

Research paper**Physical training in patients on hemodialysis has a beneficial effect on the levels of eicosanoid hormone-like substances**

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ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the changes in the levels of vasoactive eicosanoid hormone-like substances PGE₂, PGI₂ and TXA₂ in hemodialysis (HD) patients who were following a long-term physical training program during the hemodialysis session. **DESIGN:** A total of 50 patients with Chronic Kidney Disease (CKD) (stage 5) on hemodialysis and 35 healthy individuals who served as controls (C) were evaluated. The 50 CKD patients were divided into two groups: the HD group consisted of 31 patients who received usual care without any physical activity during the hemodialysis sessions, while group HD/Exer included 19 patients who followed a program of physical exercise for six months. Plasma levels of PGE₂, 6-Keto-PGF_{1α} (the stable derivative of PGI₂) and TXB₂ (the stable derivative of TXA₂) were measured by reliable enzyme-immunoassay methods (EIA) in HD and HD/Exer patients before and after the hemodialysis sessions as well as in the group of C. **RESULTS:** The plasma levels of PGE₂ and 6-keto-PGF_{1α} in group HD Exer/_{before} patients were higher than those in group HD_{before} (20.39±5.82 and 1449.19±553.41 vs 17.68±5.36 and 1295.10±384.43 pg/ml, p=0.044 and p=0.067, respectively), while the plasma levels of TXB₂ were lower in HD Exer/_{before} patients compared to HD_{before} (499.76±67.51 vs 608.01±80.23 pg/ml, p=0.041). The plasma levels of PGE₂ and 6-keto-PGF_{1α} in group HD Exer/_{after} patients were significantly higher compared to those in HD_{after} patients (23.01±5.70 and 1618.19±435.07 vs 16.57±4.97 and 1005.44±317.16 pg/ml, p<0.001 and p<0.040, respectively). However, significantly lower values in the plasma levels of TXB₂ in HD Exer/_{after} compared to HD_{after} patients (363.10±51.91 vs 439.75±62.34 pg/ml, p=0.030) were detected. As expected, PGE₂ and 6-keto-PGF_{1α} values were lower in C than in the groups of patients with CKD. **CONCLUSIONS:** The data indicate that exercise training during HD exerts a beneficial effect on the levels of the vasoactive eicosanoid hormone-like substances in patients on HD.

Key words: Chronic kidney disease, Eicosanoid hormones, Hemodialysis, Physical exercise

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Received 10-06-08, Revised 25-01-09, Accepted 25-02-09

INTRODUCTION

Eicosanoid hormone-like substances are produced from arachidonic acid (a.a.) via the action of cyclo-oxygenases and synthases. The main eicosanoid hormone-like substances are: Prostaglandin E₂ (PGE₂), Prostacyclin I₂ (PGI₂) and Thromboxane A₂ (TXA₂). Arachidonic acid is released from the cellular membranes of human cells (platelets, macrophages, glomerular mesangial cells, others) by the action of the phospholipase A₂. Arachidonic acid is converted to prostaglandin endoperoxides by cyclo-oxygenase (endoperoxide synthase). Endoperoxides are subsequently converted to prostaglandins (PGs), prostacyclin (PGI₂) and thromboxane A₂ (TXA₂).¹⁻⁵

Prostaglandin E₂ (PGE₂) is a vasodilative local hormone which belongs to the family of eicosanoid hormone-like substances. The cells that mainly produce PGE₂ are the epithelial cells, the fibroblasts, the monocytes-macrophages and the eosinophils. Recently, a different metabolic pathway of PGE₂ synthesis was disclosed. Thus, in cases of intense oxidative stress, when 15-F_{2t}-isoprostane (15-F_{2t}-IsoP) production is increased, prostaglandin E₂ is produced at high rates (15%-40%) by 15-F_{2t}- IsoP epimerization. PGE₂ has significant effects on several organs, including the kidneys. It has been found that PGE₂ induces a rise in the renal blood flow, in diuresis, natriuresis and kaliuresis. Additionally, PGE₂ increases the Glomerular Filtration Rate (GFR), inhibits the reabsorption of chloride ions (Cl⁻) and results in increased renin secretion and erythropoietin release.^{1,2,6-14}

