., 2012). Interestingly, exercise has also been shown to protect against the development of certain cancers and disease recurrence (Brown et al., 2012). These observations raise the question – how does physical activity exert anti-tumor benefits? The exact mechanisms are not known yet; the authors of this study explore one aspect of this observation in mice.

The dual role of immune system in cancers is well studied. It is known that chronic inflammation promotes cancer development e.g. inflammatory bowel disease. On the other hand, immune cells with cytotoxic properties exert a protective effect against cancer and are important for killing tumor cells. It has also been shown that exercise increases the number of immune cells in circulation. The authors of this study have conducted their experiments on a mice model to provide some insights and a plausible explanation.

Methods and Results

How was cancer modeled in mice for the experiments? The first model used was three month old lab mice injected subcutaneously with melanoma cells. The tumor volume was then monitored for 2 weeks post-injection.

How were the mice subjected to exercise? The mice were divided into control and treatment arms. The animals in treatment arm were trained to run on a circular wheel kept in their cages. The treatment started 4 weeks prior to injection with cancer cells and continued for 2 weeks post-injection. On an average each of the animals in treatment arm ran about 4.1 km/day.

What was the effect of exercise? Two weeks following injection, the mice in treatment arm had significantly smaller tumor volumes (less by 60%) compared with control.

Were other tumor models used in the study? The researchers used several mice models of cancer, each representing a phenotype.

i) To replicate the results with another type of cancer they used lung carcinoma cells injected intraperitoneally instead of melanoma cells in these mice.

ii) To mimic a slow growing tumor that may occur due to carcinogen exposure they used another mice model. In this case 4 week old mice were treated with a carcinogen (diethylnitrosamine) at 4 weeks of age.
These mice are known to develop hepatic tumors by 10 months of age.

iii) They also used a genetic model that spontaneously develops melanoma to mimic tumor development with a genetic predisposition.

iv) To mimic a metastatic phenotype they injected melanoma cells intravenously into the mice and monitored for tumor development and size in the lungs.

What was the effect of exercise in other tumor models?
The results were similar to melanoma model suggesting the benefit may not be restricted to specific tumor type. In the lung carcinoma and metastatic model, exercise was beneficial in decreasing the tumor size indicating that exercise has beneficial effect in delaying tumor growth and progression. Interestingly in the slow growing and genetic tumor models studied, the researchers observed a decrease in incidence of tumors suggesting a possible direct benefit on de novo tumorigenesis.

Is this beneficial effect immune mediated?
To study, if the beneficial effect is immune mediated, the researchers quantified the number of immune cells within the tumor by a technique called flow cytometry. It was seen that the number of natural killer (NK) cells, a group of cytotoxic immune cells was higher in mice with exercise treatment, across the different models studied. However, the number of NK cells in bone marrow, spleen and circulation were not different from control mice suggesting that exercise may increase infiltration of NK cells specifically in tumor tissues. When the researchers used antibodies to deplete NK cells, the effect of exercise was abolished. The results seem to suggest that exercise mediated antitumor effect was probably mediated by NK cells.

What causes infiltration of NK cells into tumor sites?
One of the physiological responses to exercise is an increase in circulating epinephrine level. From previous studies it is known that epinephrine can mobilize NK cells from bone marrow into circulation. Hence, the researchers measured circulating epinephrine level and found that it was significantly higher in exercise treated mice. To confirm this observation further, epinephrine injections were given as a replacement to exercise in the treatment arm. Reductions in tumor volume were seen with epinephrine treatment to earlier findings with exercise treatment. Also, the observed benefit was abolished on treatment with a beta blocker, suggesting that exercise mediated surge in epinephrine is responsible for mobilizing the NK cells.

To understand the NK cell infiltration further, the NK cells were characterized and it was noted the cells had high expression of interleukin-6 (IL6) receptor on their surface. This suggests that exercise and epinephrine primarily mobilizes IL6 sensitive NK cells from muscles into the circulation. The researchers also noted increased circulating levels of IL6 in exercise treatment mice. When the mice were treated with anti-IL6 antibodies, the benefit of exercise was abolished.

What are the limitations of this study?
The evidence obtained is primarily from experiments on mice. It is well known that immune mechanisms operate differently in mice and humans. Whether the same model operates in humans is yet to be studied. Also, if the mechanism would remain functional in immune privileged sites such as brain, testes and eye is not clear. Additionally, considering that immunocompromise can occur with the existent treatment options for cancer such as chemotherapy and radiotherapy, whether the benefit of exercise would be blunted is not known. Also, whether the beneficial effect is dependent on type of exercise is not known.

What are the implications of this study from a clinical perspective?
- This study has provided some novel insights about the mechanisms that may underlie the cancer protection effect of exercise.
- The findings highlight the potential for exercise as a part of cancer treatment.
- One of the strengths of the study is that the findings were validated in different animal models of cancer suggesting that benefit of exercise may not be restricted to certain cancers.
- The study also underscores the importance of regular exercise in day-to-day life for healthy life.

