

Research article

Effects of exercise and caffeic acid phenethyl ester after chronic exercise rat model

Ayşe Alp¹, Sadik Buyukbas², Harun Alp³✉, H. Serdar Gergerlioglu⁴, Mehmet Oz⁵, M. Kemal Basarali⁶ and Aysel Kiyici⁷

¹Diyarbakir Training and Research Hospital, Biochemistry Department, Diyarbakir, Turkey, ²Department of Biochemistry, Meram Medical Faculty, Selcuk University, Konya, Turkey, ³Department of Pharmacology and Toxicology, Veterinary Faculty, Dicle University, Diyarbakir, Turkey, ⁴Department of Physiology, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey, ⁵Department of Physiology, Selcuk University, Konya, Turkey, ⁶Department of Biochemistry, Faculty of Medicine, Dicle University, Diyarbakir, Turkey, and ⁷Department of Biochemistry, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey.

Abstract

In order to understand whether exercise and caffeic acid phenethyl ester (CAPE) has an effect on obesity and weight control, we investigated the effects of CAPE, and exercise on lipid parameters (triglyceride, total cholesterol, HDL-C, LDL-C), and adipokine substances such as leptin and resistin in rats. 40 male rat were randomly assigned into 4 groups. It was determined that CAPE does not have any significant effect on these parameters but that lipid parameters and leptin values in exercise groups decreased considerably, while no significant change occurred in resistin levels. In order to understand whether diet has an effect on exercise, body weights of all animal groups in pre and post-exercise were compared. A significant weight gain was observed ($p = 0.005$) in all groups. This study concluded that exercise has a considerable effect on leptin and lipid parameters; however, exercise alone was not sufficient for weight control and could be effective in weight control only when accompanied by a restricted diet.

Key words: Caffeic acid phenethyl ester, exercise, leptin, resistin, weight control.

Introduction

Recent studies have revealed that exercise has favorable effects on hyperglycemia, hypercholesterolemia and hypertension (HT). Related with this fact, regular exercise has been reported to reduce the risk of diabetes mellitus (DM), HT, obesity, cardiovascular diseases, and metabolic syndrome (Kraemer and Castracane, 2007). However, data acquired from exercise studies involving either humans or animals have yet to constitute consensus. The relation between physical exercise and hormone concentrations, on one hand, and the mechanism of action of exercise, on the other, has not been completely clarified. Moreover, the number of studies demonstrating the beneficial effects of exercise and the amount of drug research which could decrease the negative effects of it on the body are still unsatisfactory.

In order to understand whether alone and together exercise and caffeic acid phenethyl ester (CAPE) has an effect on obesity and weight control, we investigated the leptin, resistin, lipid parameters (triglyceride [TG] and total cholesterol levels [TC], HDL-C, LDL-C), and body

weights in rat model.

Leptin, one of the markers in the present study, is a hormone secreted from adipocytes, which suppresses food intake by acting on the hypothalamus through negative feedback mechanisms and increases energy expenditure. It has been reported that short-term training sessions (<12 weeks) do not have an impact on leptin levels so long as they do not reduce fat mass, while long-term training sessions (>12 weeks) decrease leptin levels (Kraemer and Castracane, 2007). This decrease takes places in conjunction with the decrease in fat mass. Gutin et al. (1999) assessed the leptin levels in obese children after an exercise program and observed that leptin levels in the group, comprising 24 girls and 10 boys, were reduced following a 4-month exercise program. Pasman et al. (1998) carried out a moderate exercise program with middle-aged obese men, using a very low-calorie diet. This exercise program continued for 4 months at 3–4 times per week, and a significant decrease was observed in the leptin levels (Reseland et al., 2001).

Another adipokine substance used in the present study is a recently discovered hormone called resistin, which is found abundantly in and excreted from adipocytes. It is significantly related to obesity and type 2 diabetes. Jung et al. (2008) observed a decrease in resistin levels pursuant to a 12-week exercise program and a low-calorie diet, and stated that this decrease was related to weight loss.

The possible protective effects of CAPE on leptin, resistin, and lipid parameters in groups with/without exercise were observed in the present study. CAPE has been used for many years as a traditional type of active composite of propolis extract. Recently, studies have revealed CAPE to have anti-inflammatory, antioxidant, immunomodulator, antimycotic, and anticarcinogenic characteristics (Gurel et al., 2004; Hepsten et al., 1997; Ilhan et al., 1999; Orhan et al., 1999; Uz et al., 2002).