Prostacyclin I₂ (PGI₂) is another local hormone which belongs to the family of eicosanoid hormone-like substances. PGI₂ has a powerful vasodilative action, inhibits the accumulation of platelets and obstructs the vasoconstrictive action of thromboxane A₂. Additionally, it has an antithrombotic action in the vessel intima; in the kidneys, the action of PGI₂ is similar to that of PGE₂. The cells that mainly produce PGI₂ are the endothelial cells, smooth muscle cells, macrophages and fibroblasts. PGI₂ is rapidly converted to 6-Keto-PGF_{1α}, a chemically stable but biologically inactive product.^{1,2,15-18}

Thromboxane A₂ (TXA₂) is a catabolic product of arachidonic acid. Besides this, TXA₂ is produced *in vivo* and non-enzymatically by free radical-catalyzed

lipid peroxidation via isoprostane endoperoxides rearrangement. Being a very efficient vasoconstrictor agent and inducing a potent platelet aggregation, TXA₂ is an antagonist to prostacyclin. It is considered that physiological balance between the two components plays an important regulatory role in the maintenance of normal vascular tone and in the pathogenesis of various cardiovascular disorders. As regards the kidneys, TXA₂ causes marked renal vasoconstriction; consequently, enhanced renal TXA₂ production reduces renal blood flow and glomerular filtration rate. Since TXA₂ is rapidly converted to thromboxane B₂ (TXB₂), a chemically stable but biologically inactive hydration product, thromboxane synthesis by biological tissues has been monitored by measuring TXB₂.^{1,2,19-21}

Enhanced eicosanoid hormone production has been detected in a number of diseases such as cardiovascular disorders, diabetes mellitus and inflammatory, immunological and renal diseases.^{7,8,21-29} Physical exercise induces the release of vasodilative prostaglandins (PGE₂ and PGI₂) by the skeletal muscles; consequently, these substances may contribute to arterioles vasodilation and hyperemia, which occurs in the skeletal muscles during physical exercise. Plasma levels of TXB₂ decrease during short- or long-term exercise. Some researchers, however, have reported a rise in thromboxane plasma levels during physical exercise.³⁰⁻³³ We have shown that the interstitial and plasma levels of PGE₂ and 6-keto-PGF_{1α} also increase during exercise.^{9,34,35} There are no available data with regard to changes of the above-mentioned bioactive eicosanoid hormone-like substances (PGE₂, PGI₂ and TXA₂) in hemodialysis patients who participate in a program of physical training during the hemodialysis session.

The aim of the present study was to evaluate the effect of physical exercise during the hemodialysis session on the levels of vasoactive eicosanoid hormones, derivatives of arachidonic acid, in patients undergoing hemodialysis and participating in a program of physical exercise during the hemodialysis session.

SUBJECTS AND METHODOLOGY

The study group included 35 healthy individuals who served as controls (group C), 22 men and 13

women, aged 56.7 ± 13.8 (mean \pm SD) years, and 50 patients with end-stage renal failure (stage 5) on chronic hemodialysis (HD). All our study subjects were initially evaluated at the Renal Dialysis Unit of the 1st Department of Internal Medicine at AHEPA University Hospital, Thessaloniki, Greece, where detailed medical history was recorded and careful clinical examination was performed. Patients with acute or chronic inflammatory diseases, a history of myocardial infarction, unstable angina or stroke in the past six months, a history of malignancy, as well as patients receiving cyclooxygenase inhibitors or vitamin E and other supplements, were excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki (1985 amendment) and was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, Greece. Informed written consent was obtained from all subjects included in this study prior to study initiation.

The hemodialysis patients were divided into two groups: HD patients who were not following a physical activity program and received usual care and HD patients performing an exercise program (HD/Exer). Each group (HD and HD/Exer) was studied before HD (HD_{before} and HD Exer/_{before}, respectively) and after HD (HD_{after} and HD Exer/_{after} respectively). Subgroup HD_{before} included 31 patients (21 men and 10 women), aged 58.9 ± 15.8 years, with an estimated GFR $< 15.0 \text{ ml/min/1.73 m}^2$, who had been on chronic periodic hemodialysis for a period of 64.8 ± 12.1 months. The hemodialysis procedure took place three times a week with polysulphone filters and lasted four hours. Subgroup HD_{after} included the same patients after the hemodialysis session. Subgroup HD Exer/_{before} comprised 19 patients before the hemodialysis session, with the same estimated GFR (12 men and 7 women), aged 58.1 ± 8.7 years, who had been on hemodialysis for a period of 91.2 ± 15.3 months; they participated voluntarily in a program of mild physical exercise carried out during hemodialysis for a time period of six months prior to entrance to the study. Subgroup HD Exer/_{after} comprised the same patients as subgroup HD Exer/_{before} and were studied after the HD. All HD/Exer patients underwent thorough examination of their cardiovascular and respiratory system; patients with

