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## Effect of type 2 diabetes on plasma kallikrein activity after physical exercise and its relationship to post-exercise hypotension

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### Abstract

**Aim.** – The present study was undertaken to determine the effects of type 2 diabetes (T2D) on plasma kallikrein activity (PKA) and postexercise hypotension (PEH).

**Methods.** – Ten T2D patients (age:  $53.6 \pm 1.3$  years; body mass index:  $30.6 \pm 1.0$  kg/m<sup>2</sup>; resting blood glucose:  $157.8 \pm 40.2$  mg dL<sup>-1</sup>) and 10 non-diabetic (ND) volunteers (age:  $47.5 \pm 1.0$  years; body mass index:  $28.3 \pm 0.9$  kg/m<sup>2</sup>; resting blood glucose:  $91.2 \pm 10.5$  mg dL<sup>-1</sup>) underwent two experimental sessions, consisting of 20 min of rest plus 20 min of exercise (EXE) at an intensity corresponding to 90% of their lactate threshold (90LT) and a non-exercise control (CON) session. Blood pressure (BP; Microlife BP 3AC1-1 monitor) and PKA were measured during rest and every 15 min for 135 min of the postexercise recovery period (RP).

**Results.** – During the RP, the ND individuals presented with PEH at 30, 45 and 120 min ( $P < 0.05$ ) while, in the T2D patients, PEH was not observed at any time. PKA increased at 15 min postexercise in the ND ( $P < 0.05$ ), but not in the T2D patients.

**Conclusion.** – T2D individuals have a lower PKA response to exercise, which probably suppresses its hypotensive effect, thus reinforcing the possible role of PKA on PEH.

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**Keywords:** Post-exercise hypotension; Type 2 diabetes; Blood pressure; Kallikrein activity; lactate threshold

### Résumé

Influence du diabète de type 2 sur l'activité kallicroïne et la baisse tensionnelle post-exercice physique.

**Objectif.** – Cette étude avait pour but d'évaluer l'effet du diabète de type 2 (DT2) sur l'activité kallicroïne plasmatique et la baisse tensionnelle post-exercice physique.

**Méthodes.** – Dix patients atteints de DT2 (âge  $53,6 \pm 1,3$  ans; indice de masse corporelle (IMC)  $30,6 \pm 1,0$  kg/m<sup>2</sup>, glycémie basale  $157,8 \pm 40,2$  mg dL<sup>-1</sup>) et dix témoins non diabétiques (ND) ( $47,5 \pm 1,0$  ans, IMC  $28,3 \pm 0,9$  kg/m<sup>2</sup>, glycémie  $91,2 \pm 10,5$  mg dL<sup>-1</sup>) ont été soumis à deux séquences expérimentales de 20 minutes de repos, suivies de 20 minutes d'exercice avec une intensité correspondant à 90 % du seuil lactate (90LT) et une séquence sans exercice physique. La pression artérielle (BP 3AC1-1, Microlife) et l'activité kallicroïne plasmatique ont été mesurées au repos et après exercice toutes les 15 minutes jusqu'au temps 135 minutes pendant la période de récupération.

**Résultats.** – Les témoins non-diabétiques ont présenté une baisse tensionnelle aux temps de 30, 45 et 120 minutes pendant la période de récupération post-exercice. En revanche, cette baisse tensionnelle n'a pas été observée chez les DT2 ( $P < 0,05$ ). L'activité kallicroïne plasmatique a augmenté chez les témoins non-diabétiques au temps 15 minutes post-exercice, mais non chez les DT2 ( $P < 0,05$ ).

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**Conclusion.** – Les patients atteints de DT2 présentent une plus faible réponse de l'activité kallikréine plasmatique après exercice, ce qui prévient probablement l'apparition d'une baisse tensionnelle et pourrait témoigner du rôle possible de l'activité kallikréine sur la pression artérielle post-exercice physique.

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**Mots clés :** Exercice physique ; Diabète de type 2 ; Pression artérielle ; Activité kallikréine ; Lactate seuil

## 1. Introduction

Type 2 diabetes (T2D) is characterized by hyperglycaemia and can lead to dysfunction in several organs [1], as well as to endothelial, autonomic and circulatory changes related to arterial hypertension [2]. The endothelial dysfunction often observed in T2D patients impairs the release of vasodilators such as prostaglandins, kallikrein, bradykinin and nitric oxide (NO), all of which are involved with kallikrein–kinin system (KKS) [3,4].