It has been demonstrated that at a concentration of CAPE at 10 $\mu\text{mol/kg}$ concentration completely blocks production of ROS and xanthine and xanthine oxidase system (XO) and also reduces malondialdehyde level secondary to polyunsaturate fatty acid oxidation (Yilmaz et al., 2004). CAPE inhibits protein tyrosin kinase, cyclooxygenase (non-specifically) and suppresses activity of

lipooxygenase and so it has been shown that CAPE prevents lipid peroxidation (Koltuksuz et al., 1999; Ozer et al., 2005). Antiinflammatory activity of CAPE is equal to diclofenac and hydrocortisone (Koksel et al., 2006). CAPE is a potent and specific inhibitor of activation of nuclear transcription factor NF- κ B by TNF- α (Natarajan et al., 1996). In addition to this, CAPE is a lipooxygenase inhibitor with antioxidant properties (Natarajan et al., 1996; Sud'ina et al., 1993). However, there have been no studies about effects of CAPE on leptin, resistin, and lipid parameters in groups with/without exercise. Therefore, the possible protective effects of CAPE on leptin, resistin and lipid parameters in groups with/without exercise were observed in the present study.

Methods

Animals, care and nutrition

In the study, a total of 40 Sprague-Dawley male rats were used in 4 groups of 10 rats each. The groups were arranged as Group 1S (sedentary + 40% ethanol (2ml·kg⁻¹·day⁻¹, intraperitoneally-i.p.), Group 2E (exercise + ethanol), Group 3C (sedentary + CAPE (10 μ mol·kg⁻¹·day⁻¹, i.p.) and Group 4CE (exercise + CAPE). A 1-week exercise familiarization program was conducted as a preliminary study. Afterwards, the rats prone to exercise were allocated to exercise groups, while the other rats, not prone to exercise, were allocated to sedentary groups. The study was approved by Experimental Animals Ethics Committee of Selcuk University (SUDAM).

Animals and treatment

In the long-term treadmill, exercise program was performed as a) 10 m·min⁻¹, 20 m·min⁻¹ and 25 m·min⁻¹ jogging for ten minutes on the 1st, 2nd and 3rd days, respectively; b) 25 m·min⁻¹ jogging for 20 minutes on the 4th day; and c) 30 minutes jogging for 25 m·min⁻¹ on the 5th day.

Following the exercise schedule, ethanol was administered to the rats in Group 1S for 6 weeks. The rats in Group 2E underwent 6 weeks of exercise. The rats in Group 3C were supplemented with CAPE i.p. throughout 6 weeks. The rats in Group 4CE underwent 6 weeks of exercise and were also supplemented with CAPE.

CAPE (Sigma C8221) was purchased from the Sigma Company, dissolved in 40% ethanol and administered to the rats in Groups 3E and 4CE. For 45 minutes over 6 weeks, a 25 m·min⁻¹ jogging program was applied. After the final exercise session, all the rats in each group were anesthetized with ketamine hydrochloride (50 mg·kg⁻¹) + xylazine HCL (5 mg·kg⁻¹) administered i.p. 24 hours. Blood samples were collected in sterile tubes

without anticoagulant. After centrifugation (1500 g, 10 minutes, 4°C), sera were carefully harvested and stored at -20°C until analysis. After blood sampling, animals were sacrificed by decapitation.

Biochemical parameters

Leptin concentrations were determined by the ELISA technique with commercially available reagents (US-Biological (BioAssay Elisa kit, catalogue no:L1670-30J, USA). Resistin concentrations were determined by the ELISA technique with commercially available reagents (BioVendor, Catalogue no:RD391016200R, USA). Triglyceride, total cholesterol and HDL-C were measured with colorimetric methods in Dimension Xpand auto analyzer (Dade Behring, Siemens, USA) using original Dade Behring reagents. LDL-C values were calculated according to the Friedewald formula: LDL-C= Total cholesterol-[(triglyceride/5)+ HDL]. Lipid parameters were expressed in mg/dL. All analysis was performed in Biochemistry Department of Medical Faculty of Selcuk University.

Statistical analysis

Statistical tests were carried out using SPSS for Windows 10.0. Distribution characteristics were tested with the Shapiro-Wilk test. Due to the fact that the group distributions bear non-parametric characteristics, the multiplex group comparisons were assessed by the Kruskal-Wallis test, and the Mann-Whitney U test was then administered for paired comparisons. Furthermore, the intra-group comparisons of each group regarding their pre- and post-exercise weights were performed by the Wilcoxon Signed Rank Test. Results were given as Mean \pm SD, and $p < 0.05$ was assumed as statistically significant.