severe cardiac arrhythmias (stage \geq III according to Lown), unsteady coronary disease, congestive heart failure (stage $>$ II according to the New York Heart Association), recent myocardial infarction, valvulitis or chronic respiratory failure were excluded from the study. In addition, patients suffering from resistant hypertension and severe hyperparathyroidism (I-PTH > 600 pg/ml), and individuals with osteodystrophy or severe anemia (Hb < 10 g/dl), were also excluded from the study.

Information on subject demographics, medical history, concomitant medication, smoking, dietary habits, anthropometric measurements, blood pressure measurements and heart rate were recorded according to a standardized protocol. Blood samples from the healthy control subjects were drawn in the morning after a 12-hour overnight fast in order to determine routine hematologic and biochemical parameters, as well as the parameters under investigation. In the hemodialysed patients, blood samples were drawn under the same conditions before and after the hemodialysis session. Estimation of glomerular filtration rate was performed using the modification of Diet in Renal Disease study formula,³⁶ according to the guidelines.³⁷

Exercise Training Rehabilitation Program during hemodialysis

Patients of group HD/Exer followed a 6-month rehabilitation program during the first two hours of their hemodialysis sessions under the supervision of two physical physiologists. Patients participated in the physical exercise program three times a week for 60 minutes each time. Special stationary bicycles (type Motomed Letto 713/W 1498) were moved up to the dialysis chairs or beds. Patients cycled for 30 to 60 min and afterwards performed exercise for strength and flexibility for 15 to 30 min. The first five minutes consisted of warm-up, the second period consisted of training at desired workload (cycling and exercises) and the last five minutes consisted of cool-down. Exercise intensity corresponded constantly to 13 (somewhat vigorous) of the Borg perceived exertion scale.³⁵⁻³⁸

Biochemical – Endocrine Parameters

Plasma PGE₂ was determined by a competitive enzyme-immunoassay method (EIA), using kits from Cayman. The quantification of 6-keto-PGF_{1 α} and

Table 1. Demographic and clinical characteristics of the studied subjects (mean \pm SD)

	Controls	HD	HD/ Exercise	P
Number	35	31	19	
Male/Female	22/13	21/10	12/7	0.080
Age, years	56.7 \pm 13.8	58.9 \pm 15.8	58.1 \pm 8.7	0.110
BMI, kg/m ²	23.9 \pm 2.4	24.03 \pm 2.5	24.9 \pm 2.1	0.138
Smoking: n (%)	9 (25.7)	6 (19.4)	4 (21.0)	0.180
Hypertension: n (%)	-	23 (74.2)	12 (63.5)	0.320
Diabetes: n (%)	-	12 (38.7)	5 (26.3)	0.210
Cardiovascular Disease: n (%)	-	7 (22.5)	4 (21.0)	0.180
eGFR: ml/min/ 1.73m ²	113.19 \pm 15.40	<15.0	<15.0	<0.001

HD: Hemodialysis, BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate

TXB₂ was also performed by an EIA method using kits from R and D.

The normal plasma levels according to the PGE₂ quantification method were 3-12 pg/ml with intra-assay coefficient of variation (CV) 5.1% and inter-assay CV 5.8%. The sensitivity of the method used to determine 6-keto-PGF_{1 α} in the plasma was <5 pg/ml, whereas the intra-assay coefficient of variation (CV) was 5% and the inter-assay CV 7.3%.

The performance characteristics of the TXB₂ method were as follows: sensitivity 8 pg/ml and intra- and inter-assay coefficients of variation (CV) 3.6% and 7.7%, respectively.

