Hydrochlorothiazide, but not Candesartan, Aggravates Insulin Resistance and Causes Visceral and Hepatic Fat Accumulation

The Mechanisms for the Diabetes Preventing Effect of Candesartan (MEDICA) Study

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Abstract—Treatment with angiotensin II receptor blockers is associated with lower risk for the development of type 2 diabetes mellitus compared with thiazide diuretics. The Mechanisms for the Diabetes Preventing Effect of Candesartan Study addressed insulin action and secretion and body fat distribution after treatment with candesartan, hydrochlorothiazide, and placebo. Twenty-six nondiabetic, abdominally obese, hypertensive patients were included in a multicenter 3-way crossover trial, and 22 completers (by predefined criteria; 10 men and 12 women) were included in the analyses. They underwent 12-week treatment periods with candesartan (C; 16 to 32 mg), hydrochlorothiazide (H; 25 to 50 mg), and placebo (P), respectively, and the treatment order was randomly assigned and double blinded. Intravenous glucose tolerance tests and euglycemic hyperinsulinemic (56 mU/m² per minute) clamps were performed. Intrahepatic and intramyocellular and extramyocellular lipid content and subcutaneous and visceral abdominal adipose tissue were measured using proton magnetic resonance spectroscopy and MRI. Insulin sensitivity (M-value) was reduced following H versus C and P (6.07±2.05, 6.63±2.04, and 6.90±2.10 mg/kg of body weight per minute; mean±SD; P=0.01). Liver fat content was higher (P<0.05) following H than both P and C. The subcutaneous to visceral abdominal adipose tissue ratio was reduced following H versus C and P (P<0.01). Glycosylated hemoglobin, alanine aminotransferase, aspartate aminotransferase, and high-sensitivity C-reactive protein levels were higher (P<0.05) after H, but not C, versus P. There were no changes in body fat, intramyocellular lipid, extramyocellular lipid, or first-phase insulin secretion. Blood pressure was reduced similarly by C and H versus P. In conclusion, visceral fat redistribution, liver fat accumulation, low-grade inflammation, and aggravated insulin resistance were demonstrated after hydrochlorothiazide but not candesartan treatment. These findings can partly explain the diabetogenic potential of thiazides. (Hypertension. 2008; 52:1030-1037.)

Key Words: insulin resistance ■ visceral obesity ■ liver fat ■ glucose clamp ■ magnetic resonance

Hypertension is associated with an increased risk of development of type 2 diabetes mellitus (T2DM), and it is also an important component of the metabolic syndrome.1 Obesity and insulin resistance appear to be central perturbations in this cluster of cardiovascular risk factors.2 Among antihypertensive drugs, β-blocking agents and thiazide diuretics have been reported to impair insulin sensitivity and potentially increase the risk for T2DM.3-5 The diabetogenic potential of thiazides has been implicated for single, as well as combination, therapy.6,6 It has been attributed to increased hepatic glucose production, impaired peripheral glucose uptake, and hypokalemia-mediated β-cell dysfunction.6-8 In contrast, there are several studies suggesting that inhibition of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors or blockers of the type 1 angiotensin II receptor (ARBs) are beneficial with respect to
development of T2DM as compared with other antihypertensive treatments.9–11 A meta-analysis addressing T2DM risk12 indicated a relative risk reduction of approximately 40% for ARBs in comparison with thiazide diuretics, and ARBs also carried a lower risk compared with placebo. Candesartan is a selective ARB that has been shown to be favorable compared with thiazides and placebo with respect to the development of T2DM in patients with hypertension or cardiac failure.13–15

