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ORIGINAL ARTICLE

Candesartan effect on inflammation in hypertension

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The aim of this study was to evaluate the effect of candesartan on inflammatory biomarkers in hypertensive patients with and without type 2 diabetes mellitus after a standardized oral fat load (OFL). A total of 219 patients were enrolled: 106 patients were assigned to the non-diabetic hypertensive (NH) group, and 113 to the diabetic hypertensive (DH) group. All patients received candesartan therapy for 6 months and underwent a standardized OFL at baseline and after 6 months of therapy. We evaluated systolic blood pressure (SBP) and diastolic blood pressure (DBP), blood glucose (BG), triglycerides (Tg), soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6) and high-sensitivity C reactive protein (Hs-CRP). At baseline, glycated hemoglobin, homeostasis model assessment insulin resistance index, BG, fasting plasma insulin, Tg, sICAM-1, IL-6 and Hs-CRP in the DH group were significantly higher, whereas high-density lipoprotein-cholesterol value was significantly lower compared to NH group. After 6 months of candesartan therapy, sICAM-1, IL-6 and Hs-CRP were significantly lower compared to baseline in both groups; furthermore, there was a significant decrease of SBP and DBP values in both groups. After the OFL administered at baseline, there was an increase of Tg, sICAM-1, IL-6 and Hs-CRP in both groups. After the OFL administered after 6 months of therapy, instead, there was no significant variation of BG, Tg or sICAM-1 value in both groups, whereas there was an increase of IL-6 and Hs-CRP compared to time 0. We observed that candesartan treatment attenuated the inflammatory answer in both groups of patients, even if more efficiently in nondiabetic ones.

INTRODUCTION

Inflammatory processes are largely involved in atherosclerosis development,[1] and they are strongly linked with the cardiovascular disease risk associated to some common conditions as hypertension and insulin resistance.[2]

Angiotensin II may be to a large degree responsible for triggering vascular inflammation by inducing oxidative stress, resulting in upregulation of inflammatory mediators.[3] This phenomenon appears to be particularly evident in patients affected by insulin resistance and its clinical manifestations such as metabolic syndrome and type 2 diabetes mellitus.[4] On the other side, there is increasing evidence that the pharmacological block of angiotensin II receptors leads to an improvement of different inflammatory biomarkers in hypertensive patients,[5] even when associated to metabolic syndrome[6] or with type 2 diabetes mellitus,[7] and this effect could at least partly explain the antiatherosclerotic effect of sartans.[8]

Postprandial hyperlipidemia is a continuous pro-inflammatory stimulus for the vascular wall, partly modulated by the peroxisome proliferator-actived receptorα activation.[9]

The aim of our study is to evaluate the effect of an angiotensin receptor blocker with mild peroxisome proliferator-actived receptor-α-activating action on inflammatory biomarkers in hypertensive patients with and without type 2 diabetes mellitus after a standardized oral fat load (OFL).

METHODS

Study design and patients

This multicenter trial was conducted in the Internal Medicine and Therapeutics Department at University of Pavia, and in the 'G. Descovich' Atherosclerosis Study Center, Internal medicine, Aging and Kidney disease Department at University of Bologna.

We enrolled 219 Caucasian (112 men and 107 women), aged ⩾18 of either sex, hypertensive (non-diabetic hypertensive, NH; defined as sitting systolic blood pressure (SBP) >130 and <180 mm Hg and sitting diastolic blood pressure (DBP) >80 and <100 mm Hg), outpatients; of these, 113 patients were type 2 diabetics (diabetic hypertensive, DH; according to the American Diabetes Association criteria[10] and were required to have been diagnosed as being diabetic for at least 6 months.

