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REVIEWS
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The kidney and exercise
Rinichiul și efortul fizic

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Abstract

The main functions of the kidney are the maintenance of the body homeostasis (the volume of fluids, their osmolarity, the concentration and content of electrolytes, acid-base balance), the excretion of metabolic end-products and foreign substances, the control of blood pressure, the control of erythrocyte mass through the secretion of erythropoietin, and the regulation of body calcium and phosphate balance through the activation of vitamin D.

Several renal functions are modified during exercise, and preexisting renal dysfunction can influence the assessments of exercise capability.

This paper reviews the effects of exercise on renal activity; exercise-induced haematuria, proteinuria, hyponatremia, hypokalemia and acute kidney injury. The correct management of these modifications requires an accurate diagnosis to define the treatment approach and to determine the permissible exercise.

Keywords: kidney, exercise, haematuria, proteinuria, acute kidney injury.

Rezumat

Principalele funcţii ale rinichiului constau în menţinerea homeostaziei corpului (volumul fluidelor, osmolaritatea lor, concentraţia şi conţinutul de electroliţi, menţinerea balanţei acido-bazice), excreţia produşilor finali de metabolism şi a substanţelor străine, controlul presiunii arteriale, controlul masei eritrocitare prin secreţia de eritropoietină şi reglarea balanţei de calciu şi fosfat din organism prin activarea vitaminei D.

În cursul efortului fizic, o serie din funcţiile rinichiului sunt modificate, o disfuncţie renală preexistentă putând să influenţeze capacitatea de efort.

Lucrarea face o revizie a efectelor exerciţiului fizic asupra activităţii renale; asupra hematuriei şi proteinuriei de efort, a hiponatremiei şi hipopotasemiei induse de efort şi a insuficienţei renale acute de efort. Managementul corect al acestor evenimente se bazează pe un diagnostic corect în scopul stabilirii tratamentului corect şi a aprecierii capacităţii de efort la aceşti pacienţi.

Cuvinte cheie: rinichi, efort fizic, hematurie, proteinurie, insuficienţă renală acută.

Functions of the kidney

The kidney is an organ of vital importance that fulfils numerous functions within the body:

1. *The excretory function*: it represents the depuration function required to clean the body from useless substances that are toxic for the body: the final products of metabolism (urea, creatinine, uric acid, ammonia, bile pigments, lipid and carbohydrate residues, etc.), salts (phosphates, bicarbonates and sulphates), electrolytes (Ca, Mg, Na, K, Cl), colouring agents, toxins, drugs, etc.

2. *The homeostatic function*: through the blood clearance function, the kidney maintains the constancy of the internal environment, i.e., it preserves the concentration of electrolytes in the body, the acid-base balance, maintains the plasma blood volume and blood osmotic pressure constant, and preserves the concentration of certain regular plasma constituents (glucose, amino acids and vitamins).

3. *The endocrine function* is achieved through: the secretion of prostaglandins, nitric oxide, endothelins, the synthesis of certain growth factors (insulin-like growth factor IGF-1, epidermal growth factor EGF, the transformed growth factors TGF-β1 and TGF-β2) and the kinin-forming activity.

4. *The metabolic function*: the kidney participates in gluconeogenesis, ammoniagenesis, the production and catabolism of some hormones, the control of phosphocalcic metabolism through calcitriol (1,25-dihydroxyvitamin D3), the catabolism of β2 microglobulin.

5. *The fibrinolytic function*: consists of the synthesis of

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urokinase (at the level of the urinary tract epithelium and vascular endothelium).

6. *The thermoregulation function*: renal thermogenesis is accomplished via the brown adipose tissue surrounding the kidney.

7. *The antioxidant defence function*: normally, throughout the course of metabolic processes in the kidney, extremely toxic oxygen reactive species are formed. The kidney's antioxidant defence capacity is ensured by a series of antioxidant enzymes: superoxide dismutase, catalase and glutathione peroxidase, glutathione transferase, glutathione reductase, and haeme oxygenase (Briggs et al., 2014; Rayner & Schwellnus, 2008; Tache, 2002).