Results

The results are presented in Table 1 as Mean \pm SD values. Table 2 presents data related to the weight parameters of the rats.

When Group 2E and Group 3C were compared in terms of cholesterol values, a significant increase was observed in Group 3C compared with Group 2E ($p < 0.01$). When Group 3C and Group 4CE were compared in terms of triglyceride values, a significant increase respectively was found in Group 3C compared with Group 4CE ($p < 0.01$), and in Group 3C compared with Group 2E ($p < 0.01$). Also, weight gain accompanied the increase in triglyceride levels. It was concluded that triglyceride and cholesterol levels decreased to a considerable extent in the exercise groups and concluded that TG and TC were therefore substantially affected by exercise (Table 1).

Table 1. The results of Group I (Sedentary), Group II (Exercise), Group III (Sedentary+ CAPE) and Group IV (Exercise + CAPE). Data are means (\pm SD).

Parameters	Group 1S (n = 10)	Group 2E (n = 10)	Group 3C (n = 10)	Group 4CE (n = 10)
TG (mg·dL ⁻¹)	51.9 (16.0) ^{2,3,4}	38.1 (13.1) ^{1,3}	68.4 (18.4) ^{1,2,4}	41.9 (11.1) ^{1,3}
TC (mg·dL ⁻¹)	38.1 (4.5) ^{2,3,4}	34.2 (4.7) ^{1,3}	44.6 (5.4) ^{1,2,4}	33.1 (7.6) ^{1,3}
HDL-C (mg·dL ⁻¹)	19.9 (2.6) ^{2,3,4}	19.8 (1.9) ¹	22.8 (3.0) ^{1,4}	18.5 (2.4) ^{1,3}
LDL-C (mg·dL ⁻¹)	7.82 (4.45)	6.78 (5.06)	8.12 (4.38)	6.22 (4.91)
Leptin (pg·dL ⁻¹)	645.7 (210.1)	568.5 (106.6)	753.2 (333.9)	498.9 (237.0)
Resistin (ng·dL ⁻¹)	2.32 (.46)	2.35 (.25)	3.16 (2.31)	2.78 (.74)

Superscripts denote significant ($p < 0.05$) differences between the groups.

Table 2. The results of weight gain of Group 1 (Sedentary), Group 2 (Exercise), Group 3 (Sedentary+ CAPE) and Group 4 (Exercise C+ APE) before (BE) and after exercise (AE). Data are means (\pm SD).

Parameters	Group 1S (n = 10)	Group 2E (n = 10)	Group 3C (n = 10)	Group 4CE (n = 10)
B.E. Weight (g)	289.6 (27.5)	251.6 (36.8)	294.6 (29.5)	254.6 (17.1)
A.E. Weight (g)	316.2 (34.2)	285.0 (46.4)	337.0 (23.1)	291.2 (26.8)
Weight gain (g)	26.6 (13.8)	33.4 (17.8)	42.4 (16.9)	36.6 (16.2)
Weight Gain (%)	26.6 (13.8)	13.2 (6.4)	14.8 (6.9)	14.3 (6.3)

Wilcoxon Signed Rank Test: $Z: -2.805$ $P=0.005$

When groups supplemented with CAPE were compared with the other groups in terms of leptin, resistin and lipid parameters, it was concluded that CAPE alone was not effective on these parameters (Table 1).

When Group 3C and Group 4CE were compared in terms of HDL cholesterol values, the HDL values displayed significant differences and were lower in Group 4CE ($p < 0.05$) (Table 1). However, post-exercise body weights of all the animal groups increased compared with their pre-exercise body weights, and a considerably significant weight increase was observed ($p = 0.005$) (Table 2).

Discussion

Obesity is associated with resistance to the actions of leptin, resistin, lipid parameters and insulin via mechanisms that are not yet fully understood. Therefore, the aim of this study was to investigate the effects of exercise, diet and CAPE on leptin, resistin, lipid parameters, and body weight.