The accumulation of intra-abdominal fat is proposed to play a primary role in the development of the metabolic syndrome.16 Free fatty acids and potentially other biomolecules released from the visceral fat depot can promote triglyceride synthesis and accumulation in the liver, as well as hepatic release of very low density lipoproteins and glucose into the circulation.17,18 A selective reduction of visceral fat tissue might mitigate the consequences of the metabolic syndrome and, interestingly, surgical removal of intra-abdominal fat can improve the metabolic phenotype.19 ARBs may have direct effects on adipose tissue, eg, on insulin signaling and adipogenesis, and this may occur through interaction with a local adipose RAS.20 Nonalcoholic fatty liver disease, characterized by increased content of intrahepatocyte lipids, is closely associated with visceral obesity and insulin resistance.21 Interventions that reduce intrahepatocyte lipids also improve insulin sensitivity and, specifically, hepatic insulin action.22 Similarly, lipid accumulation in skeletal muscle, specifically intramyocellular lipids, is linked to insulin resistance, but insulin-sensitizing therapy does not consistently reduce intramyocellular lipid.22,23

Thiazides are commonly recommended as first-line therapy in hypertension according to guidelines.24,25 The Mechanisms for the Diabetes Preventing Effect of Candesartan (MEDICA) Study was designed to investigate the mechanisms underlying the differences in diabeticogenic potential between a thiazide, hydrochlorothiazide (HCTZ), and candesartan, as well as placebo, in hypertensive subjects prone to insulin resistance and T2DM. We addressed effects on insulin sensitivity, β-cell function, and fat distribution and hypothesized that candesartan improves insulin sensitivity compared with HCTZ and that this is associated with differences in adipose tissue distribution and ectopic fat deposition.

Methods
This was a double-blind, 3-way crossover, placebo-controlled, randomized trial in nondiabetic subjects with hypertension and abdominal obesity, and it was performed between April 2005 and March 2006 at the Umeå, Uppsala, and Sahlgrenska University Hospitals in Sweden. The study as a whole was approved by the regional research ethics committee in Umeå and by the Swedish Medicinal Products Agency, and all of the participants gave their written informed consent.

Objectives
The primary objective was to compare the effects of 12 weeks of treatment with candesartan and HCTZ at therapeutic dose levels on insulin sensitivity measured with hyperinsulinemic euglycemic clamp. The secondary objectives were to compare the effects of treatment with candesartan and HCTZ to placebo with respect to insulin sensitivity and to compare treatment effects on β-cell function, fatty acid and adipokine levels, fat and lean body mass, abdominal fat tissue distribution, and fat content in liver and muscle.

Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enrolled Subjects (n=35)*</th>
<th>Primary Analysis Population (n=22)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.8 ± 9.9</td>
<td>54.8 ± 10.4</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>15/20</td>
<td>10/12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.3 ± 3.1</td>
<td>30.2 ± 3.0</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>143 ± 14</td>
<td>143 ± 15</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>91 ± 7</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>Fasting P-glucose, mmol/L‡</td>
<td>5.5 ± 1.2</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>2 hours P-glucose, mmol/L‡</td>
<td>6.9 ± 2.3</td>
<td>6.5 ± 1.8</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; P-glucose, plasma glucose. Data are mean ± SD or n.

*Data show the subjects who entered the placebo run-in period.
†Data show subjects who were randomly assigned and completed ≥2 study treatment periods (as predefined in the study protocol). Nine subjects were withdrawn during the placebo run-in period because of uncontrolled hypertension (4 subjects), diabetic levels of fasting or 2 hours of plasma glucose (2 subjects), headache, peripheral edema + paltipations, and personal reasons (1 subject each). Four subjects were withdrawn after random assignment but before completion of 2 treatment periods (because of headache, participation in an intense weight loss program, stressful work situation, and private reasons), and they were, thus, not included in the primary analysis population.
‡Glucose data are from oral glucose tolerance test at the randomization visit (n=28). All of the other data are from the enrollment visit.