References
**Anticoagulation in atrial fibrillation – BRIDGE Trial**


**Case scenario:** Mrs. S is a patient with atrial fibrillation and has been on warfarin for the same. She has to undergo an elective cholecystectomy. In the present scenario her warfarin should be stopped 5 days before surgery and she has to be initiated on heparin or low molecular weight heparin. This has to be stopped 24 hours before the surgery and restarted as soon as hemostasis is achieved. Along with Heparin warfarin is also restarted. This is known as bridging anticoagulation.

**Clinical question:** Is bridging anticoagulation necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective invasive procedure.

**Authors’ conclusion:** Bridging anticoagulation is not necessary in patients with atrial fibrillation requiring a short interruption in warfarin treatment.

**Background:**
The role of bridging anticoagulation during perioperative interruption of warfarin treatment in patients with atrial fibrillation is not clear. [1] As mentioned in the above case scenario, at present warfarin treatment is stopped 5 days before an elective procedure. It is resumed after achieving complete hemostasis. During this entire period of 5 to 10 days heparin is used as a bridging anticoagulation.[2] Whether heparin is truly needed during interruption of warfarin therapy before and after an operation or other invasive procedure is not known. The BRIDGE trial was designed by Douketis et al to answer this key question in patients with atrial fibrillation.[3]

**Methodology:**
The BRIDGE trial was a multi- centric, randomized, double-blind, placebo-controlled trial involving 108 centres in United States and Canada. It included patients who were eighteen years or older, and had a proven chronic atrial fibrillation or flutter, (with one of the CHADS2 risk score factors), on warfarin therapy for at least 3 months or longer and was planned for an elective operation or invasive procedure requiring interruption of warfarin therapy. This study included a total of 1884 patients over a span of 65 months [2009 to 2014].

Patients were randomly assigned to receive bridging anticoagulation therapy with low-molecular-weight heparin or matching. Both LMWH (100 IU of dalteparin per kilogram of body weight) and placebo were administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was restarted within 24 hours after the procedure. Both the placebo and LMWH were restarted within 12 to 24 hours of a low bleeding risk procedure (minor) and 48 to 72 hours after a high bleeding risk (major) procedure. Study drug administration was continued until the INR was 2.0 or higher on one occasion. Patients recruited were followed-up for 30 days after the procedure. The primary outcomes of this study were arterial thromboembolism like stroke, systemic embolism or transient ischemic attack and major bleeding (safety outcome), which was assessed 37 days after the procedure.

**Results**
- There was no significant difference in the incidence of arterial thromboembolism between the two groups. (0.4% in the no-bridging group and 0.3% in the bridging group).
- There was a higher incidence of major bleeding in the bridging group (1.3% in the no-bridging group and 3.2% in the bridging group).
- There was no significant difference between the secondary outcomes (rates of acute myocardial infarction, deep-vein thrombosis, pulmonary embolism, or death) between both the groups.
Discussion:
A systematic review and meta-analysis of 34 observational studies including 12,278 patients published in 2012 had shown that there was no difference in thromboembolic events among both the subgroups of patients. It had also shown that patients receiving bridging heparin had higher rate of all and major bleeding. [4] However the above meta-analysis concluded that requirement of randomized clinical trials to confirm need of perioperative bridging. The BRIDGE trial filled that gap and confirmed that for patients with atrial fibrillation requiring temporary interruption of warfarin treatment for an elective operation or other elective invasive procedure, a strategy of forgoing bridging anticoagulation was not inferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism. This strategy of forgoing bridging treatment also decreased the risk of major bleeding in these subsets of patients.

References:

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The study question seems to be relevant and specific as increasing number of patients are encountered in routine clinical practice who are on anti-coagulation and require elective surgical procedures for various reasons. On review, the study design stands up to scrutiny in terms of randomization, allocation concealment, comparable baseline characteristics, blinding and placebo-controlled nature of the study.

The Bridge trial has clearly shown that it is not really necessary to use bridging anticoagulation for patients with AF on anticoagulation prior to selected surgical procedures. It has also shown that this strategy helps in preventing bleeding complications. A caveat is that this study excluded patients who were undergoing cardiac, intra-cranial and intra-spinal surgeries and also of patients who have mechanical heart valves implanted already.

Is this study clinically applicable?

According to this trial, for every 100 patients who are on anticoagulation for atrial fibrillation, 2 major bleeding complications can be prevented by not using bridging anti-coagulation, without causing any significant increase in the thrombotic complications. This could be applied in most of the practice situations except for those patients who have mechanical heart valves or are undergoing cardiac, intra-cranial or spinal surgery.

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