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Exercise and Plasminogen

*Emmanuel Ifeanyi Obeagu and D.C. Nwosu

Department of Medical Laboratory Science, Imo State University, Owerri, Nigeria

E-mail: emmanuelobeagu@yahoo.com

https://orcid.org/ 0000-0002-4538-0161

Abstract

Exercise was found to cause the discharge of 'extrinsic' plasminogen activators into the circulation. The intrinsic plasma plasminogen activators were not mainly changed via factor VIII clotting activity and to a lesser extent; its related antigen was both raised. A small amount of systemic fibrin will be shown by the formation of fragment X and a little decrease in the quantity of intact Aα-fibrinogen chain available. Plasminogen and antiplasmins were not mainly changed by exercise. Exercise-related fibrinolysis is brought about mainly by the release of plasminogen activators(s) via the vessel wall but that this enhanced level of fibrinolysis is insufficient to cause a significant level of systemic catabolism. Exercise increases the levels of plasminogen.

Keywords: Exercise, plasminogen, fibrinogen, muscles,

Introduction

Exercise was found to cause the discharge of 'extrinsic' plasminogen activators into the circulation. The intrinsic plasma plasminogen activators were not mainly changed via factor VIII clotting activity and to a lesser extent; its related antigen was both raised. A small amount of systemic fibrin will be shown by the formation of fragment X and a little decrease in the quantity of intact Aα-fibrinogen chain available. Plasminogen and antiplasmins were not mainly changed by exercise. Exercise-related fibrinolysis is brought about mainly by the release of plasminogen activators(s) via the vessel wall but that this enhanced level of fibrinolysis is insufficient to cause a significant level of systemic fibrin(ogen) catabolism(Neville *et al.*, 1980).

Lack of exercise is one of the major changeable risk variables for global death, with an estimated 20% to 30% elevated danger of death compared with those who are physically active (Fletcher *et al.*, 2018).

The "behavior" of physical activity (PA) is multifactorial, including social, environmental, psychological, and genetic factors. Abundant scientific evidence has demonstrated that physically active people of all age groups and ethnicities have higher levels of cardiorespiratory fitness, health, and wellness, and a lower risk for developing several chronic medical illnesses, including cardiovascular disease, compared with those who are physically inactive. Although more intense and longer durations of physical activity correlate directly with improved outcomes, even small amounts of physical activity provide protective health benefits (Fletcher *et al.*, 2018).

Exercise

Exercise is any bodily activity that enhances or maintains physical fitness and overall health and wellness (Kylasov and Gavrov, 2011). It is performed for various reasons, to aid growth and improve strength, preventing aging, developing muscles and the cardiovascular system, honing athletic skills, weight loss or maintenance, improving health and also for enjoyment. Many individuals choose to exercise outdoors where they can congregate in groups, socialize, and enhance well-being (Bergstrom *et al*., 2016)

In terms of health benefits, the amount of recommended exercise depends upon the goal, the type of exercise, and the age of the person. Even doing a small amount of exercise is healthier than doing none.

Physical exercise is important for maintaining physical fitness and can contribute to maintaining a healthy weight, regulating the digestive system, building and maintaining healthy bone density, muscle strength, and joint mobility, promoting physiological well-being, reducing surgical risks, and strengthening the immune system. Some studies indicate that exercise may increase life expectancy and the overall quality of life (Egan and Zierath, 2013)People who participate in moderate to high levels of physical exercise have a lower mortality rate compared to individuals who by comparison are not physically active. Moderate levels of exercise have been correlated with preventing aging by reducing inflammatory potential (Woods *et al* 2011).The majority of the benefits from exercise are achieved with around 3500 metabolic equivalent (MET) minutes per week, with diminishing returns at higher levels of activity. For example, climbing stairs 10 minutes, vacuuming 15 minutes, gardening 20 minutes, running 20 minutes, and walking or bicycling for transportation 25 minutes on a daily basis would together achieve about 3000 MET minutes a week. A lack of physical activity causes approximately 6% of the burden of disease from coronary heart disease, 7% of type 2 diabetes, 10% of breast cancer and 10% of colon cancer worldwide (Kyu *et al.,* 2016).Overall, physical inactivity causes 9% of premature mortality worldwide.

Types and benefits

People divide exercise into three broad categories:

- aerobic
- anaerobic
- agility training (Kyu *et al.,* 2016).