Patients
After the screening of 42 subjects in total, 35 patients (15 men and 20 women) with diagnosed hypertension and abdominal obesity were enrolled into a placebo run-in period. Inclusion criteria were as follows: male and female patients between 18 and 70 years of age; hypertension diagnosed or treated for ≥3 months and, in addition, blood pressure after 2 to 8 weeks of washout from antihypertensive treatment, ≥140/90 mm Hg; and abdominal obesity defined by a waist circumference ≥102 cm and 88 cm in males and females, respectively. The main exclusion criteria were as follows: uncontrolled hypertension >170/105 mm Hg; diabetes mellitus diagnosed previously or indicated by plasma glucose levels during fasting or oral glucose tolerance test; history of coronary heart or cerebrovascular disease; cardiac failure at New York Heart Association stages II through IV; significant liver disease; renal impairment with serum creatinine >150 μmol/L; uncontrolled endocrine disorders; previous (within 5 years) or ongoing malignancy; recent (within 6 months) or ongoing alcohol or drug abuse; or treatment with antifungal, antibiotic, or anti-inflammatory drugs. There was 1 current smoker among the subjects. Among the 35 enrolled subjects, 3 had no previous antihypertensive medication, 13 had single therapy, 18 had dual therapy, and 1 subject had triple therapy. Altogether, 16 subjects were treated with a diuretic, 15 with a β-blocker, 8 with an angiotensin-converting enzyme inhibitor, 7 with an ARB, 5 with a calcium channel blocker, and 1 with an α-blocker. The mean duration of hypertension was 8.2 (mean ± SD) years. Baseline characteristics are shown in Table 1.

Study Interventions
A schematic overview of the treatment periods and study design is given in Figure 1. At enrollment, antihypertensive medication was stopped, and subjects entered a single-blind, placebo run-in period lasting for 2 to 8 weeks, until the blood pressure criteria for randomization were reached. After the placebo run-in period, a 75-g oral glucose tolerance test was performed. Twenty-six subjects fulfilling randomization criteria entered 3 consecutive, double-blinded, 12-week treatment periods according to a randomized order: (1) candesartan 16 to 32 mg once daily (C); (2) HCTZ 25 to 50 mg once daily (H); and (3) placebo once daily (P). Thus, treatment orders were: H-C-P, H-P-C, C-H-P, C-P-H, P-C-H, and P-H-C. In each period, treatment was initiated with 1 tablet of each type (C+P,
Intravenous Glucose Tolerance Test and Hyperinsulinemic Euglycemic Clamp

Subjects fasted overnight (≥10 hours), and they refrained from heavy exercise for 24 hours before they arrived at the study centers at 8:00 AM. They rested in the supine position, and forearm venous blood used for sampling was arterialized by wrapping heating pads around the hand and forearm. An intravenous glucose tolerance test (IVGTT) and a subsequent hyperinsulinemic euglycemic clamp were performed during the same day for assessment of insulin secretion and sensitivity.28 During the IVGTT, 0.3 g/kg of body weight of a 50% glucose solution was injected over 45 s. The incremental trapezoidal area of plasma insulin, sampled every 2 minutes during the first 10 minutes was used to measure first-phase insulin response. To allow glucose levels to return to baseline, the treatment period was stopped, and investigations were performed prematurely.

Anthropometry

Blood pressure was measured to the nearest millimeter of mercury using a sphygmomanometer and an arm cuff with dimensions adjusted according to arm circumference. The measurements were done at trough, ie, 24 hours after the last administration of study drug, and with subjects sitting for ≥5 minutes. Blood pressure was recorded twice, ≥2 minutes apart, and the average was used for analyses. The arm with the highest blood pressure at enrollment was used for all of the onward measures. Body weight, height, waist circumference, and abdominal sagittal diameter were assessed according to published methods.26 Total body fat and lean body mass were measured by the bioimpedance method.27

Statistical Analyses

Differences between treatments were assessed using 2-tailed Student paired t test for variables that were normally distributed. The Wilcoxon signed-rank test was used for variables that were not normally distributed. The SD for within-subject change in steady-state glucose infusion rate (ie, M-value) was predicted to be 25% of the mean M-value.10 With 18 evaluable subjects, this would give 80% power to detect a 17% difference between treatments in M-values at the 0.05 significance level. Assuming a dropout rate of maximally 25%, the aim was to randomly assign 24 patients. Data are presented as mean±SD, median (interquartile range), or n. For the primary comparison, ie, M-value after candesartan versus HCTZ treatment, a P<0.05 was considered statistically significant, and other analyses were performed in an exploratory manner, provided that the primary hypothesis was confirmed.

