Abstract The kidneys play an important role in regulating acid-base and water-electrolyte balance disturbances induced by exercise. In sports medicine, research on renal function during exercise in healthy individuals and athletes is less common than other areas of study such as the respiratory, circulatory, and neuromuscular systems as well as metabolism, since renal function has no direct effect on athletic performance. In this study, we reviewed previous research results obtained in our laboratory and other studies as follows: 1) effects of exercise intensity on renal plasma flow and glomerular filtration rate; 2) effects of exercise intensity on plasma hormone responses and urinary excretion of water and electrolytes; 3) effects of aging on renal function following exhaustive exercise; 4) mechanisms underlying exercise-induced diuresis in healthy volunteers; 5) mechanisms underlying exercise-induced proteinuria (EIP) in healthy volunteers; and 6) effects of exercise combined with angiotensin-converting enzyme (ACE) inhibitor (ACE-I) on the progression of diabetic nephropathy (DN) in obese diabetic model rats. The number of obese diabetes patients is increasing in advanced countries, and the number of hemodialysis (HD) patients per capita in Japan is the highest worldwide. Approximately 42% of patients with DN undergo HD treatment every year. However, regular exercise has not been positively recommended for patients with nephropathy despite being an essential clinical approach for patients with diabetes. Moreover, the ideal exercise regimen for patients with diabetes complicated by nephropathy has not been investigated much. Therefore, a future study should investigate exercise therapy for patients with DN.

Keywords: renal function, exercise intensity, exercise-induced diuresis, proteinuria, diabetic nephropathy

Introduction

The kidneys play an important role in maintaining physiological factors within the body such as pH, osmotic pressure, and electrolyte balance by excreting metabolic waste and noxious products, as well as excreting and reabsorbing water and electrolytes including Na⁺, K⁺, and Cl-. These functions are performed by excretion and reabsorption in the renal tubules and quantified as renal plasma flow (RPF) and glomerular filtration rate (GFR). Even if the amounts of excretable noxious products were to increase with an increase in metabolic rate, the RPF would be reduced during exercise. Therefore, physical exercise has a negative effect on the kidneys in terms of maintaining renal function. However, in sports medicine, research on renal function in athletes has been given less importance compared to other areas of study such as the respiratory, circulatory, and neuromuscular systems, as well as glucose and fat metabolism, since it has no direct influence on the performance of exercise. However, exercise is also used in physical therapy for the treatment of obesity, diabetes mellitus, and minor hypertension. In patients with minor nephritis in whom exercise is not restricted, knowledge of the correlation between exercise and renal function is essential. Although microalbuminuria (MAU) is used as a useful index for the early detection and diagnosis of diabetic nephropathy (DN), physical activity increases the excretion of MAU into the urine, and the evaluation of MAU of patients with diabetes is invaluable[2].

On the other hand, renal function is important in the maintenance of fluid-electrolyte balance even in healthy persons and athletes during exercise in warm conditions or in water. The purposes of this study are to review the previous literature, present some of our observations on renal function, and discuss the mechanisms underlying the changes in renal function and the roles of the kidneys during and/or after exercise.

Effects of exercise intensity on RPF and GFR

As the muscular oxygen requirement increases during exercise, the distribution of blood changes and blood flow is reduced to the internal organs, including the kidneys.
RPF and GFR decrease in response to increases in exercise intensity. However, the correlation between exercise intensity and GFR must differ to some extent from that of exercise intensity and RPF. Suzuki\(^5\) reported that RPF decreased from 35% of VO\(_{2\text{max}}\), whereas sodium thiosulfate clearance (C\(_{\text{Na}}\)), as one of the indicators of GFR, started to decrease at a VO\(_{2\text{max}}\) of 49%. According to the author\(^7\), creatinine clearance (C\(_{\text{cr}}\)), as an indicator of GFR, showed no immediate change after exercise within a VO\(_{2\text{max}}\) of 42.5-60.5%, although C\(_{\text{cr}}\) decreased to 47% and 45% immediately after a VO\(_{2\text{max}}\) of 83% and 100%, respectively. Poortmans\(^5\) also reported the absence of a change in GFR at low to medium exercise. However, studies\(^3-5\) have suggested that RPF and GFR during exercise were not affected by modifications in exercise duration.

With regard to the recovery processes of RPF and GFR following exercise, studies\(^3-5\) have revealed that low-intensity exercise induced a smaller decrease in and more rapid recovery of RPF following exercise. However, using radionuclide angiography, we\(^6\) confirmed that RPF decreased to 46.6% of the pre-exercise level immediately after, to 82.5% 30 min after, and to 78.9% 60 min after exhaustive bicycle ergometer exercise. Moreover, the notable finding was no significant change in C\(_{\text{cr}}\) immediately after moderate intensity (60.5% VO\(_{2\text{max}}\)), but a significant increase in C\(_{\text{cr}}\) after low-intensity exercise (42.5% VO\(_{2\text{max}}\)) until 120 min into the recovery period.

With regard to alterations of RPF and GFR, previous observations\(^5,7,8\) suggest that enhanced renal sympathetic nerve activity and an increase in catecholamine secretion induces modifications in RPF and GFR during the exercise and recovery periods. However, the role of the renin-angiotensin system (RAS) has not been confirmed with regard to the decrease in RPF in response to exercise\(^7-9\).