Patients with secondary hypertension, history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy were excluded, as were patients with impaired liver function (defined as plasma aminotransferase (aspartate aminotransferase (normal values: 11–39 mU ml^{-1}), and alanine aminotransferase (normal values: 11–34 mU ml^{-1})) and/or γ-glutamyltransferase (normal values: 11–53 mU ml^{-1}), impaired kidney function (defined as serum creatinine level (normal values: 0.6–1.3 mg per

100 ml)) or anemia. Patients with unstable cardiovascular conditions (for example, New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of study enrollment were also excluded. Women who were pregnant, lactating or of childbearing potential while not taking adequate contraceptive precautions were also excluded. Patients with known contra-indications or intolerance to sartans were also not included in the study.

All patients were taking different antihypertensive drugs (30 subjects (13.70%) ACE-inhibitors (17 ramipril (56.67%), 7 perindopril (23.33), 6 enalapril (20.00)); 39 subjects (17.80%) angiotensin II receptor blockers (11 losartan (28.21%), 12 valsartan (30.77%), 8 irbesartan (20.51%), 8 telmisartan (20.51%)); 32 subjects (14.61%) calcium antagonists (32 amlodipine (100%)); 27 subjects (12.33%) diuretics (27 hydrochlorothiazide (100%)); 16 subjects (7.30%) β-blockers (10 metoprolol (62.5%), 6 carvedilol (37.5%)); 12 subjects (5.48%) α-blockers (12 doxazosin (100%))) in monotherapy or in combination therapy.

At the beginning of the study, they stopped their antihypertensive therapy and they took candesartan, 32 mg per day for 6 months. At the beginning and at the end of the study (after candesartan therapy), they underwent also an OFL.

Participants comprised 112 men (51.1%) and 107 women (48.9%). There were no significant differences between centers in sex distribution, age and in hypertension duration.

At entry, type 2 diabetic patients were taking oral hypoglycemic agents (41 (36.28%) patients, sulfonylureas (14 (34.14%) glibenclamide, 19 (46.34%) glimepiride and 8 (19.51%) gliclazide); 53 (46.90%) patients, biguanide (53 (100%) metformin); 30 (26.55%) patients, metiglinide derivatives (18 (60.00%) repaglinide and 12 (40.00%) nateglinide); 82 (72.57%) patients, thiazolidinediones (48 (58.54%) pioglitazone and 34 (41.46%) rosiglitazone) and 21 (18.58%) patients, α-glucosidase inhibitor (21 (100%) acarbose)) in monotherapy or in combination therapy. One hundred and twenty-one patients were taking lipid-lowering drugs, and 146 patients were taking antiaggregation drugs. No change in diet intake or in physical activity throughout the study was recommended.

Suitable subjects, identified from review of case notes and/or computerized clinic registers, were contacted personally or by telephone.

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki Principles. All patients provided written informed consent.

Laboratory methods
Before starting the study, all patients underwent a measurement of body mass index, glycated hemoglobin, blood glucose (BG), fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), lipid profile (total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and triglycerides (Tg)), SBP, DBP, soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6) and high-sensitivity C reactive protein (Hs-CRP).

Venous blood samples were taken for all patients at 12 h overnight fasting state between 0800 and 0900 hours and were drawn into precooled sterile tubes from an indwelling catheter inserted into an antecubital vein and put into a vacutainer system (Becton Dickinson, Meylan Cedex, France) without venous stasis.

We used plasma obtained by addition of Na_2-EDTA (1 mg ml^{-1}) separated from red blood cells by centrifugation at 3000 g for 15 min at 4 °C, immediately then transferred into sterile cryovials (Greiner Labortechnik, Nürtringen, Germany) in aliquots of 1 ml and froze and stored at −80 °C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters. The estimate of insulin resistance was calculated by HOMA-IR with the formula: FPI (μU ml^{-1})×FPG (mmol l^{-1})/ 22.5, as described by Matthews et al.[11]

Blood pressure measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmoman-ometer (Erkameter 3000; ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. Blood pressure was measured by the same investigator at each visit, in the morning, after the patient had rested for

⩾10 min in a quiet room. Three successive blood pressure readings were obtained at 1 min intervals, and the mean of the three readings was calculated.