Statistical Analysis

Statistical analysis was performed using the SPSS version 13 software (SPSS Inc., Chicago, III, USA) for Windows XP. Continuous variables are expressed as mean \pm standard deviation (mean \pm SD). Comparisons of the categorical variables between the groups was performed by the χ^2 test or Fisher's exact test whenever the marginal expected count was <5; to compare the continuous variables we used the one-way analysis of variance (ANOVA). In order to explore the differences among various pairs of the four groups studied, we performed Student's tests for

independent variables with Bonferroni correction for multiple testing. In addition, we performed simple linear regression analysis and calculated Pearson's correlation coefficients so as to explore possible relations between estimated GFR and the parameters under study. A value of $p < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

Basic demographic data as well as the clinical characteristics of the studied subjects are presented in Table 1. There were no statistically significant differences among the groups with regard to sex, age, body mass index (BMI) and proportion of smokers. When comparing the HD groups, no significant differences in the proportion of patients with a history of hypertension, diabetes and cardiovascular disease were noticed.

a) Before hemodialysis, the PGE₂ plasma levels of the patients who underwent a physical training program during the hemodialysis session (Subgroup HD Exer/_{before}) were significantly higher than the PGE₂ plasma levels of controls ($p < 0.001$) and of hemodialysis patients who did not participate in the physical training program (Subgroup HD_{before}, $p = 0.044$).

After hemodialysis, the plasma PGE₂ levels in subgroup HD Exer/_{after} were much higher than the PGE₂ plasma levels in subgroup HD Exer/_{before} ($p = 0.001$), as well as the levels in subgroup HD_{after} ($p < 0.001$) (Table 2, Figure 1A).

b) The 6-keto-PGF_{1 α} plasma levels in patients before the hemodialysis in subgroup HD Exer/_{before} were higher but not significantly ($p = 0.067$) compared to the 6-keto-PGF_{1 α} plasma levels in the respective subgroup HD_{before} and significantly higher than the corresponding levels observed in controls ($p < 0.001$)

The plasma levels of 6-keto-PGF_{1 α} in subgroup HD Exer/_{after} were significantly higher than the 6-keto-PGF_{1 α} plasma levels in subgroup HD Exer/_{before} ($p = 0.002$), as well as of the patients in subgroup HD_{after} ($p < 0.040$) (Table 2, Figure 1B). Furthermore, there was a positive correlation between PGE₂ and 6-keto-PGF_{1 α} values in the patients of groups HD Exer/_{before} and HD Exer/_{after} ($r = 0.94$, $p < 0.001$, and $r = 0.99$, $p < 0.001$, respectively; Figures 2A and 2B).

c) The TXB₂ plasma levels of the patients in subgroup HD Exer/_{before} were significantly lower than the TXB₂ plasma levels in the respective patients of subgroup HD_{before} (p=0.041) and significantly higher than the TXB₂ plasma levels of controls (Group C, p<0.001).

After hemodialysis, the TXB₂ plasma levels in patients of subgroup HD Exer/_{after} were significantly lower than the TXB₂ plasma levels in patients of subgroup HD_{after} (p= 0.030).

The plasma levels of TXB₂ in patients after hemodialysis (Subgroup HD Exer/_{after}) were much lower than in the same patients subgroup HD Exer/_{before} (p=0.001) (Table 2, Figure 1C).

The ratio TXB₂/PGE₂ in groups C, HD_{before}, HD Exer/_{before}, HD_{after}, as calculated according to the values of Table 2, is 13.3 :1, 34.3 :1, 21.5 :1 and 26.5 :1, respectively. This ratio of group HD Exer/_{after} almost attains the ratio of healthy individuals (15.8:1). Similarly, the ratio 6-keto-PGF_{1α}/TXB₂ in groups C, HD_{before}, HD Exer/_{before}, HD_{after} was 3.9:1, 2.1:1, 3.2:1 and 2.2:1, respectively. This ratio of group HD Exer/_{after} almost reaches the values of healthy individuals (4.4 :1).

DISCUSSION

There are no literature data evaluating the po-

tential benefit of physical exercise applied during hemodialysis on the levels of vasoactive eicosanoid hormone-like substances.

