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The effect of short-term perindopril and telmisartan treatment on circulating levels of anti-inflammatory cytokines in hypertensive patients

Wpływ krótkotrwałego leczenia peryndoprylem lub telmisartanem na stężenie cytokin przeciwzapalnych u osób z nadciśnieniem tętniczym

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Abstract

Introduction: Both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were found to reduce plasma levels of proinflammatory cytokines. No previous study has compared their effect on the production of anti-inflammatory cytokines.
Material and methods: The study enrolled 52 patients with grade 1 and grade 2 arterial hypertension. The participants were divided into two groups treated with either perindopril (4 mg daily) or telmisartan (40 mg daily). Blood pressure, plasma lipids, glucose homeostasis markers, as well as plasma levels of uric acid, interleukins 4, 10, 13 (IL-4, IL-10, IL-13), and high sensitivity C-reactive protein (hsCRP) were measured at the beginning of the study and six weeks later.
Results: Both perindopril and telmisartan reduced systolic (SBP) and diastolic blood pressure (DBP). Although both agents increased serum levels of IL-10, this effect was more pronounced in patients treated with telmisartan. Neither telmisartan nor perindopril affected circulating levels of uric acid, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, IL-4, IL-13, and hsCRP. The effect of telmisartan on IL-10 slightly correlated with an improvement in insulin sensitivity. Treatment-induced changes in IL-10 did not correlate with hypotensive properties of perindopril and telmisartan.
Conclusions: The obtained results indicate that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers administered for a short period of time produce a relatively week effect on anti-inflammatory cytokines, limited to IL-10, and stronger for telmisartan than for perindopril. **(Endokrynol Pol 2018; 69 (6): 667–674)**

Key words: *anti-inflammatory cytokines; angiotensin-converting enzyme inhibitors; angiotensin II receptor blockers; arterial hypertension; low-grade systemic inflammation*

Streszczenie

Wstęp: Zarówno inhibitory konwertazy angiotensyny, jak i antagoniści receptora dla angiotensyny II zmniejszają stężenie cytokin o działaniu prozapalnym. Dotychczas nie porównywano wpływu obu grup leków na poziomie cytokin o działaniu przeciwzapalnym.
Materiał i metody: Badaniem objęto populację 52 osób z nadciśnieniem tętniczym 1. i 2. stopnia. Uczestników badania przydzielono do dwóch grup badawczych, leczonych odpowiednio perindoprilem (4 mg dziennie) lub telmisartanem (40 mg dziennie). Ciśnienie tętnicze, profil lipidowy, markery gospodarki węglowodanowej, a także stężenie kwasu moczowego, interleukin 4, 10, 13 (IL-4 , IL-10, IL-13) oraz białka C-reaktywnego (hsCRP) oceniono na początku badania oraz 6 tygodni później.
Wyniki: Zarówno perindopril, jak i telmisartan spowodowały spadek ciśnienia tętniczego. Chociaż oba leki podwyższały stężenie IL-10, wpływ ten był bardziej wyrażony w grupie leczonej telmisartanem. Żaden z badanych leków nie wpływał na stężenie kwasu moczowego, glukozy, cholesterolu całkowitego, cholesterolu frakcji LDL, cholesterolu frakcji HDL, triglicerydów, IL-4, IL-13 oraz hsCRP. Wpływ telmisartanu na stężenie IL-10 w umiarkowanym stopniu korelował z poprawą wrażliwości na insulinę, lecz nie z siłą hipotensyjnego działania obu ocenianych leków.
Wnioski: Uzyskane wyniki sugerują, że inhibitory konwertazy angiotensyny i antagoniści receptora dla angiotensyny II stosowane krótkotrwale powodują stosunkowo nieznaczny wpływ na stężenie cytokin przeciwzapalnych, ograniczony do wzrostu stężenia IL-10, silniej wyrażonego w przypadku stosowania telmisartanu niż perindoprilu. **(Endokrynol Pol 2018; 69 (6): 667–674)**

Słowa kluczowe: *cytokiny przeciwzapalne; inhibitory konwertazy angiotensyny; antagoniści receptora dla angiotensyny II; nadciśnienie tętnicze; przewlekły stan zapalny o niewielkim nasileniu*