Results

Among the 26 randomly assigned patients, 22 completed ≥2 treatment periods (see Table 1, footnote), and they were included in the onward analyses as predefined in the study protocol. They all fulfilled the criteria for treatment compliance, ie, taking ≥75% of the prescribed amount of each study medication. Twenty-one subjects completed all 3 of the treatment periods, and 1 subject completed 2 periods but was
withdrawn during the last treatment period (placebo) because of joint problems and suspected excess alcohol consumption. Four subjects terminated 1 randomized study period prematurely, all on placebo, because of uncontrolled blood pressure. In those cases, the end-of-treatment investigations were done in advance as advised in the protocol, and the shortening of the treatment periods varied between 2 and 6 weeks. The numbers of subjects finally reaching the high and low dose levels of study medication, ie, 2 or 1 tablet(s) once daily, were 14/8, 20/2, and 20/1 for candesartan (32/16 mg), HCTZ (50/25 mg), and placebo, respectively.

### Blood Pressure and Body Composition

Anthropometric data after each treatment period are displayed in Table 2. Blood pressure was reduced ($P < 0.05$) by both candesartan and HCTZ compared with placebo, but candesartan had a slightly greater effect than HCTZ. Heart rate was significantly lower with candesartan compared with the other treatments. There were no significant differences in body weight per minute for HCTZ, 6.63 ± 0.01 after HCTZ compared with both candesartan and placebo.

### Insulin Sensitivity

Results of blood chemistry and metabolic investigations are shown in Table 3 and Figure 2. Insulin sensitivity was lower ($P < 0.01$) after HCTZ compared with both candesartan and placebo, and the M-values, ie, glucose infusion rates, obtained during euglycemic clamps were 6.07 ± 0.25 mg/kg of body weight per minute for HCTZ, 6.63 ± 0.01 for candesartan, and 6.90 ± 2.10 for placebo (Figure 2A). These differences were more pronounced when M-values were adjusted for the ambient insulin concentrations during clamp, ie, the insulin sensitivity index, yielding an ≈20% impairment after HCTZ in comparison with both candesartan and placebo.

### Clinical Biochemistry

These results are summarized in Table 3. Glycosylated hemoglobin, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase levels were highest with HCTZ treatment. Moreover, serum amyloid A and high-sensitivity C-reactive protein levels were higher after HCTZ compared with the 2 other treatments. Fasting free fatty acid tended to be elevated with HCTZ compared with placebo.
but free fatty acid levels were similarly suppressed during the hyperinsulinemic clamp (average of 60 and 90 minutes samples; data not shown), regardless of medication. Alkaline phosphatases, bilirubin, tumor necrosis factor-α, interleukin 1α, interleukin 1β, interleukin 2, interleukin 6, and monocyte chemoattractant protein 1 did not display any significant differences between treatments (data not shown). In comparison with placebo treatment, plasma renin and aldosterone were both elevated after HCTZ, whereas renin was elevated and aldosterone reduced with candesartan. Serum sodium and creatinine did not differ among the 3 treatment periods (data not shown). As expected, serum potassium was significantly lower after HCTZ treatment compared with candesartan and placebo, although potassium supplementation was allowed. Correlation analyses indicated that the reduction in potassium level on HCTZ treatment did not account for the treatment differences in insulin sensitivity (data not shown).