In the present study, higher values of PGE₂ in the plasma of hemodialysis patients who participated in the mild physical exercise program for a long time were detected compared to values of HD patients not participating in the exercise program. It is noteworthy that the ratios TXB₂/PGE₂ and 6-keto-PGF_{1α}/TXB₂, which were found to be abnormal in HD patients, improved after physical training during the HD session and almost reached the ratios of healthy individuals. In previous studies investigating PGE₂ plasma changes in healthy individuals after vigorous physical training for a short period of time, we found that the PGE₂ plasma levels rise significantly. However, high intensity physical training cannot be applied in hemodialysis patients because it is dangerous for them.^{7-9,34}

The increase of PGE₂ plasma levels in hemodialysis patients who participated in a mild physical training program for a long period of time, as compared to those who did not undergo such a training program, could be related to certain alterations known to occur in HD patients on an exercise program. Thus, morphological, functional and metabolic adjustments of the skeletal muscles are improved in hemodialysis patients participating in such programs of physical

Table 2. Mean ± SD values of PGE₂, 6-keto-PGF_{1α} and TXB₂ and other parameters in controls (C) and in the various subgroups HD_{before}, HD_{after}, HD Exer/_{before} and HD Exer/_{after}.

No	Controls (C) and Subgroups	Age (Years)	Creatinine Clearance (ml/min 1.73m ²)	Subjects (n)	*PGE ₂ (pg/ml)	**6-keto-PGF _{1α} (pg/ml)	***TXB ₂ (pg/ml)
1	C	56.7±13.8	132.65±14.90	35	6.53±1.84	345.00±105.75	87.39±14.95
2	HD _{before}	58.9±15.8	<15.0	31	17.68±5.36	1295.10±384.43	608.01±80.23
3	HD _{after}	58.9±15.8	<15.0	31	16.57±4.97	1005.44±317.16	439.75±62.34
4	HD Exer/ _{before}	58.1±8.7	<15.0	19	20.39±5.82	1449.19±553.41	499.76±67.51
5	HD Exer/ _{after}	58.1±8.7	<15.0	19	23.01±5.70	1618.19±435.07	363.10±51.91

* PGE₂ HD Exer/_{before} vs HD_{before} p= 0.044

HD Exer/_{after} vs HD_{after} p<0.001

** 6-keto-PGF_{1α} HD Exer/_{before} vs HD_{before} p= 0.067

HD Exer/_{after} vs HD_{after} p<0.040

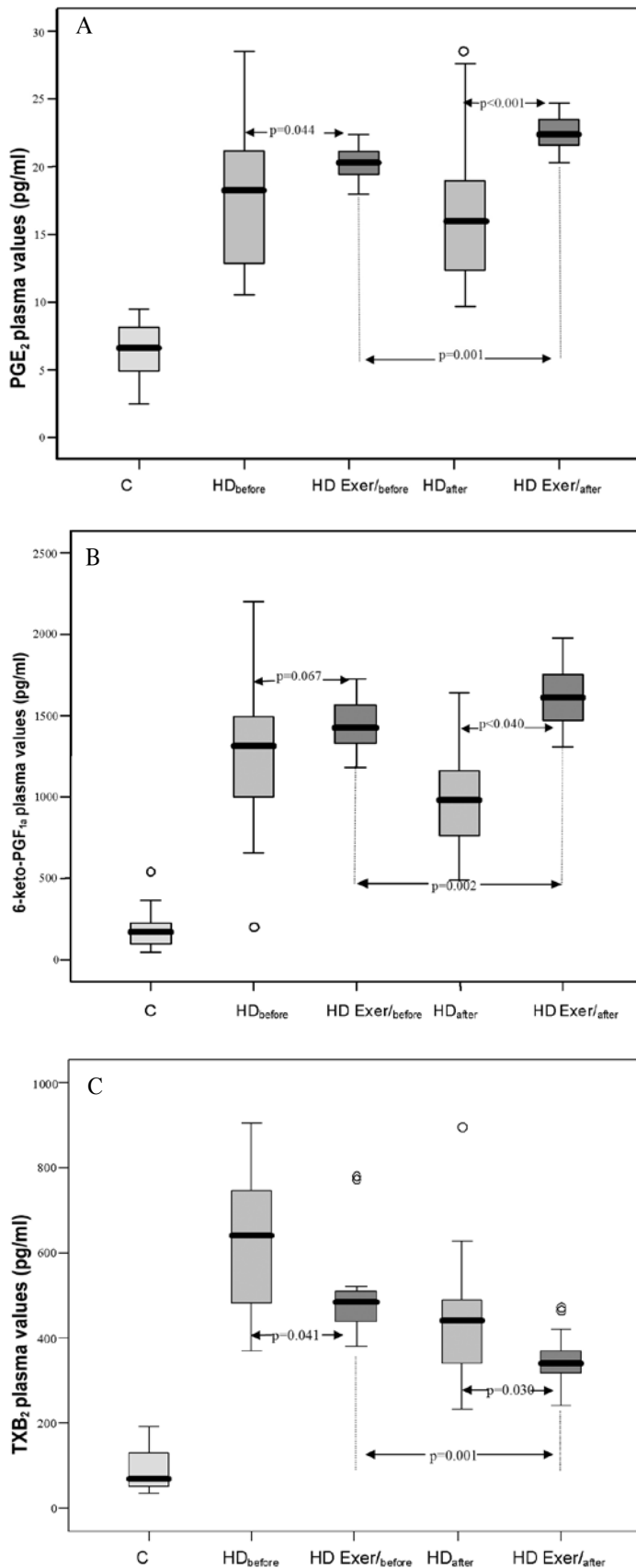
***TXB₂ HD Exer/_{before} vs HD_{before} p= 0.041