A single physical exercise session can result in significant reduction of blood pressure (BP) for minutes or hours after stopping compared with pre-exercise resting values [5,6]. This phenomenon is called 'post-exercise hypotension' (PEH), and may be associated with KKS components such as plasma kallikrein activity (PKA) and bradykinin levels in both normotensive and hypertensive individuals [7,8].

Physical exercise has been indicated as a non-pharmacological treatment [9], although its prescription must take into account several factors, such as mode, duration and intensity. The lactate threshold (LT) is a metabolic parameter widely employed for functional evaluation and exercise-intensity prescription in T2D patients [10,11], as it delineates moderate- and high-intensity domains, and represents the intensity of low metabolic stress [12]. In previous studies, T2D was found to impair PEH following exercise intensities at around the LT [11]. The aim of the present study was to analyze the occurrence of PEH, and to compare BP responses and PKA in T2D and ND individuals after aerobic exercise at an intensity corresponding to 90% of the LT (90LT). We hypothesized that, due to the endothelial and autonomic dysfunction often observed in T2D, such patients would present a reduced PEH effect and lower PKA levels in response to moderate-intensity exercise compared with ND individuals.

## 2. Subjects and methods

### 2.1. Subjects

A cohort of 10 T2D (eight men, two women) and 10 ND (eight men, two women) sedentary individuals participated in the present study (Table S1, Supplementary data). The mean duration of diagnosed diabetes was  $5.9 \pm 0.9$  years. Although non-insulin-dependent, all T2D patients were taking oral hypoglycaemic agents such as sulphonylureas and antidiabetic drugs such as metformin. Some were also taking antihypertensive medications such as diuretics and calcium-channel blockers. However, all medications were stopped and washed out 48 h prior to the first study screening and before each of the three

subsequent sessions. A diagnosis of T2D was defined as a fasting blood glucose  $> 126 \text{ mg dL}^{-1}$  [13]. All study participants received a full explanation of the study protocol and its purposes, and also gave their written informed consent. The exclusion criteria were: (a) family history of cerebral stroke or acute myocardial infarction; (b) severe secondary complications (such as blindness or diabetic foot ulceration); (c) physical or cardiovascular problems that could impair the ability to exercise; (d) end-organ injury; (e) autonomic dysfunction; (f) previous history of tobacco use; (g) premenopausal women; (h) use of hormone replacement therapy; and (i) age  $< 40$  years or  $> 60$  years. The study protocol was approved by the local Ethics Committee on Human Research (SES/DF no. 087/2007, Brazil).

All participants were recruited from a Catholic University Hospital programme, and all had been previously assessed for autonomic dysfunction according to standard tests. This meant that, at the time of recruitment, all subjects with a positive history for any of the tests were eliminated from the study. In addition, during the initial visit, our laboratory's cardiologist identified the subjects who had: resting heart rate (HR)  $> 90$  beats/min; abnormal HR recovery (failure to decrease HR by  $> 12$  beats/min within 1 min after peak exercise); and abnormal HR variability (failure to change HR R–R interval by  $\geq 10$  beats/min during 1 min of slow deep breathing). The presence of any of these responses would have excluded the individual from the study, although this did not occur with any of our participants.

### 2.2. Protocol

The participants underwent a physical examination (after a 12-h fast) consisting of weight and height measurements to determine body mass index (BMI) and abdominal circumference at the umbilical level. The following three experimental sessions were performed on separate days after a minimum interval of 72 h, with each session beginning at 08:00 h (1) incremental exercise testing (IT) for cardiological evaluation and LT determination; (2) exercise session (EXE) at 90LT; and (3) the control session (CON). Sessions 2 and 3 were performed in random order. The subjects were asked to avoid any physical exercise and alcoholic or caffeinated drinks for 24 h prior to the test sessions. A standardized breakfast meal was given to the participants 2 h before each session.

