Renal Alterations During Exercise

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Proteinuria and hematuria are common during exercise. Proteinuria is usually due to glomerular or tubular changes or to an excessive production of protein as in myeloma. Certain clinical conditions can, however, result in a functional or temporary proteinuria, especially during pregnancy, fever, orthostasis, or following physical activity. Sport-related proteinuria following marching, exercise, and stress, was first observed in soldiers after long marching. Prevalence of proteinuria during exercise ranges from 18% up to 100% depending on type of exercise and its intensity. A higher incidence of proteinuria has been observed in some sports requiring great exercise intensity and it is certainly related to muscular work intensity and would decrease after prolonged training. Indeed, exercise-induced proteinuria is strictly related to exercise intensity rather than to exercise duration. Exercise aggravates the proteinuria of various nephropathies and that of renal transplant recipients. The prevalence of hematuria is higher in the athletic than the general population and the main difference is that sport-related hematuria resolves spontaneously after physical exercise while hematuria found in nonathletic population can be chronic. Sport-induced hematuria is influenced by exercise duration and intensity. Among the mechanisms underlying the exercise induced hematuria are increased body temperature, hemolysis, increased production of free radicals, and excessive release of catecholamines. Lactic acidosis, generated during anaerobic conditions, causes the passage of erythrocytes into the urine, through increased glomerular permeability.

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players (80%), oarsmen (100%). A higher incidence of proteinuria has been observed in some sports requiring great exercise intensity; the incidence of proteinuria would be related to muscular work intensity and it could reach very high levels up to 5 mg/min.\textsuperscript{2,3} such levels being normally reached after exceeding the anaerobic threshold and being likely to decrease during prolonged training. The different incidence rates for proteinuria, which can be observed in several sports, could be related to exercise duration and intensity. A study on some swimmers in different distance events of 100, 200, and 6000 meters showed that albumin and beta-2-microglobulin disappearance was associated with the swimmers’ speed and a decrease in plasma volume, although proteinuria decreased as soon as distances were reduced.

Robertshaw et al.\textsuperscript{4} states that exercise-induced proteinuria is strictly related to exercise intensity rather than exercise duration, although it was not observed in some subjects even after strenuous exercise. Strenuous exercise results in a decrease in renal plasma flow and glomerular filtration. Despite such changes, filtration fraction doubles during strenuous exercise and keeps the passage of metabolites or other substances through the glomerulus.

Poortmans and Labilloy\textsuperscript{3} observed that maximal protein urine excretion occurs 20 to 30 minutes following strenuous exercise, and it takes 4 more hours of rest to get values back to normal. Moreover, unless proteinuria disappears within 24 to 48 hours, further evaluation should be carried out. A spontaneous decrease in exercise-induced proteinuria was found on some triathlon athletes, who had covered a distance of 100 miles. It was observed that increased mid-distance proteinuria from 5.9 µg/dL to 80 µg/dL went back to normal immediately after the race.\textsuperscript{5}

From a qualitative point of view, exercise-induced proteinuria is mixed glomerular and tubular and occurs in case of increased glomerular permeability and partial inhibition of protein tubular reabsorption. In particular, during mild to moderate exercise, a type of mainly glomerular proteinuria can be observed, while during strenuous exercise, a mixed type of proteinuria (glomerular and tubular) can occur. Glomerular proteinuria is characterized by urine protein components following exercise that are much more similar to plasma proteins rather than to normal urine proteins at rest.\textsuperscript{6} Tubular proteinuria is characterized by the presence of low-molecular-weight proteins in postexercise urine, as lysozymes and beta-2-microglobulin, which are usually filtered at glomerular level and subsequently reabsorbed at tubular level. This is due to saturation of reabsorbing mechanisms, following a higher quantity of proteins filtered at glomerular level.\textsuperscript{7} Among immunoglobulins, IgA and IgG, and rarely IgD, are excreted as entire molecules into postexercise urine.\textsuperscript{8}

It has been observed that exercise, by means of metabolite production, interferes with electrostatic glomerular barrier thus facilitating macromolecular filtration. Increased urine protein excretion may also occur due to blood pH drops, following the elevation of blood lactate levels during exercise. This mechanism has been confirmed by some studies in which a decrease in exercise-induced proteinuria was observed following sodium bicarbonate infusion, which corrects lactic acidosis.

Suzuki and Ikawa\textsuperscript{9} demonstrated that increased lactate output following strenuous exercise may result in the excretion of both albumin and low-molecular-weight proteins. They also observed that increased organic acid output and/or decreased renal circulation due to organic acids may change glomerular permeability and may inhibit the tubular absorption of low-molecular-weight protein. Glomerular basement membrane permeability to high-molecular-weight proteins can be altered by decreased surface anionic charges, due to both organic acid hyperproduction and decreased pH.