HD Exer/_{after} vs HD_{after} p=0.030

PGE₂, 6-keto-PGF_{1α}, TXB₂ HD_{before} vs C p<0.001, HD_{after} vs C p<0.001

HD Exer/_{before} vs C p<0.001, HD Exer/_{after} vs C p<0.001

HD: Hemodialysis, Exer: Exercise, PGE₂: Prostaglandin E₂, 6-keto-PGF_{1α}: 6-keto Prostaglandin F_{1α}, TXB₂: Thromboxane B₂



training during hemodialysis.³⁸⁻⁴⁰

The rehabilitation of the hemodialysis patients is enhanced, most likely because aerobic exercise induces elongation and an increase in the diameter of the striated muscle fibre, improves their capillary vasculature, as well as their aerobic capacity, and positively affects their blood pressure measurements, their brain function and the lipid profile.^{38,39}

The increased ionic calcium of the cell sarcoplasm in the skeletal muscles, which is prevalent during the muscle contractions, possibly stimulates muscle cells phosphorylase A₂; the outcome is an increased production of arachidonic acid, with subsequent increased synthesis of PGE₂.^{31,41}

Bradykinin production is increased during physical training, resulting in activation of phospholipase A₂ with further increase in the biosynthesis of PGE₂.⁴²

It should be pointed out that the biosynthesis of PGE₂ in the hemodialysis patients who participate in programs of physical exercise during the hemodialysis session could be even higher than the rates we found, since physical exercise induces an increased PGE₂ clearance via the beneficial morphological, metabolic and functional changes in the muscles involved.

The increased 6-Keto-PGF_{1α} plasma levels before and particularly after hemodialysis in hemodialysis patients who participated in the program of mild physical exercise for a long period of time could be attributed to the same

HD: Hemodialysis

Exer: Exercise

PGE₂: Prostaglandin E₂

6-keto-PGF_{1α}: 6-keto prostaglandin F_{1α}

TXB₂: Thromboxane B₂

Figure 1. Mean plasma values of PGE₂ (A), 6-keto-PGF_{1α} (B) and TXB₂ (C) in controls and in the various subgroups HD_{before}, HD Exer/_{before}, HD_{after} and HD Exer/_{after}. Comparisons C vs all the other groups, p<0.001.

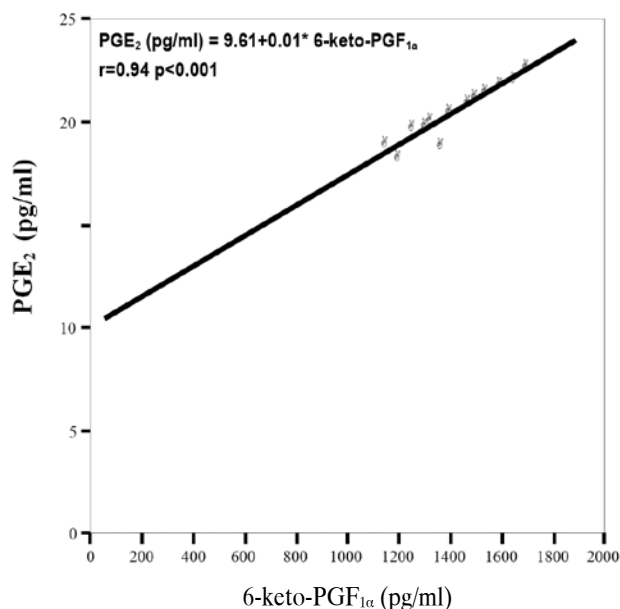


Figure 2A. Correlation between PGE₂ and 6-keto-PGF_{1α} in the group HD Exer/before.