### 2.3. Incremental exercise test (IT), exercise (EXE) and control (CON) sessions

To the IT session it was used an electromagnetic cycloergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands), beginning with a 1-min warm-up at 60 rpm and a

workload of 0 W. Then, while maintaining the speed of 60 rpm, the workload was incrementally raised by 15 W every 3 min until the participant could no longer continue. At the end of each stage, blood pressure (BP), HR and rate of perceived exertion (RPE) evaluated by Borg Scale were monitored, and then a capillary blood sample was collected for blood lactate (bLac) determination. Both the BP measurements during exercise and electrocardiography (ECG) were intended to monitor any abnormal responses, according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [9]. Ventilatory parameters were also analyzed throughout the IT session. The LT was identified by visual inspection of the exercise intensity related to the bLac concentration curve during the session, as described elsewhere [14].

The other two experimental sessions (EXE and CON) comprised the following periods: (1) pre-exercise (Rest) period, during which participants remained seated for 20 min, BP and HR were measured every 5 min and, at the end of this period, a venous blood sample was obtained for PKA determination and a capillary blood sample was obtained for blood glucose (bGluc) and bLac analyses; (2) EXE period, after a 1-min warm-up at 60 rpm with a workload of 0 W, followed by 20 min of exercise at 90LT, with the workload set according to the LT identified during the incremental test and automatically adjusted by the electromagnetic cycloergometer, which stayed constant at 60 rpm; after 10 and 20 min, BP, HR and RPE values were obtained, and a capillary blood sample taken for bLac and bGluc analyses; (3) CON period, during which participants rested in a seated position for 20 min while the same measurements were taken as during the EXE period; and (4) recovery period (RP) after each session, during which participants remained seated for 135 min for post-exercise recovery, while BP and HR were measured every 15 min (R15–R135) and, at 15, 45, 90 and 135 min (R15, R45, R90, R135), venous blood samples were obtained for PKA analysis.

#### 2.4. Standard breakfast

At 2 h prior to each session (at approximately 08:00 h), all participants ate a standard breakfast, comprising vanilla pound cake (40 g), light mango juice (200 mL) and 30 g of salty crackers totalling 315 kcal (1317 kJ; 51.6 g of carbohydrates, 4.6 g of protein, 9.5 g of fat) and a moderate glycaemic index score of 73.9.

#### 2.5. Blood pressure and heart rate measurements

BP was measured three times according to American Heart Association (AHA) procedures and average values [15], using a digital sphygmomanometer (BP 3AC1-1, Microlife AG, Widnau, Switzerland) during Rest and RP, and the auscultatory method during EXE and the corresponding CON period, using a mercury-column sphygmomanometer (Tycos, São Paulo, Brazil) and a stethoscope (Becton Dickinson, Franklin Lakes, NJ, USA). Mean arterial pressure (MAP) was calculated using the following equation:  $MAP = (2DBP + SBP)/3$ . For all HR

measurements an HR monitor (Polar Sport Tester S810i, Polar Electro Oy, Kempele, Finland) was used.

#### 2.6. Venous blood sampling

Blood samples were collected for PKA analysis in 4-mL Vacutainer siliconized tubes containing a citrate solution at 3.2% (Becton Dickinson, Franklin Lakes, NJ, USA). The samples were centrifuged at room temperature for 15 min at 1800 g, and the plasma supernatant removed, using a polypropylene pipette, and aliquoted into 0.5-mL samples, using polypropylene microtubes. All samples were stored at  $-20^{\circ}\text{C}$  until analysis.

#### 2.7. Plasma kallikrein activity

PKA was determined by spectrofluorometry (Hitachi F 2500, Tóquio, Japan), using benzyloxycarbonyl-phenylalanine-arginine-4-amino-7-methylcoumarin (Z-Phe-Arg-AMC; Calbiochem, Merck, Darmstadt, Germany) as substrate. Substrate specificity was determined by specific inhibition with plasma kallikrein serine proteinase inhibitor (PKSI). The reaction was initiated by incubating 5  $\mu\text{L}$  of plasma with 2 mL of 50 mM Tris buffer (pH 7.4), containing 100 mM of NaCl. After a 3-min preincubation period, the substrate was added to the cuvette and the reaction continuously monitored for 300 s at 380 nm excitation and 460 nm emission in a cell compartment set at  $37^{\circ}\text{C}$ . Following this, 5  $\mu\text{L}$  of 10-mM PKSI was added to the solution and the reaction monitored for an additional 100 s. PKA, expressed as fluorescence arbitrary units per minute (FAU.  $\text{min}^{-1}$ ), was calculated as the rate of substrate hydrolysis measured without PKSI minus the rate of substrate hydrolysis measured with PKSI [8].