It has been observed that postexercise proteinuria may be influenced by age. A study by Poortmans et al.\textsuperscript{10} on 170 children between 6 and 18 years of age during strenuous exercise showed that proteinuria increased with age and it could be particularly observed in males ranging in age from 6 to 9 years.

On the contrary, a study carried out on 60 subjects of pediatric and adolescent ages showed that increased albuminuria was not related to age or sex but rather to blood pressure and physical constitution. In addition, the study showed that proteinuria was only glomerular in origin since beta-2-microglobulin excretion did not change after exercise.\textsuperscript{11}

Membrane anionic charges have been found to be the pathogenetic causes responsible for exercise-induced albuminuria. A study carried out
on athletes taking part in competitive running events in the mountains evaluated urinary excretion of some proteins and showed that protein excretion is highly associated with albumin and beta-2-microglobulin disappearance.\textsuperscript{12}

Also, renin-angiotensin system and catecholamine activation resulting in decreased renal hemodynamics has been found to be responsible for inducing increased glomerular permeability. The role of the renin-angiotensin system and prostaglandins has been studied on some athletes undergoing ergometric effort. Eight normal subjects underwent strenuous exercise on three different occasions: after being administered placebo, prostaglandin inhibitor (indomethacin), or angiotensin-converting enzyme (ACE) inhibitor. The results showed that increased exercise-induced proteinuria was reduced after prostaglandin inhibitor treatment but it was not altered by placebo or inhibitor ACE treatment.\textsuperscript{13}

Exercise has a further effect on protein excretion in patients affected by nephropathies (diabetes, renal diseases, renal transplants). Groop et al.\textsuperscript{14} evaluated whether during mild exercise proteinuria in diabetic patients depends on the size of excreted proteins. Subjects were divided into two groups: 17 were affected by recent diabetes and 17 were affected by long-term diabetes; there were also 8 healthy subjects. The investigators observed that exercise did not result in protein excretion either in healthy subjects or in patients affected by recent diabetes, while it occurred in subjects affected by long-term diabetes. Moreover, proteinuria was not selective but was independent of protein size.\textsuperscript{14}

Increased postexercise proteinuria was observed in subjects affected by nephrotic syndromes due to different glomerulonephritides. In particular, increased proteinuria was evident in 25\% of the patients but it also occurred in 50\% of them, while in the remaining 25\% no change was observed.\textsuperscript{15} In kidney- or heart-transplanted subjects, postexercise proteinuria was lower than in normal subjects.\textsuperscript{16}

The role of cytokines and growth factors in nephrology is becoming increasingly important, especially as related to increased renal dysfunction. The relationship between such molecules and postexercise proteinuria has not been studied so far. Pedersen and Toft\textsuperscript{17} recently observed that athletes undergoing long and strenuous exercise show changes in the immune system characterized by low lymphocyte concentrations and the disappearance of natural immunity, lymphocyte proliferations, and secretory IgA levels, together with high levels of cytokines (IL-6, IL-1) and growth factors (like TNF). Such molecules would be produced in response to muscular damage and muscular cell proliferation.\textsuperscript{17} The contemporary occurrence of proteinuria, which can be observed in subjects undergoing strenuous exercise, in our opinion, could also be related to increased growth factors as both cause and effect of proteinuria.

Subjects showing postexercise proteinuria are not likely to develop chronic kidney disease, and therefore it is not necessary to reduce their physical activity. Moreover, such problems must be evaluated in the light of future nephrology prevention plans, because, as it has been supposed, exercise can enable us to detect functional abnormalities at a subclinical level.

**Hematuria**

Although hematuria in athletes may have been recognized as early as the first century A.D., such a condition was recognized in 1700.\textsuperscript{18} The first formal description of exercise-induced hematuria goes back to 1910\textsuperscript{19} when red blood cells were detected in the urine of 18 marathon runners after a 40-kilometer race. Since then, exercise-induced hematuria has been described in association with a variety of different sports, including soccer, running, American football, rowing, and swimming.

Microhematuria is quite prevalent in the general population. Some investigators have tried to study its incidence. In a study that examined the medical records of 100 asymptomatic servicemen over a 15-year period (12.2 visits per year), the cumulative incidence of microhematuria was 38\%.\textsuperscript{20} In another large population-based study by the Mayo Clinic, asymptomatic hematuria was found in 13\% of adult males (\textgreater{}35 years of age) and in postmenopausal women (\textgreater{}55 years of age).\textsuperscript{21}

A similar incidence rate for hematuria (13\%) was found in a population of over 1000 medical students at the Kaiser Medical Centre in Honolulu.\textsuperscript{22} The prevalence of hematuria is higher in the athletic population. The greater difference between the so-called asymptomatic hematuria, which can be found in the general population and in the athletic population, is that the latter resolves spontaneously after the physical exercise ends.
while hematuria found in nonathletic population can be chronic. The pathophysiology and etiology of sport-induced hematuria can be detailed and subdivided according to exercise duration–related mechanisms and exercise intensity–related mechanisms.