Based on these previous studies\(^1-5\), it should be recommended that daily physical activity within the intensity range of 35-40% of VO\(_{2\text{max}}\) is permissible for patients with mild nephritis because RPF and GFR are not decreased during exercise within this intensity range.

### Effects of exercise intensity on plasma hormone response and urinary excretion of water and electrolytes

Excretion of water and electrolytes into the urine following exercise is affected by an individual’s state of hydration\(^5\) as well as exercise intensity and duration. In this study, we discuss the effects of exercise intensity.

Plasma catecholamine\(^5,10\), angiotensin II (pAng II) and aldosterone (pALD) concentrations increase according to exercise intensity, and significant increases are shown at VO\(_{2\text{max}}\) values > 60.5%. Serum electrolyte concentrations including Na\(^+\), K\(^+\), and Cl\(^-\) also show significant increases only immediately after exercise with a VO\(_{2\text{max}}\) > 60.5%.\(^5\)

Urine volume (UV) and the urinary excretion of electrolytes are affected by changes in RPF, GFR, and plasma hormones related to the regulation of water-electrolyte balances, which are disturbed by increases in exercise intensity. UV decreases immediately after higher intensity (80-100% VO\(_{2\text{max}}\)) exercise as well as decreases in RPF and GFR. Freund, et al.\(^11\) reported that changes in urine flow paralleled changes in GFR (r = 0.91, p < 0.001) following exercise at 25, 40, 60, and 80% VO\(_{2\text{max}}\). On the other hand, obvious effects of exercise intensity on the urinary excretion of solutes including electrolytes (Na\(^+\), K\(^+\), Cl\(^-\), and PO\(_4^2-\) ), urea nitrogen (uUN), lactic acid (uLA\(^-\)), and urine osmolality (U\(_{\text{osm}}\)) are mostly observed 30 min after exercise. Moreover, urinary excretions of UN, Cl\(^-\), Na\(^+\), and U\(_{\text{osm}}\) significantly decreased from low intensity to the highest intensity exercise, and the degrees of these decreases depended on exercise intensity\(^9\). Although a change in the urine concentration of Na\(^+\) was largely accompanied by a change in the Cl\(^-\) concentration (r = 0.756, p < 0.001) throughout exercise with submaximal intensity (80% VO\(_{2\text{max}}\)), a remarkable dissociation between changes in the Na\(^+\) and Cl\(^-\) concentrations in the urine was observed 30 min after exhaustive exercise. The reduction in urine Cl\(^-\) concentration was 3.6-fold compared to that of the Na\(^+\) concentration in urine observed 30 min after exhaustive exercise (100% VO\(_{2\text{max}}\))\(^12\). At 30 min after exhaustive exercise, there were significant negative correlations between urinary Cl\(^-\) (uCl\(^-\)) and urinary PO\(_4^2-\) concentration (r = -0.549, p < 0.001) as well as and uCl\(^-\) and uLA\(^-\) (r = -0.722, p < 0.001). That is, the significant increases in LA\(^-\) and PO\(_4^2-\) in the urine were accompanied by a marked reduction in Cl\(^-\) concentration in the urine 30 min after exhaustive exercise. The increase in uLA\(^-\) concentration was due to the increase in blood LA\(^-\) concentration, and it started to increase once blood lactate (bLA\(^-\)) concentration exceeded 60 mg/dL (6.7 mM/L)\(^12\). Overproduction of LA\(^-\) in the exercising muscle cell induced by severe exercise led to a pH reduction in the blood, which induced a lower HPO\(_4^2-\) to H\(_2\)PO\(_4^-\) concentration ratio (HPO\(_4^2-\)/H\(_2\)PO\(_4^-\)) in the blood. We\(^12\) postulated that H\(_2\)PO\(_4^-\) and LA\(^-\) were excreted simultaneously into the renal tubules and resulted in a large concentration of anions in the tubular fluid, and that the ion balance in the tubular fluid might be maintained to enhance reabsorption of Cl\(^-\) in the tubule cells\(^12\). Later, we will discuss the correlations between enhanced reabsorption of Cl\(^-\) and the remarkable excretions of albumin and low-molecular-weight proteins into the urine after exhaustive exercise.

Meanwhile, no significant relationships between the urinary excretion of water and electrolytes and the plasma responses of hormones related to water-electrolyte balance regulation were observed throughout the exercise of low to high intensity exercise\(^9\). However, a significant positive correlation (r = 0.693, p < 0.001) between plasma aldosterone and urinary K\(^+\) concentrations and a significant negative correlation (r = -0.563, p < 0.001) between pALD and urinary Na\(^+\) concentration were indicated throughout the moderate intensity exercise in a hot environment (32.9 ± 1.1°C)\(^13\). The renin–angiotensin–aldosterone-
rone (RAA) system became activated and the antidiuretic hormone (ADH) concentration increased remarkably in response to heat exposure (temperature 70-75°C, relative humidity 10-20%), and obvious correlations were observed between the urinary excretion of water and electrolytes and the responses of hormones related to the regulation of water-electrolyte balance[14]. However, the role of these hormones including pAng II, pALD, and ADH, which increased after exercise at greater than submaximal intensity (> 80% VO2max), is unclear[4].

