THE ROLE OF PHYSICAL ACTIVITY IN THE PREVENTION OF STROKE

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SUMMARY

Although large-scale epidemiologic studies, as well as interventional trials have provided strong evidence of a consistent and robust association between physical activity and cardiovascular disease, the effect of exercise on the burden of stroke is not well understood and appreciated. This review has a purpose to summarize the literature on the effect of physical activity on stroke morbidity and mortality, and to provide current scientific evidences.

Key words: stroke, physical activity

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INTRODUCTION

Stroke is a heterogeneous disorder, which includes ischemic stroke, intracerebral and subarachnoid haemorrhage, each of which has many subtypes, and studies on stroke have been limited by their inadequate classification (1). Stroke is the third leading cause of death and the main cause of severe physical and mental impairment (1–4). Each year about 500,000 people in the United States have a stroke, and about one third of them die, making stroke the third most common cause of death after heart disease and cancer (5). During the past years several epidemiological studies have revealed the associations of a number of factors relating with stroke. Many of these factors such as increased blood pressure, cigarette smoking and diabetes mellitus, are widely accepted as being causal, others however, such as fibrinogen and homocysteine levels are still under scrutiny (2). Although, during last years many pharmacological and invasive treatments have reduced mortality and improved functional outcome, the health cost remains high (6, 7, 8). Therefore, adequate preventive measures should be the number one priority, in order to reduce the burden of the disease.

According to World Health Organization regular physical activity that is performed on most days of the week reduces the risk of developing or dying from some of the leading causes of illness and death (9). Unfortunately, it is estimated that about 60% to 85% of adults in countries around the world are simply not active enough to benefit their health (10). There are two principal categories of physical activity: occupational (OPA) and leisure-time (LTPA). The health benefits of both activities have been extensively studied, and, although the mechanisms mediating the effects of exercise are not clearly defined, multiple possible mediators have been suggested, including various physiological adaptations, altered autonomic function and metabolic adjustments. Moreover, physical activity has been associated with favorable modification of cardiovascular or cerebrovascular risk factors, such as hypertension, diabetes, obesity and hypercholesterolemia (10). It is also recognized that the volume and intensity of exercise needed to produce health benefits is considerably less than the requirements to improve physical fitness (10).

Whether physical activity actually reduces stroke risk remains controversial. Divergent findings have been reported, from clear inverse association between physical activity and stroke risk, to no decreased risk at high levels of activity (11). Thus, the role of physical activity on stroke mortality and morbidity has not been well understood and appreciated. The aim of this review is to investigate the relationship between incidence of stroke and physical activity. Therefore, in this article a comprehensive literature search was conducted and the most recent studies were consulted approaching the subject in most of its aspects.

PHYSICAL ACTIVITY AND STROKE; THE SCIENTIFIC EVIDENCE

Positive Results

Wannamethee et al. (11) studied the effect of physical activity on stroke in British middle-aged men, and concluded that moderate physical activity significantly reduces the risk of stroke, whilst more vigorous activity did not confer any further protection. In accord with the previous findings the Honolulu Heart Program (12) also revealed the benefits of physical activity in reducing the risk of thromboembolic stroke, hemorrhagic stroke, intracerebral and subarachnoid haemorrhage in older middle-aged men. In a similar way, the NHANES I Study (13) showed a consistent association of low physical activity with an increased risk of stroke. The same conclusions were underlined at the 1997 Paul Dudley White International Lecture (4) indicating the lack of physical activity as a very important and independent risk factor for stroke, focusing on the fact that the protective effect of physical activity has received little attention in women.

Harvard Alumni Health Study (14) that included more than 11,000 people, examined the risk of stroke not only by calculating the risk in sedentary against physically active individuals, but by calculating the risk in accordance with the level of physical activi-

ty and of energy expenditure. The results revealed a U-shaped curve, concluding that physical activity is associated with decreased stroke risk in men, including older men. A decreased risk was observed at energy expenditures of 1000 to 1999 kcal/wk, with further risk decrement seen at 2000 to 2999 kcal/wk (moderate activity), but not beyond. Such results also came from other studies, regarding the intensity of physical activity. In accordance with the majority of studies, there was a concordance in risk reduction from moderate intensity physical activity, but contradictory results came from some studies regarding light activity (12, 15).

Focusing only on women, the Nurses' Health Study (16), the Copenhagen City Heart Study (17), the Nord-Trøndelag Health Survey (18), have also demonstrated an inverse correlation between level of physical activity and stroke incidence.