Duration-Related Mechanisms of Exercise-Induced Hematuria

The so-called “foot-strike hemolysis” can be observed on long-distance runners. From a pathogenetic point of view, it has been supposed that the cause of anemia could be related to trauma to the red blood cells circulating through the sole of the runners’ foot. If the hemolysis is slight, no hemoglobin is lost in the urine, as plasma haptoglobin–free hemoglobin complexes are absorbed by hepatocytes. Significant hemolysis, however, can overload available haptoglobin-binding sites and the excess hemoglobin is lost through the urine. In support of this finding is the observation that hemolysis is greater in sports involving more foot trauma such as running or ultramarathon running in soft-soled shoes, while it is lower in sports like swimming or in the use of hard-soled shoes. In “foot-strike hemolysis,” the reddish discoloration of urine is not related to the presence of whole blood or red blood cells but only to hemoglobin.

Another hemolytic mechanism is associated with bladder and kidney trauma. Indeed, it has been observed that all sports causing internal trauma to renal organs such as a football or boxing match can cause renal vascular lesions, thus resulting in hematuria.

As far as bladder hematuria is concerned, Blacklock was one of the first who described cystoscopic alterations of eight marathon runners in whom no upper tract lesion was identified. Within 48 hours of the completion of the run, localized contusions with loss of urothelium and fibrinous exudate were found at characteristics sites within the bladder. The interureteral bar was involved with its extension laterally overlying the intramural ureter on each side. The posterior rim of the internal meatus showed similar changes. The counterpart of these contusions was noted on the lower posterior bladder wall, and in most instances, there was a mirror image of the lesions of the trigone. The lower posterior wall lesions were usually bilateral, suggesting contact on each side between these areas and the most prominent parts of the interureteral ridge. Resolution of the lesions was rapid, and mild hyperemia was the sole residual appearance 1 week after the event. By observing such bladder lesions, it can be supposed that the bladder injury physiology is associated with the repeated impact of the flaccid posterior vesical wall against its base, which is a thicker, fixed, and more rigid structure, because it comprises the trigone. While each impact in itself probably is minor and relatively insignificant, repetition during a long distance run can cause morphological lesions, which can be evident on a cystoscopic examination. The suggestion of this mode of injury presumes that the bladder either is empty or also emptys at the time to permit apposition of the surfaces. Therefore, the appearance of urine within the bladder would act as a hydrostatic cushion, preventing the apposition of the posterior bladder wall and trigone.

It is believed that dehydration can also provoke hemolysis. Some investigators have associated athletes’ hydration with postexercise hematuria and proteinuria. It has been stated that transient dehydration occurring during sustained exercise could aggravate further the already depressed renal system. During prolonged strenuous exercise, large quantities of water can be lost through sweat. We carried out a study on some marathon runners who took part in a running event of 5000 meters, and we observed a decrease in the body weight of about 3,5 kg. Moreover, increased blood viscosity and increased intraerythrocytic osmolarity, as well as blood plasma osmolarity and acute postexercise acidosis, may accelerate hemolysis of red blood cells.

Hematuria can also be induced by (1) increased body temperature through the destruction of erythrocytes, (2) hemolysis due to increased production of free radicals, following strenuous exercise, (3) liberation of hemolyzing factors (lysolecithin), and (4) excessive release of catecholamines.

Intensity-Related Mechanisms of Exercise-Induced Hematuria

During intense exercise, it has been observed that renal blood flow may drop from a normal 1000 mL/min at rest to 200 mL/min during exercise. This decrease occurs because blood is shunted to the working muscles with a concomitant release
of epinephrine and norepinephrine. Such hormones mediate the renal vasoconstriction of the afferent and efferent glomerular arterioles. A decrease in renal blood flow will cause the glomerular filtration rate (GFR) and renal filtration fraction (RFF) to increase, and it will result in increased glomerular permeability, thus allowing the passage of red blood cells into the urine.29

Another mechanism responsible for postexercise hematuria is related to decreased blood supply to the renal vascular system. In fact, according to Baker,30 strenuous physical exercise causes a decrease in the blood supply to spiral arteriole vessels, thus resulting in ischemia. These spiral vessels connect the interlobular arteries to the capillary bed surrounding the minor calyx. The increased renal vascular resistance as a result of their spiral structure and the drop in plasma flow will decrease the oxygen supply and increase the fragility of these vessels. When the renal blood supply returns to normal, these vessels may shed red blood cells directly into the minor calyces for excretion and eventually into the urine.