Effects of aging on renal function after exhaustive exercise

All body functions in healthy individuals decline linearly starting at 30 years of age[15]. Poortmans et al.[16] reported that the linear estimate of renal function loss averages 0.41% per year on the basis of a literature review of studies including 54,272 healthy, nonsmoking human participants of both genders. These studies[15,16] also suggested that the older an individual, the greater the renal function impairment after exercise. Therefore, we[17] examined the effects of aging on changes in renal function after exhaustive exercise in 162 healthy males 8-80 years of age. Voluntary exhaustive exercise[18] was performed using a treadmill. Blood and urine samples were taken before, immediately after, and at 30 and 60 min after exercise. Urinary excretions of albumin (UAlb), lactic acid (ULA), electrolytes (Na+, Cl-, etc.), and Ccr were determined. Fig. 1 shows changes in Ccr (upper panel) and UAlb (lower panel) in different age clusters.

The mean resting Ccr in teenagers was significantly lower than that in adults 20-30 years of age, while the average resting Ccr of participants > 45 years of age tended to decrease with age. The younger the subjects, the greater the reduction of Ccr immediately after exercise, and participants > 55 years old showed a smaller but significant reduction. The greater the reduction of Ccr, the higher the VO2max, HRmax, systolic blood pressure (SBP), and bLA concentration immediately after exhaustive exercise.

Thirty minutes after exercise, UAb remarkably increased in every age cluster. The resting UAb value was subtracted from the UAb at 30 min after exercise and defined as ♦UAb rec30 min. The value of ♦UAb rec30 min was converted to a logarithm that is shown in the lower panel in Fig. 1. ♦UAb rec30 min was significantly lower at a mean age of 12.9 (<15) years than mean age of 17.4 (16-19) years. The peak ♦UAb rec30 min was at 16-19 years of age and gradually decreased with age. A highly positive correlation (r = 0.819, p < 0.001) was found between UAb rec30 min and uLA at 30 min after exercise. On the other hand, a significant negative coefficient of correlation (r = -0.722, p < 0.001) was shown between uCl and uLA concentrations. This study[17] suggested that the organic acids (lactic acid [LA] and pyruvic acid [PA]), produced by exhaustive exercise, might alter renal glomerular permeability and/or inhibit the reabsorption of albumin at the proximal tubules. We will describe the mechanisms underlying exercise-induced proteinuria (EIP) later.

The effects of exercise on the kidneys may lessen with age due to a decreased capacity of energy production during exercise. In this regard, our hypothesis may agree with that of Poortmans et al.[16], namely that the exercise impact on some renal functions is related to the absolute load imposed on the individuals.

Mechanisms underlying exercise-induced diuresis in healthy volunteers

The response of UV to exercise occurs as responses in RPF and/or GFR[3,4,11], because UV is affected by renal function including RPF, GFR, and the reabsorption of water and other solutes in the renal tubules. However, UV increased 2-3-fold from pre-sprint levels as observed 15-
30 min after 200-400 m sprints, although it transiently decreased immediately after the sprints. This phenomenon is termed “exercise-induced diuresis (EID)” or “post-exercise diuresis.” However, the mechanisms underlying EID remain unclear.

This study was performed to examine the mechanisms underlying EID caused by a 400 m sprint. The participants were seven healthy male volunteers with no history of cardiovascular disease (age, 22.6 ± 0.6 [± SE] years; weight, 66.5 ± 3.1 kg; height, 173.8 ± 2.2 cm). Each participant performed a 400 m sprint on a running track twice at 60-min intervals. The UV, Ccr, uLA, uPA, and other blood and urinary solutes as well as plasma antidiuretic hormone (pADH), pALD, adrenaline (pAd), and noradrenaline (pNorad) were measured before and after each sprint. Fig. 2 shows the responses of UV, Uosm, Ccr, and negative free water clearance (TcH2O) to the sprints and standing sessions.

A 2.2-3.6 fold increase in UV over the respective pre-sprint level was observed after the first and second sprints. The change in the Uosm showed a mirror-image pattern to the UV change throughout the experiments. There was a negative linear relationship (r = -0.634, p < 0.001) between changes in UV and Uosm. Moreover, the TcH2O change occurred in a pattern very similar to that of UV after the first and second sprints. There was also a highly positive correlation coefficient (r = 0.899, p < 0.001) between the UV and TcH2O changes throughout the experiment. However, the change in Ccr differed from those in UV, Uosm, and TcH2O. Fig. 3 shows the responses of urinary electrolytes and organic acids (uLA + uPA) to the sprint and standing sessions. The urinary Na⁺ (uNa⁺) and uK⁺ concentrations slightly decreased after the first and second sprints. However, the uCl⁻ concentration decreased remarkably from 15 min to 45 min after both the first and second sprints, and gradually increased thereafter. In contrast, the uLA⁻ and uPA⁻ concentrations increased remarkably after both sprints, and there was a mirror-image pattern seen between uCl⁻ and (uLA⁻ + uPA⁻) changes throughout the experiment. A higher negative correlation coefficient (r = -0.852, p < 0.001) was seen among the uCl⁻ and (uLA⁻ + uPA⁻) changes. The large amounts of LA⁻ and PA⁻ produced by the sprints were thought to be filtered by the glomeruli and delivered into the renal tubules. Reabsorption of the excess organic acids was inhibited at the renal tubules, and instead of anions such as LA⁻ and PA⁻, Cl⁻ were excessively reabsorbed in the renal tubules to maintain the ion balance therein. Inhibition of Cl⁻ excretion may compete with organic acid excretion into the urine.