Benefits of exercise on health

Fitness: Individuals can increase fitness following increases in physical activity levels (Lee *et al.,* 2012).Increases in muscle size from resistance training is primarily determined by diet and testosterone. This genetic variation in improvement from training is one of the key physiological differences between elite athletes and the larger population. (Hubal *et al.,* 2005). Studies have shown that exercising in middle age leads to better physical ability later in life. Early motor skills and development have also shown to be related to physical activity and performance later in life. Children who have more proficient motor skills early on are more inclined to being physically active, and thus tend to perform well in sports and have better fitness levels. Early motor proficiency has a positive correlation to childhood physical activity and fitness levels, while less proficiency in motor skills results in a tendency to partake in a more sedentary lifestyle (Wrotniak *et al.,* 2006).

Cardiovascular system: The beneficial effect of exercise on the cardiovascular system is well documented. There is a direct correlation between physical inactivity and cardiovascular mortality, and physical inactivity is an independent risk factor for the development of coronary artery disease. Low levels of physical exercise increase the risk of cardiovascular diseases mortality. Children who participate in physical exercise experience greater loss of body fat and increased cardiovascular fitness (Lumeng and Julie , 2006). Studies have shown that academic stress in youth increases the risk of cardiovascular disease in later years; however, these risks can be greatly

decreased with regular physical exercise. Studies have shown that since heart disease is the leading cause of death in women, regular exercise in aging women leads to healthier cardiovascular profiles. Most beneficial effects of physical activity on cardiovascular disease mortality can be attained through moderate-intensity activity (40–60% of maximal oxygen uptake, depending on age). Persons who modify their behavior after myocardial infarction to include regular exercise have improved rates of survival. Persons who remain sedentary have the highest risk for all-cause and cardiovascular disease mortality (Ahaneku *et al.,* 2000). According to the American Heart Association, exercise reduces the risk of cardiovascular diseases, including heart attack and stroke.

Immune system: Although there have been hundreds of studies on physical exercise and the immune system, there is little direct evidence on its connection to illness (Fletcher *et al.,* 1996). Epidemiological evidence suggests that moderate exercise has a beneficial effect on the human immune system; an effect which is modeled in a J curve. Moderate exercise has been associated with a 29% decreased incidence of upper respiratory tract infections (URTI), but studies of marathon runners found that their prolonged high-intensity exercise was associated with an increased risk of infection occurrence (Fletcher *et al.,* 1996).However, another study did not find the effect. Immune cell functions are impaired following acute sessions of prolonged, high-intensity exercise, and some studies have found that athletes are at a higher risk for infections. Studies have shown that strenuous stress for long durations, such as training for a marathon, can suppress the immune system by decreasing the concentration of lymphocytes (Gleeson, 2007). The immune systems of athletes and nonathletes are generally similar. Athletes may have slightly elevated natural killer cell count and cytolytic action, but these are unlikely to be clinically significant(Fletcher *et al.,* 1996).Vitamin C supplementation has been associated with lower incidence of upper respiratory tract infections in marathon runners (Fletcher *et al* 1996).Biomarkers of inflammation such as C-reactive protein, which are associated with chronic diseases, are reduced in active individuals relative to sedentary individuals, and the positive effects of exercise may be due to its anti-inflammatory effects. In individuals with heart disease, exercise interventions lower blood levels of fibrinogen and C-reactive protein, an important cardiovascular risk marker. The depression in the immune system following acute bouts of exercise may be one of the mechanisms for this anti-inflammatory effect (Fletcher *et al.,* 1996).

Plasminogen

Plasminogen is the circulating zymogen of the enzyme, plasmin, the major enzyme responsible for degradation of fibrin clots .Plasmin is an important enzyme (EC 3.4.21.7) present in blood that degrades many blood plasma proteins, including fibrin clots. The degradation of fibrin is termed fibrinolysis. In humans, the plasmin protein is encoded by the PLG gene (Miyata *et al.,* 1982). Plasmin is a serine protease that acts to dissolve fibrin blood clots (Okoroiwu *et al.,I 2021;* Okoroiwu *et al.,* 2014; Ifeanyi *et al.,* 2020; Obeagu and Obeagu, 2015; Nwovu *et al.,* 2018; Obeagu; 2022; Obeagu *et al.,* 2022*).*

Apart from fibrinolysis, plasmin proteolyses proteins in various other systems: It activates collagenases, some mediators of the complement system, and weakens the wall of the Graafian follicle, leading to ovulation. It cleaves fibrin, fibronectin, thrombospondin, laminin, and von Willebrand factor. Plasmin, like trypsin, belongs to the family of serine proteases.