Besides hypoxia, during strenuous exercise, especially under anaerobic conditions, increased concentration of lactic acid can be observed. Such acidosis induces the passage of erythrocytes into the urine, through increased glomerular permeability.

Another cause of macrohematuria can be observed through myoglobinuria. Postexercise myoglobinuria occurs with the appearance of myoglobin in the urine within 24 to 48 hours. As muscle membranes are ruptured, due to extreme physical exercise, increased serum myoglobin concentration occurs. Because myoglobin has a low molecular weight, it is easily filtered through glomeruli and can be eventually found in the urine.31

We have been studying urinary changes in two basketball teams (14 players) following competitive race. The urine collected at the end of the race showed increased number of red blood cells in the urine sediment in 41.6% of players (5 athletes). Such erythrocytes underwent analysis with contrast phase microscope and were found to be dysmorphic in one athlete only, thus confirming the presence of lower tract hematuria. Further controls (after 24, 48, and 72 hours) showed a progressive red blood decrease in the urine until the 72nd hour, when the urinary sediment returned to normal.

Because in the majority of the reports reviewed most of the subjects studied were men, it had been supposed that exercise-induced hematuria could affect men only. Jones et al., on the contrary, noted hematuria in 10.7% to 12% of the women undergoing intensive physical activity 3 to 4 hours per day, 4 to 5 times per week.32 A similar observation, carried out on 383 runners (men and women) after a marathon, found hematuria (17%) and proteinuria (30%). The abnormalities were not related to sex.

Cytokines and Sports

The release of inflammation molecules and cellular activation has been shown during physical exercise. Moreover, increased production of cytokines, chemokines, and arachidonic acid metabolites were observed.33,34 Despite these biochemical alterations, there was no clinical evidence of inflammation after physical exercise. We studied lipoxins (LX), molecules with potent anti-inflammatory activity excretion.35 In particular, we demonstrated an increased urinary excretion of lipoxin metabolites (LXA4) in nine healthy volunteers after strenuous exercise. That increased excretion, due to higher lipoxin synthesis, may represent a safeguard mechanism that keeps the inflammatory reaction triggered by physical stress under control.

Physician Advice and Management

Exercise is known to reduce anxiety and depression, but this beneficial effect can be rapidly reversed when the athlete discovers blood in the urine after exercise. In fact, in most cases, recognition of this condition induces physicians to carry out further tests and, sometimes, invasive and expensive procedures.

Considering the well-known implications of hematuria and proteinuria as indicators of urological and nephrological diseases, it is important not to evaluate them in case of evident sports hematuria. Therefore, according to the literature, a 6-step approach is suggested: (1) evaluate the urine abnormality by repeating urinalysis; (2) reevaluate the patient after 48 to 72 hours of rest; (3) investigate whether there has been a history of trauma, pain, urgency, dysuria, passage of clots, or recent sore throat or viral infection; (4) determine
a history of previous renal parenchymal disease; (5) obtain blood samples for serum creatinine, blood urea nitrogen, and complete blood count; and (6) further evaluate only patients with persistent urinary abnormalities or a suspicious history. It is, eventually, necessary to carry out specific examinations, urography or cystoscopy, for recurrent hematuria or symptoms indicating a urinary tract disease.

It has been questioned whether a physician must inform the athlete or the athlete’s relatives when diagnosing sports hematuria, whether it is safe to continue training and participating in competitions. Some boxers were not allowed to fight until the urinary abnormalities had disappeared. On the contrary, other investigators stated that there is no reason to restrict activity because of microscopic hematuria. In fact, if such a prohibition had been applied, the entire American football team would have been benched, because no football player failed to have microscopic hematuria during one or more games of the season. Anyway, even though the red blood cell loss is replaced through increased erythropoiesis, it is important to recognize that some athletes may develop a macrocytic anemia. In such cases, load, speed, and duration of training sessions must be carefully watched and the athlete should not start his or her training without proper hydration. In fact, as stated earlier, inadequate hydration may also accelerate hemolysis due to osmotic factors and decrease blood renal flow.

The guidelines to be followed in case of subjects who have suffered a renal disease are different. In fact, in such conditions, there is no doubt that at least competitive athletes need a strict follow-up regarding renal function. Furthermore, athletes with impaired renal function should always be informed about the possible harmful effects of strenuous exercise on kidney function.

References