After both sprints, urinary excretion of all of the solutes decreased, except for the organic acids (uLA⁻ and uPA⁻). Among these solutes, the urinary urea nitrogen (uUN) concentration mostly decreased. The reduction in uUN
accounted for 89.6-92.6% of the decreased U_{osm} after the first and second sprints. On the other hand, there were no correlative changes between the pADH and UV or pADH and U_{osm}, although there was a higher negative correlation coefficient (r = -0.699, p < 0.01) between the ratio of U_{osm} to serum osmolality (S_{osm}) (U_{osm}/S_{osm}) and changes in UV throughout the experiments. The notable and contradictory finding of a very similar pattern of change between T_{cH2O} and UV (r = 0.899, p < 0.001) after the first and second sprints was observed in this study (Fig. 2). T_{cH2O} is an indicator of water reabsorption in the renal tubules22,23). Increased T_{cH2O}, which is a decrease in free water clearance (C_{H2O}), would result in decreased UV. However, as shown in Fig. 2, the increase in UV was accompanied by an increase in T_{cH2O} after the first and second sprints. The T_{cH2O} equation was transformed to the following equation22,23): T_{cH2O} = UV × (U_{osm}/S_{osm} - 1). In this study, the correlation coefficients between T_{cH2O} and UV and between UV and (U_{osm}/S_{osm} - 1) were 0.899 and -0.771 (p < 0.001 both), respectively. Consequently, the contradictory finding of increased UV, despite the increase in T_{cH2O} after the sprints, can be explained by the above equation. The value of (U_{osm}/S_{osm} - 1) decreased because of a decrease in U_{osm} and an increase in S_{osm} after the sprints. Considering the above mentioned findings, the decreased U_{osm} and increased UV observed after the first and second sprints were believed to be due to the impaired concentrating ability of the renal medullary tubules and collecting ducts caused by supramaximal exercises.

The mediolateral blood flow (MBF), the rate of which can be regulated independently of whole-kidney blood flow, may also affect the renal capacity to both concentrate and dilute urine because preservation of the medullary hypertonicity in the interstitium is dependent on the countercurrent exchange mechanism in the vasa recta24). Approximately 90% of the blood flow delivered to the kidneys remains in the renal cortex to perfuse the peritubular capillary bed, whereas only 5-10% of the total renal blood flow reaches the renal medulla via vessels arising from the post-glomerular vasculature of the inner cortical or juxtamedullary nephrons25). The effect of Ang II on the MBF is of particular interest because, despite its vasoconstrictor effect, it may elicit paradoxical medullary vasodilatation effects in normotensive animals25,26). MBF increases in response to potent vasoconstrictors such as Ang II25, vasopressin (ADH), or endothelin, whereas cortical blood flow (CBF) decreases25,27). Ang II stimulates the medullary production of vasodilators such as prostaglandins (PGs), nitric oxide (NO), and reactive oxygen species (ROS)25-27); consequently, the interaction of Ang II with these substrates plays an important role in MBF control. Increased MBF may decrease the medullary in-

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**Fig. 3** Responses of urinary concentrations of electrolytes (uCl⁻, uNa⁺, uK⁺) and organic acids (uLA⁻ + uPA⁻) to the first and second 400 m sprints21)

Note: 1ˢᵗ-sprint, first 400 m sprint; 2ⁿᵈ-sprint, second 400 m sprint; sprint, 1ˢᵗ-400 m and 2ⁿᵈ-400 m sprint experiments; standing, 1ˢᵗ and 2ⁿᵈ standing experiments; uCl⁻, urinary chloride; uNa⁺, urinary sodium; uK⁺, urinary potassium; uLA⁻, urinary lactic acid; uPA⁻, urinary pyruvic acid; uLA⁻ + uPA⁻, the sum of uLA⁻ and uPA⁻. The data are expressed as the mean ± standard error (±SE). *p < 0.05, **p < 0.01, and ***p < 0.001, compared with the pre-1ˢᵗ-sprint level; ##p<0.01 and ###, p<0.001 compared with the pre-2ⁿᵈ-sprint level; †p<0.05, ††p<0.01, and †††, p<0.001, compared with the values at the corresponding times in the sprint experiments.
terstitial osmotic gradient, causing changes in the osmotic forces. In this study, levels of vasoconstrictors such as pADH and pNorad were measured, whereas the plasma vasoconstrictor Ang II and vasodilator factors such as PGs, NO, and ROS were not. However, many studies have reported that plasma vasoconstrictors such as the components of the RAS, ADH, and catecholamines increase in response to increased exercise intensity. Maeda et al. reported that acute exercise enhanced renal tissue RAS, but they did not measure RAS in the tissues of the renal cortical and medullary sites separately. Furthermore, Klein et al. reported that the administration of high doses of Ang II or Norad to male Sprague-Dawley rats increased UV and decreased Uosm, urea transporter (UT)-A1, and water channel protein aquaporin-2 (AQP2) in the inner medullary region of rats. UT-A1 is a major protein responsible for reabsorbing urea and NaCl and contributing to the generation of a hypertonic renal medulla, while AQP2 is a major protein regulating water permeability in the collecting duct. Matsumura et al. indicated that the chloride channel-K1 (CIC-K1) plays a role in urine concentration and that the countercurrent system in the inner medulla is involved in the generation and maintenance of a hypertonic medullary interstitium. The same study reported that a specific Cl channel blocker decreased Cl permeability in the thin ascending limb (TAL). The findings of Matsumura et al. and Uchida et al. suggest that the remarkable decrease in Cl concentration in the tubular fluid of the TAL contributed to lower medullary hypertonicity in the interstitium, and resulted in the observed decrease in Uosm 15 and 30 min after the sprints.