BG was assayed by glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of variation (CsV) of <2%.[12]

Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV: 4.6 and 7.3%, respectively).[13]

Total cholesterol and Tg levels were determined using fully enzymatic techniques[14,15] on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0 and 2.1% for total cholesterol measurement, and 0.9 and 2.4% for Tg measurement, respectively. High-density lipoprotein-cholesterol level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid[16] intra- and inter-assay CsV were 1.0 and 1.9%, respectively; low-density lipoprotein-cholesterol level was calculated by the Friedewald formula.[17]

IL-6 was determined using commercially available enzyme-linked immuno-sorbent assay kits (R&D Systems, Minneapolis, MN, USA) according to manufacturer's instructions. The intra- and interassay CsV were 4.9 and 7.1%, respectively.[18]

Hs-CRP was measured with use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, DE, USA). The intra- and interassay CsV were 5.7 and 1.3%, respectively.[19]

sICAM-1 was assessed using commercially available enzyme-linked immu-nosorbent assay kits (R&D Systems) according to manufacturers instructions. The intra- and interassay CsV were <10%, respectively.[20]

Body mass index, glycated hemoglobin, BG, FPI, HOMA-IR, SBP, DBP, lipid profile, sICAM-1, IL-6 and Hs-CRP were evaluated at baseline, whereas BG, Tg, sICAM-1, IL-6 and Hs-CRP were evaluated before and after OFL and at the end of the 6 months of candesartan therapy. To evaluate the tolerability assessments, we recorded all adverse events.

OFL test
The fat load was given between 0800 and 0900 hours after a 12-h fast and a 3-day abstention from alcohol intake. Participants were also asked to refrain from heavy exercise during the preceding days. The test drink consisted of 350 ml whipping cream (35% fat), two tablespoons of chocolate-flavored syrup, one tablespoon of granulated sugar and one tablespoon of instant nonfat dry milk. This volume contained 1147 kcal, of which 12% were from protein, 20% from carbohydrate and 68% from fat. It had 472 mg cholesterol and a polyunsatu-rated/saturated ratio of 0.06. A weight-adjusted meal (1 g fat per kg body weight) was served to approximately 400 ml of the mixture. The fat load mixture was consumed within 10 min. After the ingestion of the fat load, subjects were only allowed to drink water during the following 12 h. Blood samples were drawn before and 3, 6, 9 and 12 h after the fat load. Subjects were required to sit in the hospital hall: only standard walk in the hospital perimeter was accepted.

Statistical analysis
Non-parametric tests were used in the statistical analysis of the data because data were not normally distributed (Kolmogorov–Smirnov test). Outcome variables with a skewed distribution were transformed to a log scale before statistical testing. A two-way repeated measures analysis of variance was performed to assess overall differences in postprandial responses. The Bonfer-roni correction for multiple comparisons was carried out.[21] The incremental area under the curve was calculated as the increased response above baseline minus any drop below baseline, based on the trapezoid rule.[22] Differences over time and association between BG and Tg levels with other variables were evaluated with stepwise multiple linear regression analysis. A P-value of less than 0.05 was considered statistically significant. All tests were two-sided. Statistical 6.0 (Statsoft, Tulsa, OK, USA) was used for statistical computations. All results are expressed as means ± standard deviation.

RESULTS
Study sample at baseline
A total of 219 patients (112 men and 107 women) were enrolled in the study. At baseline glycated hemoglobin, HOMA-IR, BG, FPI, Tg,