Pomerants et al. (2006) investigated the serum leptin levels after acute aerobic exercise of 60 males at different stages of adolescence. The study results revealed no change in leptin level after acute exercise. In a study by Kim et al. (2008), a group of 17 overweight male children were compared with a control group ($n = 9$). The exercise group undertook a 12-week exercise program of 30 minutes walking 2 days a week and 50 minutes on a running band 2 days a week. The leptin levels of the exercise group showed a significant decrease compared to the control group ($p < 0.05$), and reduced leptin levels were determined in the exercise group at the end of the 12-week exercise program in comparison to the beginning. Zoladz et al. (2005) formed a model of 8 healthy non-smoking young males undertook moderate exercise and gave blood samples five minutes before exercise, during exercise, and after exercise. Leptin levels were measured in the blood samples. The hypothesis of these researchers was that plasma leptin and ghrelin levels resulting from hunger and exercise may affect the cardiovascular response. Based on the findings of Zoladz et al. (2005) in the acute exercise model the leptin levels have been shown not to have been affected. Rämson et al. (2008) researched plasma leptin levels during intensive exercise by 8 trained male skiers. The 4-week exercise program consisted of the following: familiarization exercises in week 1, an increase in exercise intensity in weeks 2 and 3, and, in week 4, a decreased of exercise intensity to that of week 1. The exercise was carried out for 2 hours a day, 6 days a week. Two hours before starting the exercise, a carbohydrate-rich meal was eaten by the skiers. At the end of the first, second and fourth weeks, fasting blood

samples were taken before, 5 minutes after and 30 minutes after the exercise. The leptin levels during exercise of the second and third week were statistically significantly low compared to the levels before and after exercise ($p < 0.05$). Kyriazis et al. (2007) applied a single 60-minute moderate exercise session to sedentary obese males and no difference was determined in the measurements of leptin levels taken 24 and 48 hours after exercise. This showed that a single 60-minute moderate exercise session did not affect the leptin levels by any significant amount. Koch et al. (2010) demonstrated that leptin resistance, which occurs in obesity, reduces the hypothalamic response to insulin and thereby impairs peripheral glucose homeostasis, contributing to the development of type 2 diabetes. In a study by CUI et al. (2011), leptin repletion resulted in a reversal of the suppression of uncoupling protein 1 levels in brown adipose tissue, indicating an additional role for reducing body fat and leptin during peak lactation. Arikan et al. (2008) measured plasma leptin levels of athletes doing weight training, and the leptin levels of the control group were found to be higher than those of the athletes ($p < 0.01$). This study demonstrated that the sedentary control group had higher leptin levels compared with the exercise group. Kelly et al. (2007) could not find any difference between the levels of blood adipokines such as leptin and resistin in a sedentary group and in a group of 19 obese children involved in an 8-week aerobic exercise program. They concluded that 8-week exercise alone does not make any significant difference in leptin and resistin levels. Murakami et al. (2007) also evaluated blood leptin levels of two obese groups, both subject to diet restriction but only one following an exercise program. This study revealed that after a 60-minute aerobic exercise program three days a week for 12 weeks, leptin levels decreased after exercise in both groups ($p < 0.001$, $p < 0.004$), and this decrease was higher in the group with the combination of diet restriction and exercise. This demonstrates that diet restriction is effective on leptin levels and that, when diet restriction is accompanied by exercise, this effect becomes more evident. Christ et al. (2006) administered a 3-hour exercise program to 11 healthy athletes and measured leptin levels by taking blood samples at 15, 45, 80, 110, 130 and 180 minutes. A decrease was determined in the leptin concentrations ($p < 0.03$) after a 3-hour exercise session. Similar to the above-mentioned study results, the present study revealed a significant decrease in leptin levels at the end of the exercise program. It was concluded that exercise has a considerable effect on leptin levels.

Kondo et al. (2006) investigated the effect of exercise on the adipokine levels in the circulation of young obese women. Eight young obese students underwent a 30-60 minute exercise program 4-5 days a week for 7