Introduction

Arterial hypertension is regarded as the most common cardiovascular disease and the main risk factor for stroke, peripheral arterial disease, arterial aneurysms, and kidney disease [1, 2]. Despite affecting a large proportion of the population, its aetiology remains poorly defined [2]. In addition to established roles of

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the vasculature, kidneys, and central nervous system, there is mounting evidence that arterial hypertension may be related to chronic low-grade inflammation [3]. Both innate and adaptive immune responses seem to play an important role in the pathogenesis of hypertension [4]. Through the generation of inflammatory cytokines and reactive oxygen species, macrophages can directly impair vasculature endothelial and smooth muscle function, leading to vasoconstriction and resultant hypertension [5]. In turn, imbalance of distinct functions of T-cell subsets could be an initiating event in the pathogenesis of hypertension [6]. Patients with arterial hypertension are characterised by higher levels of tumour necrosis factor-α (TNF-α) [7], interleukin 6 (IL-6) [7], and high-sensitivity C-reactive protein (hsCRP) [8] even after adjustment for numerous confounding factors (age, sex, body mass index, waist-hip ratio, family history of hypertension, plasma lipids, glucose, and other inflammatory markers). Moreover, a proinflammatory state was found to precede blood pressure elevation, suggesting its causative role in the development of arterial hypertension [9].

Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (sartans) are considered as first-line treatment for arterial hypertension [10]. The clinical benefits resulting from their use cannot be explained exclusively by hypotensive properties but also by so-called "pleiotropic effects" [11]. ACE inhibitors and angiotensin II receptors blockers were found to exert anti-inflammatory, immunomodulatory, and antioxidant effects, improve the functioning of vascular endothelium, as well as regulate the growth and migration of smooth muscle cells [11–14]. Moreover, ACE inhibitors produce antithrombotic, profibrinolytic, and anti-aggregatory effects [15].

Inflammation is characterised by an interplay between pro- and anti-inflammatory cytokines [16]. The latter ones are a series of immune regulatory molecules acting mainly by the inhibition of the production of proinflammatory cytokines and/or by counteracting many biological effects of proinflammatory cytokines [16–18]. Unfortunately, studies investigating pleiotropic effects of hypotensive agents have concentrated on their action on low-grade systemic inflammation and on proinflammatory cytokines [19, 20]. Therefore, the aim of the present study was to compare the impact of an ACE inhibitor (perindopril) and an angiotensin-receptor blocker (telmisartan) on serum levels of anti-inflammatory cytokines. Interleukin 4 (IL-4), interleukin 10 (IL-10), and interleukin 13 (IL-13) were selected for study because they are major anti-inflammatory cytokines [21], while monocytes/macrophages and T lymphocytes, being key components of atherosclerotic plaque, are regarded as a rich source of these cytokines [17, 22]. We also measured hsCRP levels, which are considered to be a highly sensitive marker of low-grade systemic inflammation [23].

Material and methods

Patients

The participants of the study were selected among adult patients (aged 20–50 years) with pharmacologically-untreated European Society of Cardiology/European Society of Hypertension grade 1 or 2 arterial hypertension, who had been initially supervised and eventually treated non-pharmacologically by community-based healthcare providers. To be admitted to the study, patients with grade 1 arterial hypertension were required to have no more than two risk factors and, on the day of appointment, systolic blood pressure (SBP) in the range between 140 and 159 mm Hg and/or diastolic blood pressure (DBP) in the range between 90 and 99 mm Hg, despite complying with the lifestyle modification for at least three months before the beginning of the study. Patients with grade 2 hypertension (SBP: 160 and 179 mm Hg and/or DBP: 99 and 109 mm Hg) were included shortly after being diagnosed, and non-pharmacological interventions were not implemented before the study onset.