Table 1 Patients characteristics at baseline in NH and DH group

	NH	DH
n	106	113
Sex (M/F)	54/52	58/55
Age (years)	57 ± 8	59 ± 10
Hypertension duration (years)	6 ± 3	5 ± 2
Diabetes duration (years)	—	7 ± 3
Height (m)	1.69 ± 0.05	1.68 ± 0.04
Weight (kg)	76.8 ± 7.6	76.5 ± 7.2
BMI (kg m^{-2})	26.9 ± 1.2	27.1 ± 1.3
HbA$_{1c}$ (%)	5.2 ± 0.3	7.4 ± 0.8**
BG (mg per 100 ml)	90.6 ± 7.2	136.2 ± 10.5*
FPI (µU ml^{-1})	8.7 ± 2.7	20.2 ± 5.8*
HOMA index	1.96 ± 0.34	6.85 ± 1.82**
SBP (mm Hg)	145.8 ± 6.9	143.6 ± 6.5
DBP (mm Hg)	96.3 ± 4.6	94.7 ± 4.1
TC (mg per 100 ml)	195.4 ± 16.2	191.2 ± 15.4
LDL-C (mg per 100 ml)	127.1 ± 10.2	122.1 ± 9.1
HDL-C (mg per 100 ml)	49.3 ± 7.5	39.7 ± 3.8*
Tg (mg per 100 ml)	94.8 ± 21.6	146.9 ± 39.7*
sICAM-1 (ng ml^{-1})	163.4 ± 28.3	278.2 ± 35.6*
IL-6 (pg ml^{-1})	1.9 ± 0.8	3.3 ± 1.2**
Hs-CRP (mg l^{-1})	1.2 ± 0.3	2.4 ± 1.2*

Abbreviations: BG, blood glucose; BMI, body mass index; DBP, diastolic blood pressure; FPI, fasting plasma insulin; HbA$_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA index, homeostasis model assessment index; Hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; sICAM-1, soluble intercellular adhesion molecule-1; TC, total cholesterol; Tg, triglycerides.
Data are means ± s.d.
*$P<0.05$ vs. NH; **$P<0.01$ vs. NH.

Table 2 Baseline values in NH and DH patients and after 6 months of candesartan therapy

	Baseline NH	6 months	Baseline DH	6 months
BG (mg per 100 ml)	90.6 ± 7.2	87.9 ± 6.4	136.2 ± 10.5*	131.3 ± 9.7*,£
Tg (mg per 100 ml)	94.8 ± 21.6	87.8 ± 19.8	146.9 ± 39.7*	130.4 ± 33.5*,£
sICAM-1 (ng ml^{-1})	163.4 ± 28.3	139.5 ± 20.1*	278.2 ± 35.6*	231.8 ± 30.8*,^,○
IL-6 (pg ml^{-1})	1.9 ± 0.8	1.3 ± 0.5*	3.3 ± 1.2**	2.2 ± 1.1*,^,○
Hs-CRP (mg l^{-1})	1.2 ± 0.3	0.8 ± 0.2*	2.4 ± 1.2*	1.8 ± 0.9*,^,○

Abbreviations: BG, blood glucose; Hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; Tg, triglycerides.
Data are means ± s.d.
*$P<0.05$ vs. baseline NH; **$P<0.01$ vs. baseline NH; ^$P<0.05$ vs. baseline DH; £$P<0.05$ vs. 6-month NH; ○$P<0.01$ vs. 6-month NH.

sICAM-1, IL-6 and Hs-CRP values were significantly higher in DH group compared to NH group, whereas high-density lipoprotein-cholesterol value was significantly lower (Tables 1 and 2).

Study sample after the first OFL
After OFL, there was no significant variation of BG, whereas there was a significant increase of Tg value at time 6 in both groups compared to time 0; BG, and Tg values observed at time 0 in DH group were significantly higher than in NH group. Furthermore, BG and Tg values obtained at time 6 in DH group were significantly higher than the values obtained in NH group at time 0 and 6. Regarding inflammatory parameters, sICAM-1, IL-6 and Hs-CRP values were significantly increased in both groups at time 6 compared to time 0. Comparing the two groups, sICAM-1, IL-6 and Hs-CRP values were significantly higher in DH group at time 0 than the values obtained in NH group at the same time. At time 6 in DH group, sICAM-1, IL-6 and Hs-CRP values were significantly higher than those obtained in NH group at time 0 6 (Tables 3 and 5).