months, and 8 control students did not perform any exercise. The body weight and leptin levels of the obese participants were found to be considerably higher than those in the control group ($p < 0.01$). Exercise reduced body weight and leptin levels ($p < 0.05$) and increased HDL-C levels ($p < 0.05$) in the obese participants. No significant change was found in TC and TG levels. The study concluded that changes in leptin levels in the circulation contribute to the adjustment of metabolic condition via exercise and that this can be used as an indicator in evaluating the exercise treatment. Kondo et al. (2006) also stated that the evident decrease in both body weight and leptin levels in the circulation suggests that exercise may affect metabolic condition and that this effect can be used as an indicator in evaluating the effects of exercise. Levin et al. (2004) measured weight loss and plasma leptin levels in 42 male rats at the end of a 6-week exercise program. In exercise group, a weight loss of 33% and a decrease of 35% in leptin levels were determined. They also showed that calorie restriction together with exercise is more effective than exercise alone. Kondo et al. (2006) and Levin et al. (2004), Jung et al. (2008) concluded that combined exercise and sibutramine application decreased leptin, resistin, TC, TG and body weight. In that study, the exercise was performed not alone but accompanied by sibutramine, a pharmacological agent that acts as a weight regulator by providing an artificial saturation sensation. Therefore, it is possible that the evident decrease in leptin level resulted from exercise. In conformity with the above-mentioned study results, the present study determined that triglyceride, total cholesterol, HDL-C, LDL-C and leptin values in exercise groups decreased considerably. It was concluded that exercise is effective against various diseases, such as cardiovascular diseases caused by lipid parameters in human and animals.

In recent years there has been some controversy about the physiological role of the effect of resistin on obesity and insulin resistance in mice, rats and humans (Mcternan et al., 2006). Therefore, resistin was selected together with leptin as the other marker substance in the present study. The present study's conformities to and contrasts with previous studies on resistin, exercise and obesity are discussed below.

Pagano et al. (2005) reported that there was a relationship between resistin concentrations and adiposity, which showed that the amount of circulating resistin was related to obesity. In a study by Borst et al. (2005) of visceral skeletal muscle taken from rats, the increase observed in insulin response was most probably due to resistin and IL levels. This suggested that the source of resistin release could be visceral fatty tissue. Moreover, a decrease in serum resistin level caused by removal of visceral fat may play a role in the reversal of insulin resistance. Jung et al. (2008) stated that exercise and sibutramine application decreased resistin levels, and like Jung et al. (2008), Kadoglou et al. (2007) reported that 45-60-minutes of exercise 4 times a week for 16 weeks decreased resistin levels. However, certain studies such as Giannopoulou et al. (2005), Kelly et al. (2007), Rokling-Anderson et al. (2007), Shadid et al. (2006), Monzillo et al. (2003) and Jamurta et al. (2006), have reported the contrary result that exercise does not affect resistin levels.

As in these study results, in our chronic exercise model, resistin levels were determined to remain unaffected. Gouni et al. (2008) measured serum leptin, resistin and lipid levels after 14 days of simvastatin and ezetimibe treatment on healthy people. In that study, people were divided into three groups: Group 1S received only statin, Group 2E received only ezetimibe and Group 3C received both. A significant decrease was observed in LDL-C levels, while no significant change was found in leptin and resistin levels. Jung et al. (2008) also investigated the change of adipocytokines before and after weight loss in obese subjects. Sibutramine treatment was administered along with a 12-week exercise program on 28 obese patients who were attending obesity clinics and were on calorie-restricted diets. At the end of 12 weeks, similar to the present study results, total cholesterol ($p < 0.001$) and triglyceride ($p < 0.007$) levels were reported to have decreased. In the present study, when Group 2E and Group 3C were compared in terms of total cholesterol values respectively, a significant increase ($p < 0.01$) was observed in Group 3C compared with Group 2E, and a significant increase ($p < 0.05$) was observed in Group 3C compared with Group 4CE. With respect to triglyceride values, when Group 3C and Group 4CE were compared, a significant increase ($p < 0.01$) was observed in Group 3C compared with Group 4CE, and a significant increase ($p < 0.01$) was observed in Group 3C compared with Group 2E. Weight gain accompanied the increase in the triglyceride levels. It was concluded that triglyceride and total cholesterol decreased in the exercise groups to a considerable extent and that TG and TC were substantially affected by exercise. When Group 3C and Group 4CE were compared with respect to HDL-C values, they were found to be significantly lower in Group 4CE ($p < 0.05$).

As a result, in the present study, it was determined that exercise and CAPE caused no significant change in resistin levels. The exercise was substantially effective on leptin and lipid parameters. When pre- and post-exercise body weights of all animal groups were compared, in all groups, a significant weight gain was observed ($p = 0.005$, despite the exercise). This result was thought to arise from the without diet restriction in the rats.