The kidney and homeostasis

Numerous functions of the body may develop optimally as long as the composition and volume of body fluids are maintained within normal values. As such, cardiac output and blood pressure are dependent on the optimal plasma volume, the action of most enzymes depends on a normal pH and a normal concentration of electrolytes, cell membrane potential depends on the concentration of potassium, and membrane excitability depends on calcium concentration (Briggs et al., 2014).

The kidney's main function is to correct disturbances in the volume and composition of the body secondary to: ingestion of fluids and food, metabolism, environmental factors and exercise. In healthy persons, this correction is achieved in a few hours, so that in the long-term the volume and composition of fluids does not differ much from normal values (Briggs et al., 2014; Rayner & Schwellnus, 2008).

Intense and prolonged exercise may induce changes in renal haemodynamics, the excretory function and the release of hormones, with consequences on the body homeostasis. Some of these changes may impact or even limit the performance of athletes (Poortmans & Zambrasky, 2014).

Changes in renal functions during exercise

Renal plasma flow during exercise

A series of studies performed over the years, starting with the study of Barclay et al. from the University of Birmingham in 1947, have demonstrated without a doubt the fact that renal plasma flow decreases during exercise due to the redistribution of circulation preferentially toward the muscles, heart and lungs, in order to ensure maximum physical performance (Poortmans & Zambrasky, 2014).

The reduction in renal plasma flow is directly proportional to the intensity of exercise, i.e., it is greater as the exercise is more intense. This decrease of plasma flow is more pronounced if exercise takes place under conditions of increased heat and humidity, which favour dehydration. Furthermore, the return to normal of renal plasma flow after exercise is slower than the recovery of the arterial pulse and tension (Poortmans & Zambrasky, 2014; Briggs et al., 2014; Rayner & Schwellnus, 2008; Bellinghieri et al., 2008).

The reduction of renal plasma flow leads, on the one hand, to an increase of energy consumption in the renal tubules, due to an increase in the reabsorption of water and sodium for the recovery of intravascular volume (Briggs et al., 2014; Rayner & Schwellnus, 2008; Bellinghieri et al., 2008). On the other hand, the decrease in renal blood flow and pressure in the glomerular capillaries activates renal self-regulation (through the juxtaglomerular apparatus), in order to preserve the glomerular filtration rate (GFR), leading to vasodilatation of the afferent arteriole (mediated by prostaglandins and nitric oxide) and vasoconstriction of the efferent arteriole (mediated by the renin-angiotensin-aldosterone system, RAA). However, this leads to a decrease of the tubular blood flow, especially in the renal medulla, which increases the risk of renal tubular ischemia and acute kidney injury (AKI) during prolonged exercise, especially if associated with dehydration, rhabdomyolysis, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (Briggs et al., 2014; Turner & Coca, 2014; Rayner & Schwellnus, 2008).

The urinary excretion of water and electrolytes during exercise

Studies have demonstrated that diuresis is reduced during exercise, thus the urine eliminated during exercise is lower in volume, more concentrated and more acid. This happens because the hydroelectrolytic balance needs to be maintained in case of dehydration and seems to be due to the activation of the hypothalamo-pituitary axis during exercise, with the non-osmotic release of vasopressin (ADH) (Poortmans & Zambrasky, 2014; Rayner & Schwellnus, 2008; Bellinghieri et al., 2008). Moreover, it has been demonstrated that there is a linear correlation between the intensity of exercise and plasma ADH levels. The response of ADH secretion during exercise also depends on the duration of exercise, on the degree of hydration, and on the rate of ADH consumption at hepatic and renal level (Kenefick & Cheuvront, 2012; Rayner & Schwellnus, 2008; Bellinghieri et al., 2008).