The subjects were excluded if they met at least one of the following criteria: grade 3 arterial hypertension, secondary arterial hypertension, diabetes, congestive heart failure, any form of coronary artery disease, stroke within six months preceding the study, impaired renal or hepatic function, malabsorption syndrome, any acute and chronic inflammatory processes, or autoimmune disorders. We also excluded patients treated with any hypotensive agents, glucocorticoids, or non-steroidal anti-inflammatory drugs, as well as with drugs known to interact with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Study design

The study was performed in accordance with the 1964 Helsinki Declaration, and the protocol was accepted by the local Ethics Committee. All included patients gave written, informed consent to participate in the study. All participants were then treated with either telmisartan (40 mg daily; n = 26) or perindopril (4 mg; n = 26). Both telmisartan and perindopril were administered once daily in the morning for six weeks without any changes in dosage during the entire study period. All participants were also required to comply with dietary recommendations (total fat intake < 30% of total energy intake, saturated fat intake < 7% of energy consumed, cholesterol intake < 200 mg per day, increase in fibre intake to 15 g per 1000 kcal) and were encouraged to

Table I. *Baseline characteristics of patients*
Tabela I. *Wyjściowa charakterystyka uczestników badania*

Variable	Perindopril	Telmisartan	Difference [95% CI]
Number of patients [n]	26	26	—
Age [years; mean (SD)]	45 (10)	49 (12)	4 [–2, 10]
Women (%)	35	31	–4 [–28, 20]
Smokers (%)	38	31	–7 [–31, 17]
BMI [kg/m^2; mean (SD)]	27.8 (3.9)	28.1 (4.3)	0.3 [–2.0, 2.6]
Waist circumference [cm; mean (SD)]	93 (11)	98 (11)	5 [–1, 11]
Grade 1/grade 2 arterial hypertension (%)	15/85	19/81	4 [–17, 25]
Prediabetes (%)	50	42	–8 [–32, 16]
Metabolic syndrome (%)	42	54	12 [–14, 36]
SBP [mm Hg; mean (SD)]	149 (12)	154 (15)	5 [–3, 13]
DBP [mm Hg; mean (SD)]	90 (8)	93 (7)	3 [–1, 7]
Total cholesterol [mg/dL; mean (SD)]	230 (38)	231 (48)	1 [–23, 25]
LDL cholesterol [mg/dL; mean (SD)]	145 (37)	148 (40)	3 [–18, 24]
HDL cholesterol [mg/dL; mean (SD)]	55 (11)	53 (13)	–2 [–9, 5]
Triglycerides [mg/dL; mean (SD)]	139 (107)	152 (82)	13 [–40, 66]
Glucose [mg/dL; mean (SD)]	97 (7)	101 (15)	4 [–2, 10]
HOMA1-IR [mean (SD)]	2.6 (1.1)	3.1 (1.9)	0.5 [–0.4, 1.4]
Uric acid [mg/dL; mean (SD)]	5.8 (1.4)	6.1 (1.1)	0.3 [–0.4, 1.0]
hsCRP [mg/dL; mean (SD)]	1.24 (1.76)	1.78 (1.70)	0.54 [–0.73, 1.81]
IL-4 [pg/ml; mean (SD)]	4.47 (1.05)	4.39 (0.96)	–0.08 [–0.64, 0.48]
IL-10 [pg/ml; mean (SD)]	13.63 (2.39)	14.55 (3.25)	0.92 [–0.67, 2.51]
IL-13 [pg/ml; mean (SD)]	34.31 (19.75)	30.38 (16.81)	–3.93 [–14.14, 6.28]

SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; LDL — low density lipoprotein; HDL — high density lipoprotein; HOMA1-IR — homeostasis model assessment 1 of insuline resistance index; hsCRP — high sensitivity C-reactive protein; IL — interleukin; CI — confidence interval

take moderate to vigorous exercise for at least 30 min per day. Compliance with medication usage was assessed at each visit by interrogation and pill count. Blood pressure was measured in a sitting position using standard cuff equipment. They were determined during Korotkoff sounds 1 and 5. All measurements were made on the left arm. The values used in statistical analyses were the means of three measurements taken at intervals of at least 5 min, starting 15 min after the patient had sat down.