Table 3 Time 0 and after 6 h during OFL at baseline in NH and DH patients

	Time 0 h NH	Time 6 h NH	Time 0 h DH	Time 6 h DH
BG (mg per 100 ml)	90.6 ± 7.2	93.4 ± 7.8	136.2 ± 10.5*	142.6 ± 11.3*,○
Tg (mg per 100 ml)	94.8 ± 21.6	142.8 ± 35.4*	146.9 ± 39.7*	172.8 ± 54.6§,^,○
sICAM-1 (ng ml^{-1})	163.4 ± 28.3	182.9 ± 34.7*	278.2 ± 35.6*	301.9 ± 44.8§,^,$
IL-6 (pg ml^{-1})	1.9 ± 0.8	2.8 ± 1.3*	3.3 ± 1.2§	4.9 ± 2.0^,$,£
Hs-CRP (mg l^{-1})	1.2 ± 0.3	2.1 ± 1.0*	2.4 ± 1.2*	3.9 ± 1.9§,^,$

Abbreviations: BG, blood glucose; Hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; Tg, triglycerides.
Data are means ± s.d.
*$P<0.05$ vs. time 0 NH; §$P<0.01$ vs. time 0 NH; £$P<0.001$ vs. time 0 NH; ^$P<0.05$ vs. time 0 DH; ○$P<0.05$ vs. time 6 NH; $$P<0.01$ vs. time 6 NH.
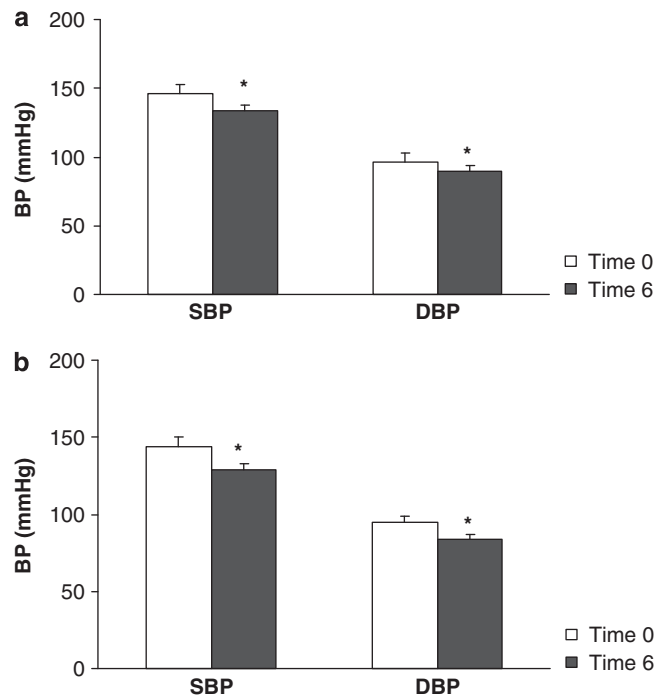

Figure 1 SBP and DBP after 6-month candesartan therapy in nondiabetic (NH) (a) and diabetic (DH) (b) hypertensive patients. (a) Data are means ± standard deviation. *$P<0.001$ vs. time 0 NH. (b) Data are means ± s.d. *$P<0.001$ vs. time 0 DH. NH, nondiabetic; DH, diabetic; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Study sample after 6 months of candesartan therapy
After 6 months of candesartan therapy, there was a significant decrease of sICAM-1, IL-6 and Hs-CRP values compared to baseline in both groups, whereas BG and Tg did not change. Comparing the two groups, BG, Tg, sICAM-1, IL-6 and Hs-CRP values obtained after 6 months of candesartan therapy were significantly higher in DH group compared to the values obtained at baseline and after 6 months of candesartan therapy in NH group (Table 2). Regarding the blood pressure profile, there was a comparable significant decrease of SBP and DBP values in both groups after 6 months of candesartan therapy compared to baseline (Figure 1).