Magnetic Resonance Spectroscopy of Liver and Calf Muscle Lipids and MRI of Abdominal Adipose Depots
Magnetic resonance spectroscopy of liver lipids is shown in Figure 3A. Liver fat content was significantly higher (P=0.03) after HCTZ than both placebo and candesartan (median: 6.6%, interquartile range [IQR]: 2.2% to 15.4%; median: 3.9%, IQR: 1.2% to 9.2%; and median: 4.8%, IQR: 2.3% to 9.9%, respectively). In addition, liver volume was greater with HCTZ compared with placebo and candesartan (P=0.061 and P<0.001, respectively), with medians of 1680 cm³ (IQR: 1352 to 1748 cm³), 1502 cm³ (IQR: 1180 to 1658 cm³), and 1412 cm³ (IQR: 1165 to 1611 cm³), respectively, indicating that the higher fat percentage was not explained by the reduction of liver water content during diuretic treatment and that there was, in fact, an absolute increase in liver fat. The increase in liver fat with HCTZ compared with placebo significantly correlated with the reduction in insulin sensitivity expressed as M-value ($r^2=0.26; P=0.04$). No significant differences in the amount of intramyocellular and extramyocellular lipids (IMCLs and EMCLs) were found between treatments. Thus, IMCL was 0.14±0.07%, 0.16±0.12%, and 0.12±0.08% (lipid/water) for candesartan, HCTZ, and placebo, respectively. The corresponding values for EMCL were 1.01±0.98%, 1.12±1.30%, and 0.95±1.08%, respectively. There was a tendency toward increase in the amount of visceral adipose tissue on HCTZ treatment compared to the 2 other treatment (P value not significant). The subcutaneous adipose tissue:visceral adipose tissue ratio was significantly lower after HCTZ compared with both candesartan and placebo (median: 0.49, IQR: 0.38 to 0.62; median: 0.55, IQR: 0.42 to 0.71; and median: 0.51, IQR: 0.40 to 0.69, respectively).

Figure 3. Liver fat content assessed with 1H magnetic resonance spectroscopy (A) and abdominal fat distribution, expressed as subcutaneous:visceral ratio assessed with MRI (B), with an image example (C). Horizontal lines in box plots show median, 10th, 25th, 75th, and 90th percentile, respectively; n=18 to 20 (missing measurements because of insufficient data quality or unwillingness to participate). SAT indicates subcutaneous adipose tissue; VAT, visceral adipose tissue.
placebo (Figure 3B; an example of MR image is shown in Figure 3C).

**Adverse Events**

There were no serious adverse events during the study. In total there were 54 reports of adverse events after randomization, 26 with onset during placebo, 12 during candesartan, and 16 during HCTZ. The most frequent events were common cold (n=9); headache (n=8); dizziness (n=5); chest (n=5), musculoskeletal (n=5), and urogenital (n=3) symptoms; and peripheral edema (n=2).

**Discussion**

This study has, for the first time, addressed effects of a thiazide diuretic and an ARB with respect to insulin resistance, as well as abdominal fat distribution and ectopic fat deposition in liver and muscle. We examined abdominally obese, hypertensive subjects who were insulin resistant, as evidenced by low average glucose utilization rates (M-values) during the euglycemic clamps. HCTZ treatment was followed by more pronounced insulin resistance compared with candesartan and placebo, whereas candesartan did not differ in comparison with placebo. In addition, HCTZ treatment was accompanied by visceral fat redistribution and increased liver fat accumulation. Serum alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase levels were elevated after HCTZ, providing further support for a clinically relevant accumulation of liver fat. There were also signs of low-grade inflammation, because C-reactive protein and serum amyloid A levels were elevated with HCTZ treatment. In contrast, β-cell function measured as first-phase insulin secretion was not altered. Nonetheless, the metabolic impact of impaired insulin sensitivity was evidenced by a slight elevation of glycosylated hemoglobin, indicating an overall increase in glycemic levels after HCTZ. Overall, none of the metabolic effects exerted by HCTZ were seen with candesartan, which was similar to placebo. Our findings may suggest 2 possible mechanisms underlying the detrimental effects of thiazides on glucose metabolism: adipose tissue dysfunction with visceral and hepatic fat deposition and chronic, low-grade inflammation. Both processes are known to promote insulin resistance.31

One attractive hypothesis is that the differences found in abdominal fat distribution and hepatic lipid content can contribute to the demonstrated aggravation of insulin resistance after thiazide treatment. Visceral fat accumulation and hepatic steatosis are both considered to promote insulin resistance. On the other hand, liver fat accumulation might also be a consequence of insulin resistance and hyperinsulinemia. An interesting concept is that of “lipid overfill.” When the subcutaneous adipose depot reaches its upper limit for triglyceride storage after chronic overfeeding, this may trigger adipocyte dysfunction, as well as lipid “spillover” into visceral adipose and ectopic fat depots, eg, intrahepatocellular and intramyocellular lipids. The negative metabolic effects of HCTZ could be accounted for, at least in part, by the demonstrated redistribution of lipid stores. This was not seen with the ARB candesartan, and, accordingly, this treatment was neutral with respect to insulin sensitivity. It is possible that the increase in RAS activity occurring as a consequence of HCTZ treatment can play an important role, because angiotensin II can inhibit adipogenesis and new recruitment of insulin-sensitive adipocytes,38 thus promoting lipid spillover.