Laboratory assays

Laboratory assays were performed at the beginning of the study and after six weeks of treatment. Before blood collection, the participants had been resting in a quiet room for at least 30 min in the seated position. To avoid diurnal variations in the parameters studied, all blood samples were taken between 8.00 and 9.00 a.m. after a 12-h overnight fast in a quiet, temperature-controlled room (24–25°C). To minimise analytical errors, all measurements were performed in duplicate within a single analytical session, and final results were averaged. Plasma lipids [(total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides], glucose, and uric acid were measured with standard methods using commercial kits (Roche Diagnostics, Basel, Switzerland). Plasma levels of insulin were assessed by the electro-chemiluminescence method (Roche Diagnostics, Basel, Switzerland). Circulating levels of hsCRP were assessed by immunoturbidimetry (Roche Diagnostics, Basel, Switzerland). Plasma levels of IL-4, IL-10, and IL-13 were determined using commercial enzyme-linked immunosorbent assay kits (Diaclone, Besancon, France) according to the manufacturer's instructions. Insulin resistance was assessed using the homeostasis model assessment 1 of insulin resistance index (HOMA1-IR) by the following formula: insulin resistance = plasma insulin [mIU/L] × plasma glucose [mg/dL]/405. The intra- and interassay coefficients of variation in our laboratory were as follows: total cholesterol — 2.5 and 3.3%; LDL cholesterol — 2.3 and

3.9%; HDL cholesterol — 2.6 and 3.6%; triglycerides — 3.9 and 4.9%; glucose — 2.0 and 3.4%; insulin — 4.1 and 5.9%; uric acid — 3.7 and 4.8%; hsCRP — 3.9 and 5.2%; IL-10 — 4.3 and 6.3%; IL-4 — 9.2 and 13.7%; and IL-13 — 4.8 and 14.3%.

Statistical analysis

The Shapiro-Wilk test was used to determine whether the data were distributed normally. To achieve approximately normal distribution, skewed variables (triglycerides, HOMA1-IR, hsCRP, and hormones) were natural log-transformed. Comparisons between the groups were performed using Student's *t*-test for independent samples. The differences between the means of variables within the same treatment group were analysed with Student's paired *t*-test. For categorical variables, the χ^2 test was used. The clinical importance of the result was assessed based on the 95% confidence interval (CI). The relationship between the measured variables was calculated using Pearson's *r*-tests. Differences were regarded as statistically significant if 95% confidence intervals did not include the null value and/or two-tailed p values were below 0.05.

Results

At the beginning of the study, both groups were comparable with respect to sex, age, smoking, body mass index, waist circumference, medical history, and insulin sensitivity, as well as to circulating levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, uric acid, hsCRP, IL-4, IL-10 and IL-13 (Table I). No serious adverse effects were reported during the study period, and all patients completed the study.

Expectedly, both agents administered for six weeks reduced SBP and DBP, with no difference between both agents (Table II). Telmisartan and perindopril increased serum IL-10 levels but did not change glucose, HOMA1-IR, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, hsCRP, IL-4, and IL-13. Both drugs had a neutral effect on body mass index and waist circumference. Between-group comparisons showed that treatment-induced changes in IL-10 were more pronounced, while post-treatment levels of this interleukin were higher in patients treated with telmisartan than in patients receiving perindopril. Moreover, there were differences between the action of both drugs on HOMA1-IR. At the end of the study period, there were no differences between both treatment arms in blood pressure, plasma lipids, glucose homeostasis markers, uric acid, hsCRP, IL-4, and IL-13 (Table II).

At the beginning of the study, there were correlations between: a) IL-10 and SBP ($r = –0.35$, $p < 0.05$), glucose levels ($r = –0.40$, $p < 0.05$), and HOMA1-IR ($r = –0.43$, $p < 0.001$); b) IL-4 and DBP ($r = –0.31$, $p < 0.05$), as well as between IL-13 and LDL cholesterol levels ($r = 0.35$, $p < 0.05$). At the end of the study, IL-4 levels still correlated with diastolic blood pressure ($r = –0.46$, $p < 0.001$). Treatment-induced changes in IL-10 did not correlate with the effect of treatment on systolic and diastolic blood pressure. No other correlations were observed.