During exercise, there are also electrolyte changes. Sodium (Na) is an active osmotic electrolyte, the renal excretion of Na playing a major role in the regulation and control of extracellular volume, including that of plasma volume. The renal elimination of Na decreases during intense exercise. The mechanism is complex and incompletely elucidated; it seems to be due to a reduction in the glomerular filtration of Na and to the activation of the renin-angiotensin-aldosterone system (RAA), secondary to exercise, which leads to an increase in the tubular reabsorption of Na (Poortmans & Zambrasky, 2014; Rüst et al., 2012; Rayner & Schwellnus, 2008).

Disturbances in sodium balance are nevertheless rare during exercise and are rather due to changes in water balance (dehydration with hyperNa, water intoxication with hypoNa) (Rayner & Schwellnus, 2008; Rüst et al., 2012; Verbalis, 2014; Dennen & Linas, 2014).

Exercise-related hyponatremia has been described during exercise. This appears due to non-osmotic ADH release (induced by intense and prolonged exercise), associated with water intoxication through an increased intake of fluids. It may be accentuated by the significant loss of salt through perspiration under conditions of heat and increased humidity (Patel et al., 2005; Bellinghieri et al., 2008; Rayner & Schwellnus, 2008). Usually it lacks

symptoms, but some may appear: nausea, vomiting, headaches, drowsiness, confusion, irritability. Severe hyponatremia may lead to cerebral oedema, loss of consciousness, coma and more rarely, even to death (Noakes, 2002; Palmer et al., 2003; Rayner & Schwellnus, 2008; Verbalis, 2014).

The effects of exercise on the urinary excretion of potassium (K) are variable. In well-hydrated persons, no changes in the excretion of K are observed during moderate exercise. During intense and prolonged exercise, there is an increase in the urinary excretion of K, without changes in serum potassium (Rayner & Schwellnus, 2008; Bellinghieri et al., 2008).

For these reasons, the excessive consumption of fluids should be avoided by marathon runners. Such intake should be adapted individually depending on the length of the race and climate conditions, but also on body mass, rate of perspiration and weight before and after exercise (Kenefick & Cheuvront, 2012; Rayner & Schwellnus, 2008; Hsieh, 2004).

Exercise-related proteinuria

Exercise-induced proteinuria was first observed in recruits in 1878 and subsequently, it was described in participants in the Boston marathon in 1899. A series of subsequent studies have demonstrated that proteinuria induced by exercise may also appear after exercise and is reversible (Kohler et al., 2015; Rayner & Schwellnus, 2008).

Its incidence is variable, between 11 and 100% after intense exercise. It seems that its occurrence depends on the intensity and type of exercise more than on its duration (Heathcote et al., 2009; Poortmans et al., 2015; Kohler et al., 2015). In addition, even though initially it was presumed to be more severe in untrained persons, further studies have demonstrated that at the same intensity of exercise, the level of exercise proteinuria is the same (Shavandi et al., 2012; Poortmans et al., 2015; Kohler et al., 2015; Rayner & Schwellnus, 2008).

Proteinuria normally appears 20-30 minutes after the end of exercise and the return to normality is achieved in a few hours, independently of the athlete's degree of dehydration (Poortmans et al., 2015; Poortmans & Zambraski, 2014; Rayner & Schwellnus, 2008).

The mechanism of development of exercise proteinuria is still incompletely elucidated. It has been observed that glomerular type proteinuria (characterized by the loss of medium molecular weight proteins such as albumin) appears following lower intensity exercise compared with tubular type proteinuria (characterized by the loss of low molecular weight proteins such as alpha 1 microglobulin). Intense exercise results in mixed glomerular and tubular proteinuria (characterized by the presence of both medium molecular weight and low molecular weight proteins) (Poortmans et al., 2015; Kohler et al., 2009; Kohler et al. 2015; Jayne & Yiu, 2014).