Pitsavos et al. investigated the interaction between physical activity and left ventricular hypertrophy on stroke mortality, based on a 40-year follow-up of the Corfu cohort from the Seven Countries Study. Physical activity levels were assessed by self-reports of habitual, occupational and leisure-time activities. Moderate physical activity decreased the risk of stroke by 49% in men with LVH as compared to sedentary without LVH (hazard ratio = 0.51, $p < 0.01$), while hard exercise did not confer any significant reduction in stroke risk (19).

Finally, a recent meta-analysis by Lee et al. (20), examined the overall association between physical activity and stroke risk. He enrolled 18 cohort (11 from the United States, and 7 from elsewhere) and 5 case-control studies and he pointed out that highly active individuals had a 25% lower risk of stroke incidence or mortality in the cohort studies than had low active individuals. For the case-controls studies, highly active individuals had a 64% lower risk of stroke than had low-active individuals. When the cohort and case-control studies were combined, highly active individuals had a 27% lower risk of stroke incidence or mortality than did low-active individuals.

Non-significant Results

However, there are studies that showed non-significant results. The ARIC Study group (21) reported no significant reduction of stroke risk as a result of physical activity regardless of intensity or energy expenditure. In another study by Harmsen et al. (22), a cohort of 7,495 men from a general population sample of 9,998 men aged 47–55 years were followed-up for about 12 years. Leisure-time physical activity, as well as body mass index, alcohol abuse, and low occupational class were not found to be risk factors for stroke. Additionally, in a case-control study by Elekjaer et al. (23) the authors did not identify any lifestyle factor with a significant impact on the risk of ischemic stroke, with the possible exception of smoking.

A PATHOPHYSIOLOGICAL EXPLANATION

There is a distinct lack of evidence and a paucity of studies revealing the possible mechanisms in which physical activity and exercise could act in order to reduce the risk of stroke. The protective effect of physical activity on stroke may be explained in part through its role in controlling various known risk factors, such as hypertension, cardiovascular disease, increasing sensitivity to insulin, diabetes and body weight (24–30). In addition physical activity can play an antithrombotic role by reducing blood viscosity, fibrinogen levels and platelet aggregability and by enhancing fibrinolysis, all of which might reduce cardiac and cerebral events (24, 39, 45).

The Role of Exercise on Blood Lipids

During the previous years most abnormalities of serum lipids have traditionally been regarded as a risk factor for coronary heart disease, but not for stroke. However, several recent studies have established a more precise, direct relationship between increased serum lipids and stroke risk (28, 29). Moreover, a large number of studies have demonstrated consistent benefits with regard to stroke risk reduction by means of drug-mediated lowering of cholesterol levels (30–33). Although part of this stroke reduction risk effect could be attributed to mechanisms related to statin lipid-lowering properties, such as improved endothelial function, plaque stabilization, and antithrombotic, anti-inflammatory, and neuroprotective properties (34–36), its main cause remains the lipoprotein level alteration. It has been suggested that physical activity causes similar favorable changes in the lipoprotein profile, such as the decrease of triacylglycerols, the increase of total high-density-lipoprotein cholesterol (HDL-C), HDL3-C, apo A-I, and apo B, and the elevation of the lipoprotein lipase activity (37, 38). Thus, one of the possible biological mechanisms in which physical activity and exercise actually reduce the risk of stroke could be serum lipid modification.

The Role of Exercise on Platelet Aggregation, Coagulation and Activity

Other biological mechanisms are also associated with physical activity, including reductions in plasma fibrinogen and platelet activity, as well as elevations in plasma tissue plasminogen activator activity (9, 10, 39). It has also been suggested that even regular leisure-time activity is associated with reductions in platelet count, white cell count, C-reactive protein, coagulation factors VIII and IX, vWF and fibrinolytic variables (tPA, fibrin, D-dimer). The benefit of physical activity on cerebrovascular disease may be at least partly a result of a short-term effect through these factors (40–42).