The present study’s findings indicated that EID might result from reduced urine concentrating ability, which could be due to washout of the renal medullary interstitial osmotic gradient caused by the increased renal MBF (itself mediated by increased levels of vasodilators released in response to the increased levels of vasoconstrictors) and the remarkable decrease in uCl− concentration after supramaximal 400 m sprints.

**Mechanisms underlying EIP in healthy volunteers**

EIP is related to exercise intensity. The maximal rate of protein excretion usually occurs during the first 20-30 min after the cessation of exercise with levels over 70-80% of maximal oxygen intake (VO2max). EIP involves large to medium molecular weight proteins such as immunoglobulin A, immunoglobulin G, albumin (Alb), total protein (TP), and lower molecular weight proteins (LMWP) such as α1-microglobulin (α1-M) and β2-microglobulin (β2-M). EIP is a mixed glomerular-tubular type due to an increased glomerular permeability and a partial tubular-reabsorption inhibition of LMWP when heavy exercise is performed. It has long been recognized that a reduction of RPF is induced by activation of renal sympathetic nerve and the RAS during exercise, which induces vasoconstriction of the renal arteriololes. The exercise-induced RPF reduction produces a concomitant effect on the GFR. Moreover, the filtration fraction (FF; GFR/RPF) increases because the GFR decreases relatively less than the RPF during exercise. The increased FF probably enhances the diffusion process of macromolecules into the tubular lumen. Previous studies suggest that exercise decreases the glomerular electrostatic barrier and, thereby, could partly explain the enhanced transglomerular passage of macromolecules. On the other hand, the intravenous infusion of Norad or Ang II reportedly produced proteinuria, while the oral administration of ACE-I reduced proteinuria in patients with nephropathy. According to these studies, exercise-induced modifications of renal hemodynamics and the FF as well as activation of the renal sympathetic nerve and the RAS are thought to directly or indirectly increase permeability of the glomerular capillary membrane to proteins. However, the causes of increased LMWP, such as α1-M and β2-M, concomitantly observed following exhaustive exercise, may not be sufficiently explained only by advanced permeability of the glomerular capillary membrane to proteins including high to medium molecular weight proteins.

Therefore, we tried to confirm that exhaustive exercise produces no increase in urinary excretion of glomerular type protein, such as Alb, in a state of inhibited increase in pAng II after oral ingestion of ACE-I. We simultaneously observed whether the urinary excretion of tubular-type proteins such as α1-M and β2-M increases after exhaustive exercise.

According to the previous study by Kodama et al., we used captopril (Capt) as an ACE-I. Ten healthy male volunteers with no history of any diseases who were 21.6 ± 1.0 (± SD) years of age, weighed 69.7 ± 3.5 kg, and were 175.3 ± 1.7 cm tall participated in this study. The participants provided informed consent in accordance with the Declaration of Helsinki under careful supervision, including a medical history interview prior to testing and the monitoring of electrocardiography and blood pressure throughout the experiment. The subjects were orally administered Capt 50 mg (Sankyo, Tokyo, Japan) in a fasting state the morning after an overnight fast. Thirty minutes later, a maximal voluntary exercise test for 10-12 min was performed using a treadmill. Plasma renin activity (PRA), pAng II, pAd, pNorad, and bLA− concentrations, and urinary excretions of glomerular type proteins such as uAlb and uTP, and tubular-type proteins such as α1-M and β2-M were observed throughout the experiment.

Fig. 4 shows the responses of plasma hormones (pAd, pNorad, Ang II, PRA), Ccr, and urinary proteins (Total protein, uTP; uAlb, β2-M) to exhaustive exercise with administration of Capt and without Capt administration. There were no differences in responses of pAd and pNorad following exhaustive exercise between Capt administration (Capt treatment) and control experiment (without...
Capt administration).

However, PRA gradually and significantly increased up to 30 min after the oral administration of Capt and slightly decreased thereafter, while pAng II also significantly increased immediately after exhaustive exercise. However, an increased level of pAng II in the Capt treatment was approximately 45% of that in the control, and this level was comparable with that observed after 60.5% \( \dot{V}O_{2\text{max}} \) intensity exercise\(^7\). There were no significant differences in changes of Ccr and urinary excretion of proteins (U_Tp, U_Alb, U_{\beta2M}) between the Capt treatment and control groups; that is, despite the increase in pAng II being inhibited after oral administration of Capt, a remarkable excretion of mixed glomerular-tubular type proteins was observed in the urine 30 min after exhaustive exercise. Therefore, this study’s findings\(^7\) suggest that Ang II does not play an important enough role to induce proteinuria after exhaustive exercise in healthy subjects, since the level of urinary excretion of proteins after exhaustive exercise at a lowered concentration of pAng II caused by

![Fig. 4 Changes in plasma hormone concentrations (pAd, pNorad, pAngII, PRA), urinary excretion of proteins (U_Tp, U_Alb, U_{\beta2M}) and Ccr following exhaustive exercise with and without the administration of Capt.](image)

Note: B, before exhaustive exercise; A, directly after exhaustive exercise; pAd, plasma adrenaline; pNorad, plasma noradrenaline; pAng II, plasma angiotensin II; plasma renin activity (PRA); U_Tp, urinary excretion of total protein; U_Alb, urinary excretion of albumin; U_{\beta2M}, urinary excretion of \( \beta_{2} \)-microglobulin; Ccr, creatinine clearance.