The factors involved in the development of exercise proteinuria could be:

a) Metabolic acidosis that appears during intense exercise increases the permeability of the glomerular basement membrane and alters its electrical charge. Metabolic acidosis also alters the electrical charge of proteins and favours their loss through urine.

b) The reduction of renal blood flow during exercise through renal vasoconstriction leads to renal hypoxia and an increase in the permeability of the glomerular basement membrane to proteins.

c) It has been demonstrated that prostaglandin inhibitors reduce exercise proteinuria, while angiotensin conversion enzyme inhibitors do not change the values of proteinuria induced by exercise. Nevertheless, it has been found, in mice, that angiotensin II inhibitors reduce exercise proteinuria.

d) Tubular reabsorption is mediated by receptors. They may be oversaturated when glomerular filtration increases, leading to the development of tubular proteinuria.

e) Genetic predisposition (Gündüz et al., 2005; Haraldsson et al., 2008; Rayner & Schwellnus, 2008; Jayne & Yiu, 2014; Kohler et al., 2015).

Clinically, exercise-induced proteiuria is asymptomatic and is randomly detected with dipstick tests.

If proteinuria is detected within 24-48 hours after intense exercise in healthy persons, without being associated with the intake of nephrotoxic drugs (SAIDs), and completely disappears after 24-48 hours, it can be considered benign (Rayner & Schwellnus, 2008).

If it is persistent and/or is associated with haematuria and/or exceeds 1g/day, it requires additional investigation for the diagnosis of a renal or systemic disease (hypertension) and the assessment of exercise ability (Rayner & Schwellnus, 2008).

For these reasons, it is recommended that all athletes undergo a routine dipstick test for proteinuria before exercise, in order to avoid difficulties in interpreting proteinuria possibly occurring after exercise (Hoffmann et al., 2013; Rayner & Schwellnus, 2008).

Exercise-related haematuria

Exercise-related haematuria has been described in association with a great variety of sports, both in trained athletes and in untrained persons (Rayner & Schwellnus, 2008; Luciani et al., 2010). It has been described in sportsmen practicing contact sports (boxing, football, hockey), as well as in sports such as swimming, canoeing, etc. (Rayner & Schwellnus, 2008; Luciani et al., 2010; Lepers et al., 2013).

The incidence of exercise-related haematuria is variable and depends on the type, intensity and duration of exercise (it is more frequent after intense and prolonged exercise): it was 11.4% in athletes and 20-63% in marathon runners (Rayner & Schwellnus, 2008; Luciani et al., 2010; Kohanpour et al., 2012).

The mechanism of occurrence of exercise-related haematuria is incompletely elucidated; several factors seem to be involved, which act at different levels of the renal-urinary system:

1. Renal: ischemia (secondary to the decrease of renal blood flow, especially in the renal papilla, which occurs during intense and prolonged exercise), AKI (acute kidney injury), vascular fragility, trauma (contact sports, falls), nephroptosis (jogging), lithiasis.
2. Ureteral: lithiasis.

3. Vesical: lithiasis, trauma (runners: repeated compression of the anterior wall of the bladder to the posterior wall), infections.

4. Urethral: direct trauma (cyclists, horse riding), lithiasis, infections, cold (Patel et al., 2005; Rayner & Schwellnus, 2008; Luciani et al., 2010; Kohler et al., 2015).

Clinically, it is usually benign and disappears spontaneously after 24 to 48 hours (Rayner & Schwellnus, 2008; Jayne & Yiu, 2014; Kohler et al., 2015).

If haematuria continues after 48 hours and is associated with: colic or flank pain; proteinuria; presence of urinary casts (red cell, white cell, pigmented); positive urine culture; oliguria 12 hours after intense exercise, additional investigations are required in order to exclude a renal disorder (IgA nephropathy that may be asymptomatic but exacerbated by exercise) or a urinary tract disease (Rayner & Schwellnus, 2008; Luciani et al., 2010).