The Role of Exercise on Endothelium-dependent Vascular Function

A recent study concerning the possible effects of regular physical activity on vessel behavior showed that exercise training significantly enhanced responses to acetylcholine and flow-mediated dilation, and that even short-term exercise training improved endothelium-dependent nitric oxide-mediated vascular function (42). In the recent years evidence has shown that exercise directly affects the functional activity of the endothelium. By increasing the mechanical shear forces on the luminal surface of the endothelium monolayer, exercise-induced increases in blood flow enhance the vasodilatory capacity of the arteries in animal models and in patients. The endothelium does not only play a unique role in controlling vascular tone but exerts several important antiatherosclerotic functions, such as preventing the adherence of platelets and inflammatory cells to the vascular surface. Thus the improvement of endothelium function by exercise is most likely to be of major importance for the atheroprotective effects of regular physical activity (42). In coronary artery disease patients' regular

physical activity has been shown to improve endothelial function by increasing phosphorylation of endothelial nitric oxide synthase (eNOS), improving agonist-mediated endothelium-dependent vasodilatory capacity, adding another possible mechanism of stroke risk reduction (43, 44). The bioactivity of endothelium--derived nitric oxide (NO) reflects its rates of production and inactivation by superoxide ($O2^{\bullet -}$), a reactive species dismutated by extracellular superoxide dismutase (ecSOD). Treadmill exercise training was found to increase eNOS and ecSOD expression, as well as improving endothelium-dependent vasorelaxation and determinants of nitric oxide bioavailability (in mice), and therefore could be considered as another possible risk reduction mechanism in humans (45, 46). Such findings add valuable data that aid understanding of the pathophysiological processes which occur during physical activity, provide also more evidence on an aetiological basis of the beneficial effects of exercise training on vascular function, and indicate that they are not solely mediated by the effects of exercise on other risk factors as well, which is what other studies had statistically demonstrated without pathophysiological evidence (47).

On the other hand high intensity exercise could have a potentially negative effect as elevated aerobic metabolism that occurs during high intensity exercise can increase the production of free radicals. Increased free-radicals production and tissue damage cannot be directly measured in humans but can possible overwhelm the body's natural defenses and pose a health risk due to an increased level of oxidation stress. The opposing position maintains that while free radicals production increases during exercise, the body's normal antioxidant defenses become "up regulated" through both endurance and sprint training adaptations. This latter position explains the beneficial effects of regular exercise on the incidence of various forms of cancer and heart disease (49).

Other possible biological mechanisms through which physical activity reduces stroke risk, mentioned in other studies, including the lowering of plasma viscosity associated with leisure time physical activity, and a similar lowering of plasma fibrinogen levels following exercise training (48).

Although the biological background of the benefit and of the possible positive effects of physical activity can be supported in part by such hypotheses, most studies claim that the association between physical activity and stroke risk reduction appears to be mediated indirectly, through beneficial effects on body weight, arterial blood pressure, serum cholesterol, glucose tolerance and other risk factors that can lead to cardiovascular complications. The addition of moderate aerobic exercise to medical antihypertensive therapy in African-American patients with severe hypertension seems to attenuate excessive elevations in blood pressure during physical exertion even with modest reductions in blood pressure at rest. This reflects a lower myocardial oxygen demand and a lower aortic artery wall tension offering additional cardiovascular protection in these high risk patients (49). Apart from its known favorable influence on these variables, physical activity is progressively beginning to demonstrate independent biological mechanisms of action, but more research is required, in order to arrive at more convincing results (48).

It is plausible for physical activity to decrease stroke risk by curtailing obesity, decreasing blood pressure, maintaining normal glucose tolerance and improving insulin sensitivity. However, after additional adjustment in analyses for body mass index, hypertension, and diabetes mellitus, these variables explain only a very modest portion of the benefit of physical activity. Furthermore, new pharmaceutical treatments have shown beneficial effects on stroke morbidity and morrtality. New-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction (50); while calcium antagonists and angiotensin-converting-enzyme-inhibitors have shown to reduce stroke mortality in hypertensive patients (51, 52). Additionally, low sodium diet and high consumption of fruit and vegetables has been related with low incidence of stroke and cardiovascular disease in general (53). Therefore, other pathways mentioned above may provide scientific evidences by which physical activity decreases stroke risk.

CONCLUSION

Although many studies have presented the beneficial role of physical activity on the primary prevention of stroke; contradictory results come from some studies regarding light or high activity levels. The role of other risk factors such as age, smoking, coronary heart disease, hypertension, and many others, in modifying this association as well as the optimum amount and intensity of physical activity should be re-evaluated in order to arrive at more convincing conclusions. These conclusions will allow primary care physicians to safely include in their recommendations to all of their patients currently under risk for stroke, the participation in an exercise-based risk reduction program. The importance of such statements becomes obvious, when one considers that, despite the positive physical and mental health benefits of exercise, long-term adherence to exercise programs remains problematic.

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