#### 2.8. Blood glucose and lactate analysis

Blood (25  $\mu\text{L}$ ) was collected from the ear lobe and placed in heparinized glass tubes (Perfecta, São Paulo, Brazil) for glucose and lactate analyses. The samples were transferred to Eppendorf microtubes containing 50  $\mu\text{L}$  of 1% sodium fluoride (NaF) and stored at  $-20^{\circ}\text{C}$  until needed for electroenzymatic analysis (YSI 2700 STAT, Yellow Springs, OH, USA).

#### 2.9. Ventilatory analysis

Peak oxygen uptake ( $\text{VO}_{2\text{peak}}$ ) for each participant was obtained, based on gas-exchange measurements (MetaLyzer 3B, Cortex, Metalyzer 3B, Cortex Biophysik, Leipzig, Germany).

#### 2.10. Statistics

Data are presented as means  $\pm$  standard error of mean (SEM). Normality of the data was determined by Shapiro-Wilk test, while Student's *t* and Mann-Whitney tests were applied for between-group comparisons. For BP analysis, one-way ANOVA with Bonferroni adjustment was used and, for the intrasession PKA analysis, Friedman's test was applied with a post-hoc Dunn

test. The level of significance was set at  $P < 0.05$ , and the analyses were carried out using Statistica 7.0 software (StatSoft, Tulsa, OK, USA).

### 3. Results

#### 3.1. Physiological responses

The physiological responses observed during the sessions, as well as the aerobic capacity parameters obtained during the incremental test are presented in Table S2.

#### 3.2. Blood pressure

Table S3 presents the mean systolic BP (SBP) values at Rest, and after the CON and EXE periods, for T2D and ND individuals. SBP was reduced after EXE compared with pre-exercise Rest at R30 ( $-7.6 \pm 1.27$  mmHg;  $P < 0.05$ ), R45 ( $-7.3 \pm 1.19$  mmHg;  $P < 0.05$ ) and R120 ( $-6.9 \pm 1.15$  mmHg;  $P < 0.05$ ) in ND participants. In T2D patients, there was no significant reduction of SBP after EXE compared with pre-exercise Rest ( $P < 0.05$ ). Similarly, no changes were observed in diastolic BP (DBP) after EXE in both T2D and ND participants vs pre-exercise Rest values.

DBP during the post-exercise RP ranged from  $76.7 \pm 1.1$  to  $80.3 \pm 1.1$  mmHg in the diabetic group, and from  $74.1 \pm 2.1$  to  $81.2 \pm 2.0$  mmHg in the ND group, with no significant differences between groups. After EXE, significant reductions in MAP were observed only in the ND group at R30 and R45 ( $88.9 \pm 2.1$  mmHg and  $87.8 \pm 2.3$  mmHg, respectively) compared with pre-exercise Rest ( $91.5 \pm 2.0$  mmHg).

Values of delta SBP during exercise showed larger decreases in the ND group compared with T2D patients at R30, R45 and R120 ( $P < 0.05$ ; Fig. 1).

#### 3.3. Plasma kallikrein activity

In the ND group, there was an increase in PKA after EXE compared with Rest values only at R15 (from  $178.04 \pm 26.44$  FAU.  $\text{min}^{-1}$  to  $272.96 \pm 34.58$  FAU.  $\text{min}^{-1}$ ;  $P < 0.05$ ), whereas

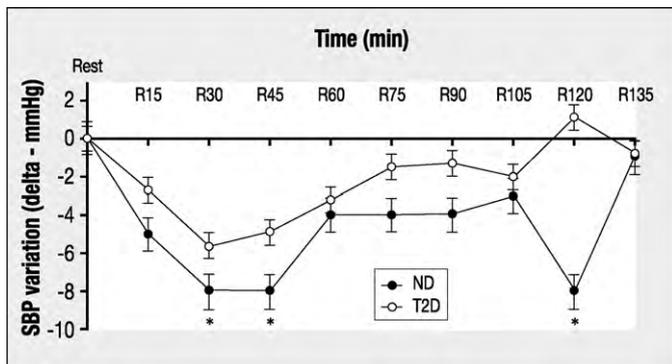


Fig. 1. Changes in systolic blood pressure (SBP delta) during the post-exercise recovery period (R15–R135) compared with pre-exercise Rest values in type 2 diabetics (T2D) and non-diabetics (ND). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$  vs ND.