Blockade of the angiotensin II type 1 receptor is associated with anti-inflammatory effects and reduction of cellular oxidative stress, ie, the amount of intracellular reactive oxygen species. Conversely, the present data on circulating C-reactive protein and serum amyloid A levels suggest that thiazide treatment, potentially via RAS activation, can trigger a low-grade inflammation. Although there were signs of systemic inflammation, it is possible that the local adipose RAS plays a critical role, driving adipose tissue inflammation and secretion of inflammatory mediators into the circulation. The “RAS-inflammation hypothesis” is also supported by previous clinical work showing reduced C-reactive protein levels on ARB treatment.41

Thus, for both pathways proposed to be involved in thiazide-associated insulin resistance, ie, lipid overfill and inflammation, excessive RAS activity and angiotensin II action, affected by elevated aldosterone in this study, may be important underlying mechanisms. However, either of the 2 could also be explained by alternative, RAS-independent mechanisms that are not fully understood. For example, our finding of a higher heart rate with HCTZ compared with candesartan suggests a higher ratio of sympathetic/parasympathetic nerve activity, and that could impair insulin action. Interestingly, it has also been reported that RAS-mediated insulin resistance can be exerted directly at the major insulin-responsive glucose-metabolizing tissue, ie, skeletal muscle, via interference with insulin signaling. Moreover, there are potentially diabetogenic effects of elevated RAS activity involving pancreatic β-cell function and insulin secretion,43 and thiazides can impair insulin secretion.4 However, we found no consistent differences between the ARB and thiazide (ie, RAS blockade versus amplification) with respect to acute insulin response on glucose challenge.

Notably, our results did not show any beneficial metabolic effect of candesartan in comparison with placebo. Because several ARBs are reported to be partial peroxisome proliferator-activated receptor-γ activators, they could be expected to improve insulin sensitivity and reduce intrahepatic and intra-abdominal fat deposition. It should, however, be recognized that our study only assessed short-term effects during 3-month treatment periods and that more pronounced effects of candesartan, and possibly also of HCTZ, on fat partitioning and metabolic functions may occur in a longer-term perspective.

We suggest that increased RAS activity and action can be unifying mechanisms behind adverse fat distribution, low-grade inflammation, insulin resistance, and glucose intolerance in patients treated with thiazide diuretics. Of note, other pathways cannot be excluded, and we have not identified the basic mechanisms explaining the differences in the metabolic profile after thiazide and ARB treatments. Ongoing analyses of substudies within the Mechanisms for the Diabetes Preventing Effect of Candesartan Trial specifically address vascular/endothelial function, autonomic nerve activity, adipose tissue gene expression, and adipocyte function.
Perspectives

The MEDICA Study demonstrated that HCTZ treatment can produce visceral fat redistribution, liver fat accumulation, aggra-

vated insulin resistance, and low-grade inflammation in abdom-

inally obese hypertensive subjects. No such alterations were seen with an ARB, candesartan, which was similar to placebo treatment. Our findings can partly explain the diabetogenic potential of thiazide diuretics. After the demise of β-blockers as first-line antihypertensive therapy,46 modern guidelines often advocate thiazide diuretics as the first choice.24,25,47 With accumu-

lating evidence for adverse metabolic effects of thiazides, this recommenda-

tion may be questioned. Together with previous studies, our present work supports the use of ARBs as an alternative to thiazide treatment in patients at high risk of developing type 2 diabetes mellitus.

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Disclosures

J.W.E. and L.J. are currently employed by AstraZeneca. M.K.S. is a con-


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