Study sample after the second OFL
After OFL, there was no variation of BG, Tg or sICAM-1, whereas there was an increase of IL-6 and Hs-CRP at time 6 in both groups compared to time 0.

Table 4 Time 0 and after 6 h during OFL after 6-month candesartan therapy in NH and DH patients

	Time 0 h NH	Time 6 h NH	Time 0 h DH	Time 6 h DH
BG (mg per 100 ml)	87.9 ± 6.4	88.5 ± 6.6	131.3 ± 9.7*,°	135.1 ± 9.9*,°
Tg (mg per 100 ml)	87.8 ± 19.8	112.6 ± 23.5	130.4 ± 33.5*	143.4 ± 38.4*,$
sICAM-1 (ng ml⁻¹)	139.5 ± 20.1	151.2 ± 23.7	231.8 ± 30.8*	246.3 ± 32.1§,$
IL-6 (pg ml⁻¹)	1.3 ± 0.5	1.7 ± 0.7*	2.2 ± 1.1§	3.0 ± 1.2^,$,£
Hs-CRP (mg l⁻¹)	0.8 ± 0.2	1.3 ± 0.5*	1.8 ± 0.9§,°	2.6 ± 1.3§,^,$

Abbreviations: BG, blood glucose; Hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; Tg, triglycerides. Data are means ± s.d.
*$P<0.05$ vs. time 0 NH; §$P<0.01$ vs. time 0 NH; £$P<0.001$ vs. time 0 NH; ^$P<0.05$ vs. time 0 DH; °$P<0.05$ vs. time 6 NH; $$P<0.01$ vs. time 6 NH.

Table 5 Parameters AUC in the study

	NH	DH
At the baseline		
BG AUC (mg per 100 ml×12 h)	51436.27 ± 3974.72	93274.65 ± 5893.14
Tg AUC (mg per 100 ml×12 h)	47486.92 ± 21651.49	76785.28 ± 37485.62
sICAM-1 AUC (ng ml⁻¹×12 h)	101232.36 ± 5176.69	142799.82 ± 7632.67
IL-6 AUC (pg ml⁻¹×12 h)	1398.67 ± 413.95	2764.46 ± 784.62
Hs-CRP AUC (mg l⁻¹×12 h)	974.57 ± 392.73	1638.73 ± 542.38
After 6 months		
BG AUC (mg per 100 ml×12 h)	37248.32 ± 2548.13	69337.26 ± 4210.42
Tg AUC (mg per 100 ml×12 h)	31689.522 ± 12358.11	58169.36 ± 29552.33
sICAM-1 AUC (ng ml⁻¹×12 h)	68431.58 ± 3297.36	119238.29 ± 6364.18
IL-6 AUC (pg ml⁻¹×12 h)	924.74 ± 279.31	1877.82 ± 551.99
Hs-CRP AUC (mg l⁻¹×12 h)	536.18 ± 215.68	1132.68 ± 478.23

Abbreviations: BG, blood glucose; DH, diabetic hypertensive patients; Hs-CRP, high-sensitivity C reactive protein; IL-6, interleukin-6; NH, nondiabetic hypertensive patients; sICAM-1, soluble intercellular adhesion molecule-1; Tg, triglycerides. Data are means ± s.d.

Comparing the two groups, BG value was significantly higher in DH group at time 0 compared to the value obtained in NH group at time 0 and 6. Furthermore, BG value was significantly higher in DH group at time 6 compared to the value obtained in NH group at time 0 and 6. Tg and sICAM-1 values were significantly higher in DH group at time 0 than in NH group at the same time. Furthermore, Tg and sICAM-1 values were significantly higher in DH group at time 6 compared to the values in NH group at time 0 and 6. IL-6 value was significantly higher in DH group at time 0 than the value obtained in NH group at the same time. Furthermore, IL-6 value was significantly higher in DH group at time 6 than the value obtained in NH group at time 0 and 6. Hs-CRP value was significantly higher in DH group at time 0 than the value observed in NH group at time 0 and 6; furthermore, Hs-CRP value was significantly higher in DH group at time 6 than the value obtained in NH group at time 0 and 6 (Tables 4 and 5).