Conclusion

Our study revealed that CAPE was not effective on weight control, lipid parameters, and adipokine substances such as leptin and resistin, but that exercise was considerably effective on leptin and lipid parameters. However, exercise alone was not sufficient to lose weight and can be effective in weight control only when accompanied by a restricted diet. Exercise with a restricted diet will be especially useful for people with diseases of the heart-circulatory system, high cholesterol and obesity to continue their lives in a healthy way.

Acknowledgments

The study was supported by Selcuk University.

References

Arikan, S., Akkus, H., Halifeoglu, I. and Baltaci, AK. (2008) Compari-

- son of plasma leptin and zinc levels in elite athletes and sedentary people. *Cell Biochemistry Function* **26**, 655-658.
- Borst, S.E.i Conover, C.F. and Bagby, G.J. (2005) Association of resistin with visceral fat and muscle insulin resistance. *Cytokine* **32**, 39-44.
- Christ, E.R., Zehnder, M., Boesch, C., Trepp, R., Mullis, P.E., Diem, P. and Décombaz, J. (2006) The effect of increased lipid intake on hormonal responses during aerobic exercise in endurance-trained men. *European Journal of Endocrinology* **154**, 397-403.
- Cui, J.G., Tang, G.B., Wang, D.H. and Speakman, J.R. (2011) Effects of leptin infusion during peak lactation on food intake, body composition, litter growth and maternal neuroendocrine status in female Brandt's voles. *American Journal of Physiology* **300**, 447-459.
- Giannopoulou, I., Fernhall, B., Carhart, R., Weinstock, R.S., Baynard, T., Figueroa, A. and Kanaley, J.A. (2005) Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metabolism* **54**, 866-875.
- Gouni-berthold, I., Berthold, H.K., Chamberland, J.P., Krone, W. and Mantzoros, C.S. (2008) Short-term treatment with ezetimibe, simvastatin or their combination does not alter circulating adiponectin, resistin or leptin levels in healthy men. *Clinical Endocrinology* **68**, 536-541.
- Gurel, A., Armutcu, F., Hosnuter, M., Unalacak, M., Kargi, E. and Altinyazar, C. (2004) Caffeic acid phenethyl ester improves oxidative organ damage in rat model of thermal trauma. *Physiological Research* **53**, 675-682.
- Gutin, B., Ramsey, L., Barbeau, P., Cannady, W., Ferguson, M., Litaker, M. and Owens, S. (1999) Plasma leptin concentrations in obese children: changes during 4-mo periods with and without physical training. *American Journal of Clinical Nutrition* **69**, 388-394.
- Hepsen, I.F., Bayramlar, H., Gülteke, A., Ozen, S. and Evereklioglu, T.F. (1997) Caffeic acid phenethyl ester to inhibit posterior capsule opacification in rabbits. *Journal of Cataract & Refractive Surgery* **23**, 1572-1576.
- Ilhan, A., Koltuksuz, U., Ozen, S., Uz, E., Ciralik, H. and Akyol, O. (1999) The effects of caffeic acid phenethyl ester (CAPE) on spinal cord ischemia/reperfusion injury in rabbits. *European Journal of Cardio-Thoracic Surgery* **16**, 458-463.
- Jamurtas, A.Z., Theocharis, V., Koukoulis, G., Stakias, N., Fatouros, I.G., Kouretas, D. and Koutedakis, Y. (2006) The effects of acute exercise on serum adiponectin and resistin levels and their relation to insulin sensitivity in overweight males. *European Journal of Applied Physiology* **97**, 122-126.
- Jung, S.H., Park, H.S., Kim, K.S., Choi, W.H., Ahn, C.W., Kim, B.T., Kim, S.M., Lee, S.Y., Ahn, S.M., Kim, Y.K., Kim, H.J., Kim, D.J. and Lee, K.W. (2008) Effect of weight loss on some serum cytokines in human obesity: increase in IL-10 after weight loss. *Journal of Clinical Biochemistry & Nutrition* **19**, 371-375.
- Kadoglou, N.P., Perrea, D., Iliadis, F., Angelopoulou, N., Liapis, C. and Alevizos, M. (2007) Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. *Diabetes Care* **30**, 719-721.
- Kelly, A.S., Steinberger, J., Olson, T.P. and Dengel, D.R. (2007) In the absence of weight loss, exercise training does not improve adipokines or oxidative stress in overweight children. *Metabolism* **56**, 1005-1009.
- Kim, H.J., Lee, S., Kim, T.W., Kim, H.H., Jeon, T.Y., Yoon, Y.S., Oh, S.W., Kwak, H. and Lee, J.G. (2008) Effects of exercise-induced weight loss on acylated and unacylated ghrelin in overweight children. *Clinical Endocrinology* **68**, 416-422.
- Kraemer, R.R., Chu, H. and Castracane, V.D. (2002) Leptin and exercise. *Experimental Biology and Medicine* **227**, 701-708.
- Kraemer, R.R. and Castracane, V.D. (2007) Exercise and humoral mediators of peripheral energy balance: and adiponectin. *Experimental Biology and Medicine* **232**, 184-194.
- Koch, C., Augustine, R.A., Steger, J., Ganjam, G.K., Benzler, J., Pracht, C., Lowe, C., Schwartz, M.W., Shepherd, P.R., Anderson, G.M., Grattan, D.R. and Tups, A. (2010) Leptin rapidly improves glucose homeostasis in obese mice by increasing hypothalamic insulin sensitivity. *Journal of Neuroscience* **30**, 16180-16187.