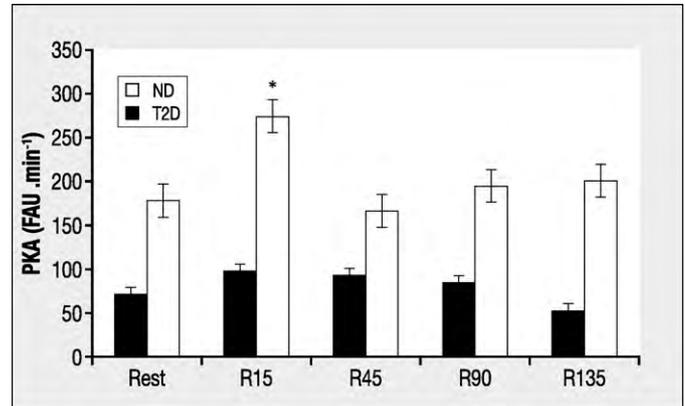


Fig. 2. Plasma kallikrein activity (PKA) in type 2 diabetics (T2D) and non-diabetics (ND) during pre-exercise Rest and the post-exercise recovery period (R15–R135 min). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$  vs Rest.

there were no significant PKA changes seen in the T2D group (Fig. 2).

### 4. Discussion

The present study compared BP and PKA responses in T2D and ND individuals following aerobic exercise. The main finding was that, in contrast to NDs, T2D patients did not present PEH after 20 min of aerobic exercise performed at 90LT. Despite a decrease in SBP of 5.6 to 0.8 mmHg after EXE in T2D, the reduction was not statistically significant. Another finding of the present study was that PKA was increased in the ND group, but not in T2Ds, following the exercise protocol, which would explain, at least in part, the significant reduction in SBP observed in the ND volunteers. These results are in agreement with our initial hypothesis and suggest that T2D can impair the PKA response to moderate exercise as well as the occurrence of PEH, which could be the result of endothelial dysfunction related to the disease [16,17]. The possible association of PKA and PEH has been demonstrated by previous investigations in hypertensive individuals [7,8]. Moraes et al. [8] analyzed the effects of 30 min of aerobic cycloergometer exercise (CE) at 70% of the HR reserve and of circuit weight-training (CWT) on post-exercise BP and PKA in hypertensive and normotensive volunteers, and observed that post-exercise PKA increased immediately and at 60 min after CE and CWT, respectively [8]. They also reported PEH (in SBP) at 45 and 60 min post-exercise, and an increase in PKA at 60 min post-exercise during both sessions that, according to the authors, might be related to the KKS.

Our present results demonstrate that PKA increased after EXE only in the ND group at R15, with no significant changes in T2D patients. These findings suggest better hypotensive response and higher KKS activity in ND compared with T2D after cycloergometer exercise at 90LT. It is also important to keep in mind that, despite slight differences between the two groups, the age of the participants did not correlate with any of the studied variables, thus indicating no influence of age on the results.

Endothelial dysfunction plays a determinant role on BP control in T2D [17,18]. The integrity of the vascular endothelium

is essential for modulating the effects of factors involved in endothelium-dependent vasodilatation [1]. Patients with T2D present insulin resistance and impaired beta-cell function leading to hyperglycaemia, factors that are associated with impaired endothelium-dependent vasodilatation as a result of attenuation of NO production and greater vasoconstrictor tonus [19].

Mechanical stress, represented by exercise intensity, is one factor that might have an influence on the release of endothelial vasodilators such as kallikrein and, consequently, the occurrence, or not, of PEH. Yet, despite the fact that both relative and absolute exercise intensities did not differ between the T2D ( $65.1 \pm 3.8$  W, 56.3% of maximum power output) and ND ( $65.8 \pm 5.3$  W, 48.2% of maximum power output) participants, only the ND group presented a significant PEH response in the present study.