Discussion

Unlike previous reports concerning proinflammatory cytokines [24–26], the effect of short-term perindopril and telmisartan treatment on anti-inflammatory cytokines was, at most, moderate. The only cytokine, the levels of which was significantly affected by hypotensive therapy, was IL-10. Interestingly, the treatment arms differed in the degree of rise in circulating levels of this cytokine, which cannot be explained by the hypotensive properties of both agents. In line with this view, perindopril and telmisartan reduced SBP and DBP to similar extents, post-treatment values of blood pressure did not differ between perindopril- and telmisartan-treated patients, and the treatment-induced increase in IL-10 did not correlate with the strength of hypotensive action of both drugs. IL-10 was found to produce a multidirectional inhibitory effect on atherogenesis, including a decrease in matrix metalloproteinase activity, pro-inflammatory cytokine release and action, cyclooxygenase-2 expression in lipid-loaded foam cells, and changes in lipid metabolism in macrophages [27]. Considering the important role of IL-10 deficiency in atherogenesis and its complications, the obtained results seem to be clinically relevant. They suggest that telmisartan may be of greater benefit to patients with arterial hypertension than perindopril, despite the fact that perindopril, being a tissue-type ACE inhibitor, was found to exert a much stronger effect than plasma-type ACE inhibitors on monocyte and lymphocyte secretory function and on circulating levels of proinflammatory cytokines [24–26].

In the light of obtained results, it seems reasonable to assume that a more beneficial effect of telmisartan than of perindopril on IL-10 levels may be, at least in part, attributed to differences in the impact of both drugs on insulin sensitivity. Apart from its angiotensin receptor blocker activity, telmisartan was shown to act as a partial agonist for peroxisome proliferator-activated receptor-γ, which is implicated in the regulation of energy homeostasis [28, 29]. In our study, IL-10 was the only cytokine, the levels of which correlated with HOMA1-IR. Moreover, the effect of telmisartan, but not of perindopril, on IL-10 levels correlated with treatment-induced changes in insulin sensitivity. Inter-

Table II. *The effect of short-term perindopril and telmisartan treatment on blood pressure, body mass index, waist circumference, plasma lipids, uric acid, glucose homeostasis markers, low-grade systemic inflammation, and anti-inflammatory cytokine levels in patients with arterial hypertension*

Tabela II. *Wpływ krótkotrwałego leczenia perindoprilem i telmisartanem na wartość ciśnienia tętniczego, wskaźnik masy ciała, obwód talii, profil lipidowy, markery homeostazy węglowodanowej, jak również na stężenie kwasu moczowego, białka C-reaktywnego, interleukiny 4, interleukiny 10 oraz interleukiny 13 u pacjentów z nadciśnieniem tętniczym*