The data are expressed as the mean ± standard error (±SE). *p < 0.05, **p < 0.01, and ***p < 0.001, compared with the resting level; #p<0.05, ###p<0.001, compared with the values at the corresponding times in the Cont-experiment.
oral administration of Capt was the same as that at higher pAng II concentration without Capt treatment.

On the other hand, we12 observed two groups, one of which showed remarkable excretion of urinary proteins, while the other produced less excretion, although pAng II, pAd, and pNorad concentrations increased to the same levels in both groups after exhaustive exercise. Among the 69 healthy male volunteers who performed the exhaustive exercise12), we selected two groups of 20 subjects, one of which showed the highest excretion of uAlb (L-uAlb, n=20). Subsequently, to estimate the mechanisms underlying EIP, we compared the levels of uAlb (L-uAlb, n=20). Subsequently, to estimate the mechanisms underlying EIP, we compared the levels of uAlb, pAng II, pAd and pNorad concentrations, C\textsubscript{\text{cr}}, uAlb, α\textsubscript{1}-M, β\textsubscript{2}-M, electrolytes (Na\textsuperscript{+}, K\textsuperscript{+}, Cl\textsuperscript{−}, PO\textsubscript{4}\textsuperscript{2-} ) and uLa\textsuperscript{−} after exhaustive exercise in both groups. As shown in Table 1, the H-uAlb group showed significantly higher increases in the urinary excretion of proteins including α\textsubscript{1}-M, β\textsubscript{2}-M, uAlb, and uTP following exhaustive exercise than those in the L-uAlb group. It should be noted that the uAlb in the H-uAlb group increased about 10-fold compared to that of the L-uAlb group from 30 to 60 min after exercise, although there was no significant difference in the changes of UV and C\textsubscript{cr} following exercise between the H-uAlb and L-uAlb groups. However, as shown in Table 2, there were no differences in increases in pAd, pNorad, and pAng II concentrations immediately after exercise between these groups, although the H-uAlb group showed significant higher bLa\textsuperscript{−} concentration immediately and 30 min after exercise than the L-uAlb group.

Remarkable differences in the previously mentioned variables observed between the H-uAlb and L-uAlb groups were urinary Cl\textsuperscript{−} and uLa\textsuperscript{−} concentrations at 30 min after exercise and bLa\textsuperscript{−} concentration measured im-

### Table 1. Responses of UV and urinary excretion of proteins (α\textsubscript{1}-M, β\textsubscript{2}-M, Alb and TP) in the H-UAlb and L-UAlb groups to exhaustive exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>pre-ex</th>
<th>post-ex</th>
<th>rec 30 min</th>
<th>rec 60 min</th>
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</thead>
<tbody>
<tr>
<td>UV ml/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>0.75 ± 0.48</td>
<td>0.55 ± 0.34***</td>
<td>0.86 ± 0.53</td>
<td>0.46 ± 0.16**</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>0.62 ± 0.28</td>
<td>0.49 ± 0.18*</td>
<td>0.75 ± 0.38</td>
<td>0.56 ± 0.24</td>
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<tr>
<td>α\textsubscript{1}-M µg/min</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>H-UAlb (n=20)</td>
<td>4.0 ± 3.6</td>
<td>(0.6 ± 16.4)</td>
<td>14.6</td>
<td>19.0 ± 25.9***</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>3.1 ± 2.2</td>
<td>(0.4 ± 17.5)</td>
<td>6.1</td>
<td>19.0 ± 14.0***</td>
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<tr>
<td>β\textsubscript{2}-M µg/min</td>
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<tr>
<td>H-UAlb (n=20)</td>
<td>0.12 ± 0.10</td>
<td>0.45 ± 0.89</td>
<td>9.71 ± 10.81***</td>
<td>0.79 ± 1.14***</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>0.07 ± 0.05</td>
<td>0.79 ± 1.52*</td>
<td>5.03 ± 6.50**</td>
<td>0.47 ± 0.99</td>
</tr>
<tr>
<td>UAlb µg/min</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>20.6 ± 21.4</td>
<td>148.9 ± 294.7</td>
<td>1208.6 ± 1111.9***</td>
<td>1254.2 ± 184.4</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>10.2 ± 10.3</td>
<td>96.3 ± 107.5**</td>
<td>125.6 ± 80.8***</td>
<td>16.3 ± 10.7</td>
</tr>
<tr>
<td>UTP µg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>79.7 ± 58.6</td>
<td>217.3 ± 404.9</td>
<td>1245.7 ± 531.7***</td>
<td>223.9 ± 229.2*</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>77.2 ± 50.9</td>
<td>200.6 ± 167.8**</td>
<td>341.8 ± 187.8***</td>
<td>96.2 ± 58.8*</td>
</tr>
</tbody>
</table>

UV, urine volume; α\textsubscript{1}-M, α\textsubscript{1}-microglobulin; β\textsubscript{2}-M, β\textsubscript{2}-microglobulin; UAlb, urinary albumin excretion; UTP, urinary total protein excretion. The data are expressed as the mean ± standard deviation (±SD). *<0.05, **p<0.01, ***p<0.001, compared to pre-exercise level, and difference between two groups.
immediately after exercise. The uCl⁻ in the H-uAlb group was reduced by 81.5% from resting level, although the L-uAlb group showed a reduction of only 57.4% at 30 min after exhaustive exercise. There was a significant difference (p < 0.001) in uCl⁻ measured at 30 min after exercise between groups. On the other hand, the uLA⁻ concentration measured at 30 min after exercise was significantly higher in the H-uAlb group than in the L-uAlb group.