The T2D patients reached a peak oxygen consumption ( $VO_{2peak}$ ) of  $1.8 \pm 0.5$  L·min<sup>-1</sup>, while the ND group achieved  $2.08 \pm 0.2$  L·min<sup>-1</sup>. Although this is an indication of sedentariness in both groups, these data suggest a trend towards reduced functional capacity in T2D, which is consistent with other studies of diabetic patients [11,20]. In fact, low aerobic capacity is related to an increased risk of developing cardiovascular and metabolic disorders such as T2D, as well as reduced longevity [21].

Given the haemodynamic and metabolic limitations of T2D patients, peripheral fatigue is likely to take place earlier during exercise, preventing such individuals from reaching their true maximum cardiorespiratory capacity, represented by maximum power output ( $P_{max}$ ) and maximum HR ( $HR_{max}$ ). This would explain why the  $VO_{2peak}$ ,  $P_{max}$  and  $HR_{peak}$  values in the T2D group were lower than those predicted, with the % $VO_{2peak}$  at which LT was achieved tending to be higher in T2D compared with ND.

The release of endothelial vasodilators, such as endothelium-derived hyperpolarizing factor and prostacyclins, and KKS activation are impaired in conditions such as atherosclerosis, arterial hypertension and diabetes [22]. Kinins are potent vasodilatory peptides, released in several tissues and in the blood circulation that play an important role in BP control [23]. Physical exercise can stimulate the KKS, triggering an increase in the release of kinins, which is then adjusted according to metabolic demands. The modality, intensity and duration of exercise are other factors that may also affect its modulation.

Pontes et al. [7] investigated the effects of two exercise modalities (ground-running and water-running) in hypertensive individuals. The exercise sessions lasted 45 min at an intensity of 50% of  $VO_{2peak}$ . They observed an increase in PKA immediately and at 60 min after the exercise during both sessions. BP, measured every 10 min for 90 min post-exercise, decreased throughout this period, with significantly greater decreases ( $P < 0.05$ ) observed at 30 min after both water-running ( $-35$  mmHg) and ground-running ( $-27$  mmHg). According to the authors, PEH resulted from a decrease in peripheral vascular resistance due to the action of vasodilators such as kinins.

In the present study the exercise duration was shorter than that of Pontes et al. [7], and the ND group, but not the T2D group, presented with PEH. Thus, the present results indicate

impaired activation of the KKS and BP control after exercise in T2D patients. Also, lower kallikrein concentrations in tissues have been observed in hypertensive individuals [24], and reduced urinary kallikrein excretion in hyperglycaemic diabetics [25].

Lima et al. [11] investigated the occurrence of PEH in T2D and the effects of exercise intensity on BP responses in two cycloergometer trials at 90 and 110% of LT. PEH was observed at both intensities with T2D ( $58.5 \pm 10.2$  years), with a more significant decrease after the higher-intensity (110% of LT) exercise. The occurrence of PEH after moderate-intensity exercise observed by Lima et al. [11] might be explained by the use of antihypertensive and hypoglycaemic medications, which can affect BP and PKA responses. Also, the angiotensin-converting enzyme inhibitors taken by the individuals in that study would have increased the bioavailability of bradykinin [26,27]. In the present study, every medication was washed out 48 h before each study session to avoid any effects on BP and PKA.

In conclusion, T2D can alter BP and PKA responses to exercise, although more studies are needed to further elucidate the mechanisms involved in BP and KKS control in response to exercise performed at different intensities and durations in T2D patients. The increase in PKA and the occurrence of PEH indicate a possible role of the KKS in post-exercise BP control. Changes in the KKS, such as the lower PKA observed in the present study, may be related to the smaller hypotensive effect seen in T2D patients after submaximum aerobic exercise.

One limitation of the present study is the fact that only one component of the complex KKS was analyzed. Although the PKA changes seen in the present study suggest an important role of the system in triggering the hypotensive effect of physical exercise, additional factors are involved in the vasodilatory response — and, thus, the PEH response — that were not addressed, such as plasma bradykinin and NO concentrations, and changes in components of the renin–angiotensin–aldosterone system, which is known to counterbalance the KKS. Although there is a need for further studies addressing these issues in T2D patients, on the basis of our preliminary results, we conclude that T2D patients have a lower PKA response to exercise, which probably suppresses its hypotensive effect, thus reinforcing the possible role of PKA on PEH.

### Conflict of interest

The authors have no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2010.03.008.

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