Variable	Perindopril	Telmisartan	Difference (95% CI)
Systolic blood pressure [mm Hg; mean (SD)]			
Baseline	149 (12)	154 (15)	5 [–3, 13]
After 6 months	136 (14)[#]	136 (13)[#]	0 [–8, 8]
Change	–13 (9)	–18 (11)	–5 [–11, 1]
Diastolic blood pressure [mm Hg; mean (SD)]			
Baseline	90 (8)	93 (7)	3 [–1, 7]
After 6 months	84 (7)[#]	85 (8)[#]	1 [–3, 5]
Change	–6 (6)	–8 (7)	–2 [–6, 2]
Body mass index [kg/m2; mean (SD)]			
Baseline	27.8 (3.9)	28.1 (4.3)	0.3 [–2.0, 2.6]
After 6 months	26.7 (6.5)	27.0 (6.7)	0.3 [–3.4, 4.0]
Change	–1.1 (3.5)	–1.1 (3.2)	0.0 [–1.9, 1.9]
Waist circumference [cm; mean (SD)]			
Baseline	93 (11)	98 (11)	5 [–1, 11]
After 6 months	90 (12)	93 (11)	3 [–4, 10]
Change	–3 (8)	-5 (9)	–2 [–7, 3]
Total cholesterol [mg/dL; mean (SD)]			
Baseline	230 (38)	231 (48)	1 [–23, 25]
After 6 months	224 (36)	217 (47)	–7 [–30, 16]
Change	–6 (19)	–14 (24)	–8 [–20, 4]
LDL cholesterol [mg/dL; mean (SD)]			
Baseline	145 (37)	148 (40)	3 [–18, 24]
After 6 months	140 (32)	136 (42)	–4 [–25, 17]
Change	–5 (28)	–12 (30)	–7 [–18, 4]
HDL cholesterol [mg/dL; mean (SD)]			
Baseline	55 (11)	53 (13)	–2 [–9, 5]
After 6 months	54 (10)	56 (18)	2 [–6, 10]
Change	–1 (8)	3 (10)	4 [–1, 9]
Triglycerides [mg/dL; mean (SD)]			
Baseline	139 (107)	152 (82)	13 [–40, 66]
After 6 months	138 (102)	147 (143)	9 [–60, 78]
Change	–1 (43)	–5 (49)	–4 [–30, 22]
Glucose [mg/dL; mean (SD)]			
Baseline	97 (7)	101 (15)	4 [–2, 10]
After 6 months	95 (8)	97 (12)	2 [–4, 8]
Change	–2 (3)	–4 (6)	–2 [–6, 2]
HOMA1-IR [mean (SD)]			
Baseline	2.6 (1.1)	3.1 (1.9)	0.5 [–0.4, 1.4]
After 6 months	2.4 (1.2)	2.6 (1.6)	0.4 [–0.4, 1.2]
Change	–0.2 (0.5)	–0.5 (0.5)	–0.3 [–0.5, –0.1][&]
Uric acid [mg/dL; mean (SD)]			
Baseline	5.8 (1.4)	6.1 (1.1)	0.3 [–0.4, 1.0]
After 6 months	5.7 (1.1)	5.9 (1.0)	–0.2 [–0.4, 0.8]
Change	–0.1 (0.3)	–0.2 (0.4)	–0.1 [–0.3, 0.1]
hsCRP [mg/dL; mean (SD)]			
Baseline	1.24 (1.76)	1.78 (1.70)	0.54 [–0.73, 1.81]
After 6 months	0.97 (1.30)	1.60 (1.64)	0.63 [–0.19, 1.45]
Change	–0.27 (2.18)	–0.18 (0.96)	0.09 [–0.85, 1.03]
IL-4 [pg/mL; mean (SD)]			
Baseline	4.47 (1.05)	4.39 (0.96)	–0.08 [–0.64, 0.48]
After 6 months	4.08 (0.82)	3.89 (0.92)	–0.19 [–0.68, 0.30]
Change	–0.39 (0.47)	–0.50 (0.41)	–0.11 [–0.36, 0.14]

Table II *(cont.). The effect of short-term perindopril and telmisartan treatment on blood pressure, body mass index, waist circumference, plasma lipids, uric acid, glucose homeostasis markers, low-grade systemic inflammation, and anti-inflammatory cytokine levels in patients with arterial hypertension*

Tabela II *(kont.). Wpływ krótkotrwałego leczenia perindoprilem i telmisartanem na wartość ciśnienia tętniczego, wskaźnik masy ciała, obwód talii, profil lipidowy, markery homeostazy węglowodanowej, jak również na stężenie kwasu moczowego, białka C-reaktywnego, interleukiny 4, interleukiny 10 oraz interleukiny 13 u pacjentów z nadciśnieniem tętniczym*

Variable	Perindopril	Telmisartan	Difference (95% CI)
IL-10 [pg/mL; mean (SD)]			
Baseline	13.63 (2.39)	14.55 (3.25)	0.92 [–0.67, 2.51]
After 6 months	15.70 (2.64)#	18.50 (2.88)#	2.80 [1.26, 4.34]*
Change	2.07 (1.21)	3.95 (2.45)	1.88 [0.80, 2.96]§
IL-13 [pg/mL; mean (SD)]			
Baseline	34.31 (19.75)	30.38 (16.81)	–3.93 [–14.14, 6.28]
After 6 months	30.73 (19.99)	27.85 (16.48)	–2.88 [–13.08, 7.32]
Change	–3.58 (3.70)	–2.53 (2.41)	1.05 [–0.69, 2.79]