DISCUSSION

Postprandial hypertriglyceridemia has been suggested to be a strong risk factor for cardiovascular disease, independently from the fasting plasma lipid level.[23] In the large Copenhagen City Heart Study cohort, followed up for 26 years, the adjusted risk for myocardial infarction, ischemic heart disease and all-cause mortality were nearly 1.5 for each 1 mmol l⁻¹ increase in nonfasting triglyceridemia.[24]

In fact, normolipidemic patients affected by coronary artery disease appear to have a slowed postprandial lipid clearance than normolipidemic healthy subjects.[25] Moreover, the postprandial hyperlipidemia is linked to an acute endothelial dysfunction on moderately dyslipidemic

patients[26] and the slower is the postload Tg clearance, the speeder the coronary atherosclerosis progression.[27]

In our study, we have evaluated the effect of treatment with candesartan, an angiotensin receptor blocker with weak peroxisome proliferator-actived receptor-α agonist activity, on the OFL-induced inflammation in type 2 diabetic and NH patients. The most adequate way to experimentally reproduce the postprandial lipemia condition appears to be the administration of a standardized OFL to fasting patients.[28] This model has been widely applied in relatively small sample of subjects to study the postprandial lipemia effect on inflammatory parameters,[29,30] circulating markers of endothelial dysfunction[31,32] and prothrombotic variables.[33,34]

So, we observed that 6-month treatment is associated to a significant improvement of basal level of sICAM-1 (−17.3%), IL-6 (−31.6%) and Hs-CRP (−33.3%) in nondiabetics, whereas in BG (−3.7%), Tg (−11.2%), sICAM-1 (−16.5%), IL-6 (−36.6%) and Hs-CRP (−25.0%) in diabetics. These data are in line with what already observed by other research groups patients affected by hypertension[35] or chronic heart failure.[36] Before the treatment with candesartan, the OFL determined a significantly lower increase in Tg (+17.7 vs. +50.5%) and Hs-CRP (+62.5 vs. +75.0%) in diabetics than in non-diabetic patients. Six months of treatment with candesartan prevented the OFL-related changes in Tg and sICAM-1 level in non-diabetic patients, whereas it was associated to a reduced increase in IL-6 (+28.6 vs. +47.4%) and Hs-CRP (+62.5 vs. +75.0%). In diabetics, the candesartan treatment was associated to a reduced OFL-related increase in Tg (+10.0 vs. +17.7%), sICAM-1 (+6.5 vs. +8.5%) and IL-6 (+36.4 vs. +48.5%) level. From this observation, we could argue that the anti-inflammatory effect of candesartan is somewhat higher in non-diabetic patients, so supporting the hypothesis that the anti-inflammatory activity of this drug is only partly related to its weak peroxisome proliferator-actived receptor-α activity, but probably to other independent characteristics of the molecule.[37] Some of the candesartan anti-inflammatory effects mediated by suppression of nuclear factor-κB activation and chemokine expression appear to be dose dependent[38] and the strong effect that we observed in our study could be related to the use of the maximal consented dose of this drug.

Our study has some limitations. The first one is the relatively small sample of the studied patients that reduces the ability to infer the results. Another one is that we did dose a limited number of inflammation biomarkers, concentrating our attention to the most studied ones. However, at the best of our knowledge, this is the first study investigating the effect of an angiotensin II receptor antagonist on the inflammation associated to postprandial hyperlipidemia.

In conclusion, in our study carried out on type 2 diabetic and NH patients we observed that candesartan treatment attenuated the inflammatory answer in both group of patients, even if more efficiently in nondiabetic ones.

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