Plasmin is released as a zymogen called plasminogenfrom the liver into the systemic circulation. Two major glycoforms of plasminogen are present in humans - type I plasminogen contains two glycosylation moieties (N-linked to N289 and O-linked to T346), whereas type II plasminogen contains only a single O-linked sugar (O-linked to T346). Type II plasminogen is preferentially recruited to the cell surface over the type I glycoform. Conversely, type I plasminogen appears more readily recruited to blood clots (Wu *et al.,* 2019).

In circulation, plasminogen adopts a closed, activation-resistant conformation. Upon binding to clots, or to the cell surface, plasminogen adopts an open form that can be converted into active plasmin by a variety of enzymes, including tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), kallikrein, and factor XII (Hageman factor) (Law *et al.,* 2012). Fibrin is a cofactor for plasminogen activation by tissue plasminogen activator. Urokinase plasminogen activator receptor (uPAR) is a cofactor for plasminogen activation by urokinaseplasminogen activator(Forsgren M *et al* 1987). The conversion of plasminogen to plasmin involves the cleavage of the peptide bond between Arg-561 and Val-562 (Miyata *et al.,* 1982).

Plasmin deficiency may lead to thrombosis, as clots are not adequately degraded. Plasminogen deficiency in mice leads to defective liver repairdefective wound healing, reproductive abnormalities (Silverstein *et al* ., 1984).

Blood coagulation is a complex enzymatic event culminating in the formation of an insoluble threadlike protein called fibrin. Together with platelets, fibrin forms a haemostatic plug to prevent excessive bleeding. Fibrin blood clots are ultimately dissolved in due course in order to restore vascular patency.

The enzymes involved in this physiologically important process are part of the fibrinolytic system (Walsh, 2001).

The central component in the fibrinolytic system is the glycoprotein plasminogen, which is produced by the liver and is present in plasma and most extravascular fluids. Plasminogen is a precursor enzyme (zymogen) which, following partial cleavage by a plasminogen activator is converted to its active and proteolytic form, plasmin. Its primary target is fibrin, but it is also able to degrade several constituents of the extracellular matrix and to convert a number of pro-hormones and cytokine precursors to their active form. Plasmin also appears to be involved in the metastatic spread of cancer.

The generation of plasmin occurs preferentially on the fibrin surface, which offers binding sites for plasminogen and its principle activator in blood, t-PA. This binding stimulates plasminogen activation, but also localizes the action of plasmin to sites of fibrin formation which promotes efficient clot lysis. Further regulation is provided by the presence in plasma of inhibitors, primarily the plasmin inhibitor and the plasminogen activator inhibitor 1 (PAI-1).

The important role of plasminogen in fibrinolyis makes it an interesting parameter to evaluate in various diseases. A decreased plasminogen level may in some situations compromise the body's ability to degrade fibrin and as such predispose to thrombosis. Hereditary plasminogen deficiency, as a cause of thrombosis, have also been reported in several cases. However, plasminogen deficiency is usually an acquired condition and since plasminogen is the inactive precursor of plasmin, most acquired defects are found in situations with increased fibrinolytic activity. An acquired deficiency is often seen with severe liver disease and acute disseminated intravascular coagulation (DIC), or as a result of thrombolytic therapy with plasminogen activators. Plasmin activity is inhibited mainly by binding to the plasmin inhibitor, which forms a stable complex with plasmin devoid of proteolytic activity.

Plasminogen activators

Plasminogen activators are serine proteases that catalyze the activation of plasmin via proteolytic cleavage of its zymogen form plasminogen. Plasmin is an important factor in fibrinolysis, the breakdown of fibrin polymers formed during blood clotting. There are two main plasminogen activators: urokinase (uPA) and tissue plasminogen activator (tPA). Tissue plasminogen activators are used to treat medical conditions related to blood clotting including embolic or thrombotic stroke, myocardial infarction, and pulmonary embolism (Rivera-Bou, 2016). Plasminogen activators are inhibited by plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, and protein C inhibitor.

Tissue-type plasminogen activator (t-PA)

Tissue-type plasminogen activator (t-PA) is the principal endogenous activator of plasminogen in blood. It is produced as a single-chain molecule by the vascular endothelial cells and is secreted into the plasma continuously or by an acute release reaction following stimulation of certain endothelial cell receptors. Rapid fluctuations in t-PA concentration can be observed in response to exercise, venous occlusion, alcohol and drugs, such as DDAVP and anabolic steroids. Individuals, who do not show increased t-PA activity when exposed to some of these stimuli, may be a risk group for deep vein thrombosis. Plasmin cleavage of t-PA produces a more active two-chain molecule. However, unlike many other serine proteases, t-PA is active in its single-chain form, especially in the presence of fibrin or fibrin(ogen) fragments. Single-chain t-PA is a 68 kDa glycoprotein, consisting of 530 amino acids and containing 7-13% carbohydrate. In human plasma, t-PA occurs mainly as a complex together with its principal inhibitor PAI-1. The level of t-PA antigen is about 5 mg/ml, whereas the concentration of free t-PA is only about 1 mg/l or 0.5 IU/ml (specific activity range 500,000 to 700,000 U/mg). The single-chain t-PA molecule is converted by plasmin to a two-chain form by cleavage of the Arg275-Ile276 peptide bond. Binding to fibrin concentrates and correctly orientates t-PA and plasminogen, as well as inducing conformational changes in the molecules that promote efficient clot lysis.