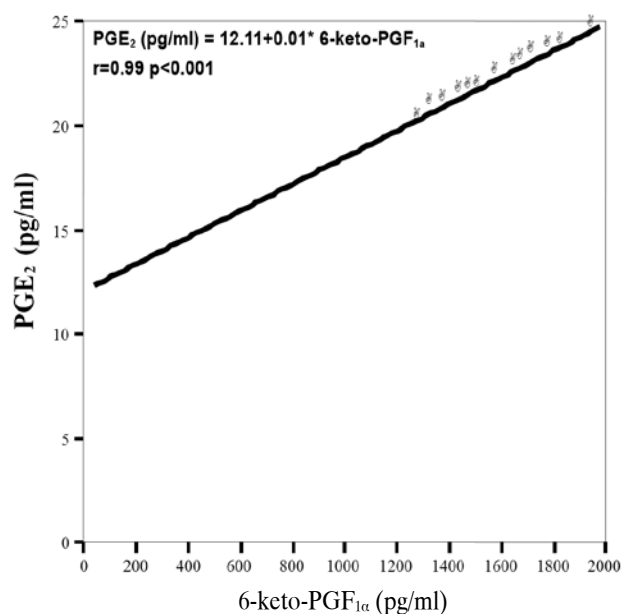


Figure 2B. Correlation between PGE₂ and 6-keto-PGF_{1α} in the group HD Exer/after.

reasons that also caused the increase of PGE₂.⁴² It should be emphasized that in previous studies an analogous increase of 6-keto-PGF_{1α} in biological fluids after intense physical training was detected.^{9,35} It seems that the favourable biochemical-endocrine adjustments which are observed as a result of brief intense physical exercise in healthy individuals are also observed in hemodialysis patients who exercise mildly but for a longer period of time.

The decrease of plasma TXB₂ levels in patients on hemodialysis following a program of physical training could be attributed to morphological, metabolic and functional changes in the skeletal muscles, like those observed during similar training programs, as well as to the decrease of platelet activation during exercise.³⁸⁻⁴⁰ This finding is similar to that of previous studies, in which a significant decrease of TXA₂ was detected in healthy humans during dynamic contractions.^{9,34} These changes in the eicosanoid hormone-like substances in hemodialysis patients may contribute to the vasodilation and hyperemia that occur in the working muscles during exercise.³⁰ We would like to point out that the favourable alterations in the plasma levels of PGE₂, 6-keto-PGF_{1α} and TXB₂ in hemodialysis patients detected in the present study have been demonstrated in healthy subjects during exercise.^{5,30,34,35} Nevertheless, the present findings in

HD patients constitute novel observations.

It should be briefly mentioned that patients with CKD, whether undertaking HD or not, experience multiple benefits from physical exercise; resistance exercise training program in patients with severe CKD was found to cause a significant increase in the size of forearm veins.⁴³ In hemodialysis patients, handgrip training and intermittent compression of the upper arm veins led to increased diameter of forearm arteries and veins and improved endothelium-dependent vasodilation.⁴⁴ Moreover, three months of aerobic exercise training was found to improve arterial stiffness in patients on hemodialysis.⁴⁵ It was also suggested that a low-intensity exercise program during HD increased the rate of urea removal, perhaps due to the acute increases in blood flow to working muscles and reduction in oxidative stress.^{7,8,46} There is also evidence that exercise during hemodialysis can be used as an adjunctive therapy to enhance dialysis efficacy.^{46,48}

Our data support the view that the plasma levels of the vasodilative eicosanoid hormones, derivatives of arachidonic acid (prostaglandin E₂ and prostacyclin I₂), in patients on hemodialysis who follow a program of physical training carried out during the hemodialysis session were increased, as compared to those

in patients on hemodialysis who were not following a program of physical training. By contrast, the plasma levels of vasoconstrictive thromboxane B₂ were simultaneously reduced. These alterations suggest that an exercise program of moderate or low intensity during HD, apart from being safe, is also substantially beneficial in many respects since it improves their vasoactive hormonal profile. Consequently, such an exercise program can be used as an adjunctive therapy to enhance dialysis efficacy.

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