There was a relationship between uLA⁻ and bLA⁻ changes as follows: uLA⁻ = 8.7e 0.046bLA⁻ (r = 0.926, p < 0.001).

Moreover, there was a significantly high correlation coefficient (r = 0.995, p < 0.001) between urinary cation (Na⁺ + K⁺) and anion (Cl⁻ + PO₄⁻ + LA⁻) concentrations. As shown in Fig. 5, higher coefficients of correlation were indicated between uAlb, uβ₂-M, and uLA⁻ concentrations. These variables were converted into logarithmic (log) values and are illustrated in Fig. 5.

According to the fact that oral administration of ACE-I inhibited an increase in uAlb in patients with nephropathy, it is possible that an increase in glomerular-type proteins such as albumin might be primarily caused by enhanced glomerular membrane permeability due to increased Ang II levels. However, EIP involves not only glomerular-type, but also tubular-type proteins such as α₁-M and β₂-M. The mechanisms underlying the elevated excretion of tubular-type proteins after exhaustive exercise could not be explained only by enhanced glomerular membrane permeability caused by increased Ang II. Moreover, there were two characteristic findings observed after exercise, one of which was remarkable excretion of mixed glomerular-tubular type proteins into the urine.

Table 2. Responses of blood lactate (bLA⁻), plasma adrenaline (pAd), noradrenaline (pNorad) and angiotensin II (pAngII) concentrations to exhaustive exercise in the H-UAlb and L-UAlb groups.

<table>
<thead>
<tr>
<th></th>
<th>pre-ex</th>
<th>post-ex</th>
<th>rec 30 min</th>
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</thead>
<tbody>
<tr>
<td><strong>bLA⁻ mg/dl</strong></td>
<td></td>
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</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>12.0 ± 4.9</td>
<td>105.3 ± 13.7***</td>
<td>59.3 ± 24.8***</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>10.2 ± 2.7</td>
<td>90.1 ± 19.3***</td>
<td>42.0 ± 18.3***</td>
</tr>
<tr>
<td><strong>pAd ng/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>0.015 ± 0.008</td>
<td>0.100 ± 0.088***</td>
<td>0.023 ± 0.015</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>0.027 ± 0.016</td>
<td>0.110 ± 0.121***</td>
<td>0.029 ± 0.024</td>
</tr>
<tr>
<td><strong>pNorad ng/ml</strong></td>
<td></td>
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<tr>
<td>H-UAlb (n=20)</td>
<td>0.132 ± 0.058</td>
<td>1.123 ± 0.983***</td>
<td>0.204 ± 0.118***</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>0.130 ± 0.044</td>
<td>0.978 ± 0.677***</td>
<td>0.205 ± 0.112***</td>
</tr>
<tr>
<td><strong>pAng II pg/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-UAlb (n=20)</td>
<td>16.9 ± 12.7</td>
<td>71.1 ± 35.5***</td>
<td>30.5 ± 24.9</td>
</tr>
<tr>
<td>L-UAlb (n=20)</td>
<td>17.8 ± 10.5</td>
<td>71.8 ± 39.7***</td>
<td>22.8 ± 12.0*</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± standard deviation (±SD): significance of differences compared to pre-exercise values and difference between two groups: * p<0.05, ** p<0.01, *** p<0.001.
despite the fact that the increase in pAng II concentration was significantly inhibited after exercise by oral administration of Capt prior to exercise. The other finding was that there were two groups, one of which showed remarkable excretion of uAlb (H-uAlb) and the other produced less excretion (L-uAlb), although pAng II concentration increased to the same level in both groups after exhaustive exercise.

According to these findings, it seems that elevated pAng II does not play an important enough role to produce a mixed type of proteinuria after exhaustive exercise in healthy subjects. Our previous studies\textsuperscript{12,37} suggested that an increase in bLA⁻ concentration and a remarkable excretion of LA⁻ into the urine produced by exhaustive exercise are involved in the appearance of postexercise proteinuria, which is a mixed glomerular-tubular type. Meanwhile, Poortmans et al.\textsuperscript{39} suggested that neither increased lactate ion nor decreased pH appears to be related to postexercise proteinuria based on the fact that Cantone et al.\textsuperscript{40} failed to observe any increase in protein excretion in a resting state during the infusion of a lactate solution leading to 15 mmol/L in the blood. On the other hand, Gardner\textsuperscript{41} reported that urinary protein excretion increased in acidosis by an infusion of 1% NH\textsubscript{4}Cl solution, and was inhibited in alkalosis.

It might be estimated that glomerular membrane permeability to proteins may be due to changes in charge selectivity in the glomerular basement membrane (GBM). Zambraski et al.\textsuperscript{42} suggested that exercise may decrease the glomerular capillary electrostatic barrier in rats, and thereby may be an important factor in EIP. It is estimated that the degree of metabolic acidosis due to more increased bLA⁻ after exhaustive exercise was significantly higher in the H-uAlb group, and resulted in more change in charge selectivity in the GBM in the H-uAlb than in the L-uAlb group. On the other hand, Poortmans et al.\textsuperscript{43} reported that the reabsorption of Alb and β₂-M at the proximal tubules was inhibited by lysine perfusion in humans. They\textsuperscript{43} concluded that post-exercise proteinuria is of mixed type after exhaustive short-term exercise, which increased glomerular permeability and partial tubular re-absorption inhibition of proteins.