- Koksel, O., Ozdulger, A., Tamer, L., Cinel, L., Ercil, M., Degirmenci, U., Unlu, S. and Kanik, A. (2006). Effects of caffeic acid phenethyl ester on lipopolysaccharide-induced lung injury in rats. *Pulmonary Pharmacology and Therapeutics* **19**, 90-95.
- Koltuksuz, U., Ozen, S., Uz, E., Aydinc, M., Karaman, A., Gülteke, A., Akyol, O., Gürsoy, M.H. and Aydin, E. (1999). Caffeic acid phenethyl ester prevents intestinal reperfusion injury in rats. *Journal of Pediatric Surgery* **34**, 1458-1462.
- Kondo, T., Kobayashi, I. and Murakami, M. (2006) Effect of exercise on circulating adipokine levels in obese young women. *Endocrine Journal* **53**, 189-195.
- Kyriazis, G.A., Caplan, J.D., Lowndes, J., Carpenter, R.L., Dennis, K.E., Sivo, S.A. and Angelopoulos, T.J. (2007) Moderate exercise-induced energy expenditure does not alter leptin levels in sedentary obese men. *Clinical Journal of Sport Medicine* **17**, 49-51.
- Levin, B.E. and Dunn-Meynell, A.A. (2004) Chronic exercise lowers the defended body weight gain and adiposity in diet-induced obese rats. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* **286**, R771-778.
- McTernan, P.G., Kusminski, C.M. and Kumar, S. (2006) Resistin. *Current Opinion in Lipidology* **17**, 170-175.
- Monzillo, L.U., Hamdy, O., Horton, E.S., Ledbury, S., Mullooly, C., Jarema, C., Porter, S., Ovalle, K., Moussa, A. and Mantzoros, C.S. (2003) Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obesity Research* **11**, 1048-1054.
- Murakami, T., Horigome, H., Tanaka, K., Nakata, Y., Katayama, Y. and Matsui, A. (2007) Effects of diet with or without exercise on leptin and anticoagulation proteins levels in obesity. *Blood Coagulation & Fibrinolysis* **18**, 389-394.
- Natarajan, K., Singh, S., Burke, T.R., Grunberger, D. and Aggarwal B.B. (1996) Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF- κ B. *Proceedings of the National Academy of Sciences of the United States of America* **93**: 9090-9095.
- Orhan, H., Marol, S., Hepsen, I.F. and Sahin, G. (1999) Effects of some probable antioxidants on selenium-induced cataract formation and oxidative stress-related parameters in rats. *Toxicology* **139**, 219-232.
- Ozer, M.K., Cicek, E., Gokalp, O., Koyu, A., Parlakpınar, H. and Acet, A. (2005) Myokardiyal iskemi reperfüzyon sonrası böbrek hasarında nitrik oksit rolü ve CAPE'nin etkisi. *Süleyman Demirel Üniversitesi Tıp Fakültesi Dergisi* **12**, 23-27. (In Turkish).
- Pagano, C., Marin, O. and Calcagno, A. (2005) Increased serum resistin in adults with Prader-Willi syndrome is related to obesity and not to insulin resistance. *The Journal of Clinical Endocrinology & Metabolism* **90**, 4335-4340.
- Pomerants, T., Tillmann, V., Karelson, K., Jürimäe, J. and Jürimäe, T. (2006) Ghrelin response to acute aerobic exercise in boys at different stages of puberty. *Hormone and Metabolic Research* **38**, 752-757.
- Pasman, W.J., Westterterp-Plantenga, M.S. and Saris, W.H.M. (1998) The effect of exercise training on leptin levels in obese males. *American Journal of Physiology-Endocrinology and Metabolism* **274**, E280-E286.
- Rämson, R., Jürimäe, J., Jürimäe, T. and Mäestu, J. (2008) The influence of increased training volume on cytokines and ghrelin concentration in college level male rowers. *European Journal of Applied Physiology* **104**, 839-846.
- Reseland, J.E., Anderssen, S.A., Solvoll, K., Hjermann, I., Urdal, P., Holme, I. and Drevon C. (2001) Effect of long-term changes in diet and exercise on plasma leptin concentrations. *American Journal of Clinical Nutrition* **73**, 240-245.
- Rokling-Andersen, M.H., Reseland, J.E., Veierød, M.B., Anderssen, S.A., Jacobs, J.R., Urdal, P., Jansson, J.O. and Drevon, C.A. (2007) Effects of long-term exercise and diet intervention on plasma adipokine concentrations. *American Journal of Clinical Nutrition* **86**, 1293-1301.
- Shadid, S., Stehouwer, C.D. and Jensen, M.D. (2006) Diet/Exercise versus pioglitazone: effects of insulin sensitization with decreasing or increasing fat mass on adipokines and inflammatory markers. *The Journal of Clinical Endocrinology and Metabolism* **91**, 3418-3425.
- Sud'ina, G.F., Mirzoeva, O.K., Pushkareva M.A., Korshunova G.A., Sumbatyan N.V. and Varfolomeev, S.D. (1993). Caffeic acid phenethyl ester as a lipoxigenase inhibitor with antioxidant properties. *FEBS Lett.* **329**:21-24.
- Uz, E., Sogut, S., Sahin, S., Var, A., Ozyurt, H., Gülec, M. and Akyol, O. (2002) The protective role of caffeic acid phenethyl ester (CAPE) on testicular tissue after testicular torsion and detorsion. *World Journal of Urology* **20**, 264-270.