*statistically significant difference between both groups; #statistically significant difference between post-treatment and baseline values in the same group; §statistically significant difference between the changes in both treatment groups; SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; LDL — low density lipoprotein; HDL — high density lipoprotein; HOMA1-IR — homeostasis model assessment 1 of insuline resistance index; hsCRP — high sensitivity C-reactive protein; IL — interleukin; CI — confidence interval

estingly, insulin-resistant subjects were characterised by lower systemic levels of IL-10 than subjects with normal sensitivity to this hormone [30] and therefore an increase in IL-10 in our subjects, many of whom fulfilled the criteria of metabolic syndrome, may reflect in part an improvement in insulin receptor action. The difference in post-treatment IL-10 in both study arms may also be associated with stimulation of B_1 receptor type by increased amounts of bradykinin, secondary to the inhibitory effect of ACE inhibitors on its breakdown [31]. This explanation is supported by the finding of higher IL-10 levels in bradykinin B_1 receptor knock-out mice than in control wild-type animals, while no similar data are available for B_2 receptors [32]. Finally, unlike ACE inhibitors, decreasing angiotensin II availability to its AT_1 and AT_2 receptors, angiotensin receptor blockers spare AT_2 receptors [33], increasingly recognised as an integrative part of the protective arm of the renin-angiotensin system [34]. The finding that anti-inflammatory actions resulting from AT_2 receptor stimulation were associated with enhanced production of IL-10 [35] seems to be in line with this explanation.

Unlike IL-10, short-term hypotensive therapy produced a neutral effect on IL-4 and IL-13 concentrations. Moreover, neither at baseline nor during treatment did circulating levels of IL-4 and IL-13 correlate with blood pressure. These findings may suggest that neither of the cytokines play an important role in the mechanisms of action of ACE inhibitors and angiotensin II receptor blockers. Taking into account the presence of correlations between IL-4 and diastolic blood pressure, it seems that IL-4 may participate to the development of hypertension rather than be involved in pleiotropic effects of drugs modulating renin-angiotensin-aldosterone system activity. In turn, baseline levels of IL-13 positively correlated with LDL cholesterol. Because in animal studies IL-13 halted the progression of atherosclerosis and promoted plaque stabilisation [36], the obtained results suggest that IL-13 may partially counteract the unfavourable effect of hypercholesterolaemia on the development and/or progression of atherosclerosis and its complications. Both IL-4 and IL-13 share a common receptor signalling pathway (IL-4Rα/IL-13Rα1/STAT6) [37], and therefore their actions partially overlap. Differences in observed correlations may, however, be explained by specific functions of IL-4 and IL-13, being a consequence of engagement of the alternative IL-4Rα/γc and IL-13Rα2 receptors, and/or by differences in ligand affinity for the same IL-4Rα/IL-13Rα1 receptor complex [38–40].

Another interesting finding of our study was that neither perindopril nor telmisartan treatment administered for six weeks had a significant effect on hsCRP levels. Moreover, the impact of treatment on anti-inflammatory cytokines did not correlate with its action on hsCRP, irrespective of whether correlations were assessed at baseline or during treatment. The latter observation is in disagreement with our previous reports, which showed that the changes in proinflammatory cytokines were paralleled by a decrease in hsCRP [24–26, 41]. On the basis of the obtained results, we may draw two conclusions. Firstly, six weeks is a too short a period to reveal systemic anti-inflammatory effects of perindopril and telmisartan. Secondly, circulating levels of hsCRP do not precisely reflect the action of ACE inhibitors and angiotensin II receptor blockers on the production and metabolism of anti-inflammatory cytokines and/or do not contribute to their synthesis and release.

We are aware of some limitations of this study. Firstly, a small number of participants and a short period of treatment limit the statistical significance of the findings. Secondly, it is difficult to answer the question of whether the obtained results can be considered as a class effect of ACE inhibitors and angiotensin II receptor blockers, or as specific to perindopril and telmisartan. Thirdly, because perindopril and telmisartan were used in relatively small doses, it cannot be excluded that their effect would be stronger if they were given in maximal doses. Finally, it is not known whether the impact of perindopril and telmisartan on anti-inflammatory cytokines is similar in patients with coexisting diabetes and/or coronary artery disease, not included in the current study.

Conclusions

In conclusion, although both perindopril and telmisartan reduced SBP and DBP in hypertensive patients, their action on anti-inflammatory cytokines was relatively mild and limited to IL-10. The effect on IL-10, representing a pleiotropic action of both agents, was stronger for telmisartan than perindopril, and this finding suggests that angiotensin II receptor blockers may offer extra benefits in comparison with ACE inhibitors. Because of numerous study limitations, the obtained results should be supported in a larger clinical trial.

Conflict of interest

The authors declare no conflict of interest.

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