Our previous studies\textsuperscript{12,37} suggested that the large amounts of LA⁻ and PA⁻ produced by heavy exercise were filtered at the glomerulus, entered the tubular lumen, and inhibited reabsorption of Alb and β₂-M at the proximal tubules. These may be the leading mechanisms underlying EIP in healthy volunteers, even though the precise mechanisms were not clarified.

Effects of exercise combined with ACE-I on the progression of diabetic nephropathy in obese-diabetic model rats

An essential clinical approach for obese diabetes patients is diet and exercise regimens. However, compared to the animals placed on food-restriction in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which is an animal model of obesity-induced diabetes, the use of an exercise regimen significantly increased the uAlb and kidney weight and enlarged the glomerular and mesangial areas\textsuperscript{44}, although improvements in glucose tolerance and lipid metabolism were seen in both the food-restriction and exercise regimen groups. The progression of nephropathy accompanied by an exercise regimen alone might be caused by increased blood pressure (BP) during exercise, because the exercise group showed a significantly higher BP than that in the diet regimen group throughout the treatment\textsuperscript{40}. However, some studies\textsuperscript{45,46} have shown that diet yields a smaller improvement in insulin resistance than exercise does, although diet alone is sufficient for decreasing lean body mass. Moreover, our previous study\textsuperscript{47} suggested that exercise intervention might be an essential option for the improvement of serum lipids since diet alone is not effective.

On the other hand, some studies\textsuperscript{48,49} suggest that the administration of the antihypertensive drug azelnidipine (Azel), a calcium channel blocker, is attractive not only for treating hypertension with accompanying diabetic complications, but also for preventing the development of DN. Therefore, we\textsuperscript{50} examined the effect of Azel alone or in combination with exercise on BP, kidney morphology, and urinary protein excretion in OLETF rats. Using 24 male OLETF rats and six normal control Long-Evans Tokushima Otsuka (LETO) rats, these treatments were performed from 21 to 30 weeks of age, an appropriate developmental stage for an exercise regimen for DN. OLETF rats were evenly divided into the following groups: sedentary (OLETF-Sed), Azel (OLETF-Azel), exercise (OLETF-Ex), and Azel plus exercise (OLETF-Azel & Ex). Azel (10 mg/kg/day) was administered in the chow; animals in the exercise groups exercised voluntarily every day on a rotator wheel (Shinano, Tokyo, Japan), and their running distances were recorded weekly. All groups were allowed access to tap water ad libitum. The effects of 10 weeks of exercise alone and in combination with Azel on BW, BP, glucose tolerance, serum lipid concentrations, kidney morphology, uAlb, and uTP were examined in this study\textsuperscript{50}. Exercise treatment alone decreased BW and improved dyslipidemia and glucose intolerance (GI), but did not decrease BP. Azel treatment alone prevented an increase in SBP in OLETF rats, but did not significantly reduce it. Kurashige et al.\textsuperscript{51} noted an approximately 80 mmHg decrease in SBP in stroke-prone SHR when Azel 10 mg/kg/day was administered by a technique called oral gavage from 20 to 31 weeks of age. In our study\textsuperscript{50}, Azel was added to the powdered rat chow. This difference in the method of Azel administration might be responsible for the lack of a significant decrease in BP by Azel treatment alone in this study\textsuperscript{50}. Azel treatment alone inhibited an increase in BW and decreased serum triglyceride concentration, but did not improve GI.
The combined treatment of Azel with exercise significantly decreased BW and BP and improved dyslipidemia and GI.

Fig. 6 shows that $U_{\text{Alb}}$ did not change in any of the OLETF groups from 10 to 23 weeks of age; rather, it significantly increased in the OLETF-Sed and OLETF-Ex groups from 23 to 29 weeks of age (higher in the OLETF-Sed group) and was significantly lower in both the OLETF-Azel and OLETF-Azel & Ex groups compared to the OLETF-Sed and OLETF-Ex groups from 26 to 29 weeks of age.

Azel, either alone or in combination with exercise, more effectively ameliorated indices of kidney damage, including mesangial area $A_M$, glomerular volume $V_G$, GBM thickness, and $U_{\text{Alb}}$ and $U_{\text{TP}}$ values.

In this study, exercise alone was not as effective at attenuating the indices of nephropathy as was the combination of exercise and Azel despite the fact that it significantly improved the lipid profile and glucose clearance. Exercise may also exhibit DN progression beyond the preventative effects produced by improvements in dyslipidemia and glucose metabolism in the exercise treatment alone as observed in this study. Thus, one DN progressive factor may be an elevation in BP during exercise since the urinary excretion of proteins in the OLETF-Ex group was progressively increased during the exercise regimen.

This study's findings demonstrate that the combined treatment of regular exercise with the antihypertensive drug Azel produced improvements in GI and dyslipidemia in the absence of the progression of DN.

In conclusion, further studies should investigate the ideal exercise therapy regimen for patients with DN since physical exercise has been restricted for these patients to date despite regular exercise being an essential clinical approach for obese patients with diabetes.

Conflict of Interests

The author declare that there is no conflict of interests regarding the publication of this article.

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