- Yilmaz, H.R., Uz, E., Yucel, N., Altuntas, I. and Ozcelik, N. (2004). Protective effect of caffeic acid phenethyl ester (CAPE) on lipid peroxidation and antioxidant enzymes in diabetic rat liver. *Journal of Biochemical and Molecular Toxicology* **18**, 234-238.
- Zoladz, J.A., Konturek, S.J., Duda, K., Majerczak, J., Sliwowski, Z., Grandys, M. and Bielanski, W. (2005) Effect of moderate incremental exercise, performed in fed and fasted state on cardio-respiratory variables and leptin and ghrelin concentrations in young healthy men. *Journal of Physiology and Pharmacology* **56**, 63-85.

Key points

- Caffeic acid phenethyl ester is not effective on weight control, lipid parameters, and adipokine substances such as leptin and resistin.
- Exercise can be effective in weight control only when accompanied by a restricted diet.

AUTHORS BIOGRAPHY

Ayse ALP

Employment

Diyarbakir Training and Research Hospital, Biochemistry Department, Diyarbakir, Turkey

Degree

MD

Research interests

Exercise models, hormones and humoral mediators

E-mail: drayseozcan@gmail.com

Sadik BUYUKBAS

Employment

Department of Biochemistry, Meram Medical Faculty, Selcuk University, Konya, Turkey

Degree

MD

Proteins, enzymes and hormones.

E-mail: drsadik56@gmail.com



Harun ALP

Employment

Department of Pharmacology and Toxicology, Veterinary Faculty, Dicle University, Diyarbakir, Turkey

Degree

PhD

Research interests

Acute-subacute-chronic-subchronic toxicity, bioequivalence and enzymes and hormones.

E-mail: alpharun@gmail.com

H. Serdar GERGERLIOGLU

Employment

Department of Physiology, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey

Degree

MD

E-mail: gergerlioglu@gmail.com

Mehmet OZ

Employment

Department of Physiology, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey

Degrees

PhD

M. Kemal BASARALI

Employment

Department of Biochemistry, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Degrees

PhD

Research interests

Proteins, enzymes and hormones

E-mail: kemalbasarali@yahoo.com

Aysel KIYICI

Employment

Department of Biochemistry, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey

Degree

MD

✉ Dr. Harun ALP

Department of Pharmacology and Toxicology, Veterinary Faculty, Dicle University, Diyarbakir, Turkey