Urokinase-type plasminogon activator (u-PA)

Urokinase-type plasminogen activator (u-PA) is mainly produced in the kidneys as an inactive single-chain molecule (scu-PA). u-PA has its major function in tissue-related proteolysis and is believed to play only a secondary role to t-PA as a physiological activator in blood (Mikus *et al.*, 1993).

The activation of scu-PA by catalytic amounts of plasmin results in a two-chain structure with increased activity towards plasminogen. Through this mechanism, initial traces of plasmin may catalyze the production of active u-PA, leading to the formation of more plasmin. u-PA can only activate plasminogen in the presence of fibrin. However, it does not bind to fibrin and is not activated by fibrin. In human plasma, u-PA antigen concentrations range from 2 to 7 ng/ml. Higher values are often found in subjects with liver cirrhosis and hepatoma.

Plasminogen aspects

Plasminogen is synthesized in the liver and is maintained in plasma at a stable concentration of around 200 mg/l. The reference interval for plasminogen activity is 75% to 135%. In full-term neonates the plasminogen concentrations are about half those of adults, with levels gradually rising to normal by 6 months. Plasminogen levels vary little through adult life in relation to age, sex and smoking habits. There is no diurnal variation and levels are not affected by exercise. Histidine-rich glycoprotein (HRG) and plasmin inhibitor are two plasma proteins that form reversible complexes with the lysine-binding sites of plasminogen. Approximately 50% of plasminogen is bound to histidine-rich glycoprotein and about 15% to the plasmin inhibitor. Complexing with these proteins has an inhibitory effect on the binding of plasminogen to fibrin. This means that the plasma concentration of free plasminogen is determined not only by plasminogen levels but also by HRG and plasmin inhibitor. In some cases increased HRG levels may be associated with the increased risk of thrombosis.

Situations associated with decreased or elevated plasminogen levels;

Decreased plasminogen levels:

- Argentine hemorrhagic fever
- DIC
- Elevated HRG
- Hereditary plasminogen deficiencies
- Hyaline membrane disease
- Hyperthyroidism
- Leukemia
- Liver disease
- Neonates
- Sepsis

- Thrombolytic therapy
- Elevated plasminogen levels
- African males
- Anabolic steroids
- Hypothyroidism
- Obesity

Function

Produced mainly in the liver, plasminogen is the inactive zymogen form of plasmin, and circulates in plasma in a closed conformation that cannot be activated. Binding clots or cell surface causes its conformation to change, allowing it to be activated by plasminogen activators. Plasminogen activators do so by cleaving the R561/V562 peptide bond, producing the active protein plasmin, which catalyzes the degradation of fibrin polymers that make up the structure of blood clots (Law *et al.,* 2012).

Inhibition

The main inhibitor of tissue plasminogen activator and urokinase is plasminogen activator inhibitor-1 (PAI-1).Plasminogen activator inhibitor-1 is a serine protease, synthesized by endothelial cells, that specifically inhibits tissue plasminogen activator (tPA) and urokinase (uPA). Tissue plasminogen activator and urokinase are the activators of plasminogen and results in the breakdown of blood clots (fibrinolysis)(Declerck and Gils (2013).

PAI-1 levels have also been studied in patients and how they influence certain diseases. Elevated serum levels of PAI-1 have been found in obese individuals (Mimuro, 1991). Elevated levels of PAI-1 also seem to increase the risk of atherothrombotic events and may also promote vascular disease (Carter and Church, 2009).

Plasminogen activator inhibitor-2 (PAI-2) is also a serine protease that inactivates tPA and uPA. PAI-2 is produced by the placenta and only found in high quantities in the blood

Conclusion

Exercise was found to cause the discharge of ‘extrinsic’ plasminogen activators into the circulation. The intrinsic plasma plasminogen activators were not mainly changed via factor VIII clotting activity and to a lesser extent; its related antigen was both raised. Exercise increases the levels of plasminogen.

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