Exercise-related acute kidney injury (AKI)

AKI is the most severe renal complication that may occur after exercise; unrecognized, it can be fatal due to hyperkalemia. The exact incidence is unknown. The risk to develop AKI depends on various factors such as: the type of exercise, the intensity and duration of exercise, the state of hydration, environmental conditions and the use of drugs during exercise (Bellinghieri et al., 2008; Rayner & Schwellnus, 2008; Hiraki et al., 2013).

Exercise-related AKI may be triggered by several conditions such as:

a) Severe *dehydration* determines a severe diminution of renal blood flow, with renal ischemia and acute tubular necrosis (Rayner & Schwellnus, 2008; Waikar et al., 2014; Turner & Coca, 2014).

b) *Hyperthermia* may develop during intense exercise under conditions of excessive heat and humidity, in athletes who are not acclimatized. On the one hand, hyperthermia leads to excessive sweating and dehydration, with a reduction of renal blood flow. On the other hand, hyperthermia may affect a series of organs, especially skeletal muscles, directly and indirectly. It decreases the blood flow in muscles, which leads to ischemia, aggravates physiological rhabdomyolysis and results in the release of myoglobin. In time, it can be associated with intravascular haemolysis, which may lead to the release of haemoglobin (Vega et al., 2006; Rayner & Schwellnus, 2008; Junglee et al., 2013; Waikar et al., 2014; Turner & Coca, 2014).

c) *Myoglobinuria*: skeletal muscle damage (rhabdomyolysis) leads to the release of myoglobin (Mb). This is a globin chain that contains a haeme pigment. In an acid environment (metabolic acidosis and re-assimilation of bicarbonate in the proximal convoluted tubule), globin dissociates from haeme. This has a direct renal toxic effect interfering with tubular transport mechanisms. Myoglobinuria leads to AKI only in association with other factors (intravascular volume depletion, haemoconcentration, renal vasoconstriction, other nephrotoxins) (Rayner & Schwellnus, 2008; Junglee et al., 2013; Turner & Coca, 2014; Kohler et al., 2015).

d) *Haemoglobinuria***:** it has less dramatic effects on the kidneys. Intravascular haemolysis may appear during exercise through direct mechanical trauma on the red blood cells (more severe in case of structural abnormalities) or through hyperthermia. The haemoglobin (Hb) released is less toxic for the kidney because it irreversibly links to haptoglobin, leading to the presence of a molecule larger than Mb, which passes more difficultly through the glomerular filter. Filtered Hb has toxic effects on the renal tubules through the same mechanism as Mb. It may impact on the renal function only in association with other factors (volume depletion, acidosis, arterial hypotension) (Rayner & Schwellnus, 2008; Waikar et al., 2014; Turner & Coca, 2014).

e) *Nephrotoxic drugs*: NSAIDs are used by athletes, especially by marathon runners. These are completely contraindicated because they severely compromise renal function. On the one hand, they inhibit the synthesis of prostaglandins (which are strong vasodilators and protect the renal blood flow) and on the other hand, they may cause acute interstitial allergic nephritis (Rayner & Schwellnus, 2008; McCullough et al., 2011; Waikar et al., 2014).

In order to prevent exercise-related AKI, a few measures must be observed:

- Athletes should consume sufficient fluids during exercise and in the first hours after exercise, especially under conditions of excessive heat and humidity.
- If exercise is performed under conditions of heat and humidity, athletes should acclimatize before exercise.
- Athletes should avoid the consumption of any drugs before exercise (especially no painkillers or NSAIDs 48 hours before exercise) and during exercise.
- Athletes should request medical advice in case of anuria 12 hours after exercise (Rayner & Schwellnus, 2008; Kenefick & Cheuvront, 2012; Junglee et al., 2013).

Conclusions

1. Renal changes that occur during exercise are numerous and have diverse causes.
2. They should be carefully examined and identified.
3. When present, they should be quickly detected in order to determine the therapeutic approach and to assess the athlete's exercise capabilities.

Conflicts of interest

Nothing to declare.

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