Effect of Renin-Angiotensin System Blockade on Insulin Resistance and Inflammatory Parameters in Patients With Impaired Glucose Tolerance

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OBJECTIVE — The study investigated the effect of angiotensin receptor blockers (ARB) on glucose homeostasis and inflammatory parameters in patients with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — We prospectively studied the insulin sensitivity index (ISI) and homeostasis model assessment–insulin resistance (HOMA-IR) in 13 obese males with IGT and in 13 matched control subjects with normal glucose tolerance (NGT) during hyperglycemic testing over 90 min. Adiponectin, retinol-binding protein 4 (RBP4), and high-sensitive C-reactive protein (hsCRP) were analyzed. Measurements were performed at baseline and after a 4-week treatment with 160 mg/day valsartan. The results of the IGT and NGT groups were compared.

RESULTS — At baseline, HOMA-IR (IGT 4.1 ± 3 vs. NGT 2.3 ± 1.0, $P < 0.01$), hsCRP (IGT 3.9 ± 1.9 vs. NGT 1.8 ± 1 mg/l, $P < 0.05$), and RBP4 (IGT 27.1 ± 2.1 vs. NGT 24.0 ± 2.0 ng/ml, $P < 0.05$) were significantly higher, whereas ISI (IGT 1.5 ± 0.9 vs. NGT 1.8 ± 1.2, $P < 0.05$) and plasma adiponectin (IGT 3.2 ± 0.9, NGT 5.2 ± 2.4 μg/ml, $P < 0.05$) were significantly lower in the IGT group compared with the NGT group. Under ARB, there was an increase in both groups of adiponectin (IGT 4.1 ± 1.9 μg/ml, NGT 6.3 ± 2.9 μg/ml, $P < 0.05$) and an increase in ISI (IGT 1.5 ± 0.9 to 2.3 ± 1 μg/ml, NGT 1.8 ± 1 to 2.5 ± 2 μg/ml, $P < 0.05$). HOMA-IR (4.1 ± 3 to 2.6 ± 2; $P < 0.01$), hsCRP (3.9 ± 1.9 to 1.8 ± 1 mg/l, $P < 0.05$), and RBP4 (27.1 ± 2.1 to 22.1 ± 1.8 ng/ml, $P < 0.01$) decreased significantly in the IGT group.

CONCLUSIONS — Insulin sensitivity and associated inflammatory factors improve under ARB in IGT patients.

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Insulin resistance has a causal role in type 2 diabetes, a crucial risk factor for cardiovascular and renal disease (1). Impaired glucose tolerance (IGT) represents an intermediate state of abnormal glucose regulation between normal glucose homeostasis and manifest diabetes. IGT is defined as elevated 2-h plasma glucose concentration >140 and <200 mg/dl after a 75-g oral glucose load in an oral glucose tolerance test (2). A combination of β-cell dysfunction and insulin resistance with decreased insulin sensitivity or responsiveness to the metabolic action of insulin plays a pathogenetic role. Insulin resistance is common in subjects with visceral adiposity, hypertension, hyperglycemia, and dyslipidemia. Patients with metabolic syndrome have a high risk of developing frank diabetes (3).

Adiponectin is a fat-derived hormone specifically produced and secreted by adipocytes. This adipocytokine is considered an important modulator of insulin sensitivity in patients with IGT (4,5). Adiponectin levels decrease in the obese, which may be a contributing factor to insulin resistance. Anti-inflammatory properties also have been attributed to adiponectin. This is indicated by serum concentrations of adiponectin, which are inversely associated with inflammatory markers such as C-reactive protein (CRP). Retinol-binding protein 4 (RBP4) is another adipocyte-secreted molecule and is elevated in serum before development of overt diabetes (6).

The interaction of these different metabolic and inflammatory parameters in IGT has not been fully clarified. Our study investigates insulin sensitivity and associated risk factors focusing on obese subjects with IGT. We tested the effect of a short-term 4-week angiotensin receptor blocker (ARB) treatment on glucose disposal and inflammatory markers in subjects with IGT.

RESEARCH DESIGN AND METHODS

Study design
A total of 57 male adults with a waist circumference >102 cm were tested. Screening included physical examination and blood and urine chemistry. IGT was diagnosed based on an oral glucose tolerance test (2). Smokers and patients with known vascular, infectious, or inflammatory diseases, micro- and macroalbuminuria, serum creatinine ≥1.2 mg/dl, secondary forms of or uncontrolled hypertension (greater than European Society of Hypertension class 1), ongoing medication with blockade of the renin-angiotensin system (RAS), and diabetes were excluded.

A total of 15 subjects had IGT, 3 subjects had diabetes, and 39 subjects had NGT. Thirteen subjects with IGT fulfilled all inclusion criteria and completed the entire study. We selected 13 tightly matched control subjects from the NGT group.

The 24-h blood pressure measurements were taken using an automated portable device at the beginning and end of the study (Spacelabs Medical, Redmond, WA). Measurements of the study parameters were performed at rest and during hyperglycemic stress testing at baseline (U1) and after a 4-week treatment with valsartan (U2).

The study was approved by the Ethical Committee of the Technical University of Munich. Every participant gave written informed consent. This investigator initiated trial was confirmed by the Federal Institute for Drugs and Medical Devices (BfArM, Germany) and registered by the European Clinical Trials Database (EudraCT, no. 2005-001278-28).

Hyperglycemic clamp
A modified clamp technique following the De Fronzo protocol was used to achieve a hyperglycemic level of a target blood glucose between 160 and 180 mg/dl (7). Initially, the subjects received an intravenous bolus of 1.5 ml 20% glucose solution/kg to raise plasma glucose acutely above 200 mg/dl. Plasma glucose concentrations during the procedure were monitored at 1-min intervals (glucose analyzer, HITADO Diagnostic Systems). When blood glucose reached a level of 180 mg/dl, the desired hyperglycemic plateau of >160 mg/dl and <180 mg/dl was maintained by initiating an adjusted continuous infusion of 20% glucose depending on the actual blood glucose concentration. Once a steady state was reached and maintained for over 90 min, laboratory parameters were measured (Fig. 1). Serum glucose, serum insulin, and C-peptide were measured after a 12-h fast at baseline.

Laboratory methods
Serum insulin concentrations were measured using electrochemiluminescence. Adiponectin plasma concentrations were determined by an enzyme-linked immunosorbent assay. RBP4 was measured using the Human RBP4 Quantikine ELISA Kit DRB400. All other measurements were performed with routine laboratory tests and methods certified by the Institute of Clinical Chemistry, Technical University Munich, Germany. Insulin sensitivity was quantified using the validated model of homeostasis model assessment–insulin resistance (HOMA-IR) (8). Insulin sensitivity index was calculated as
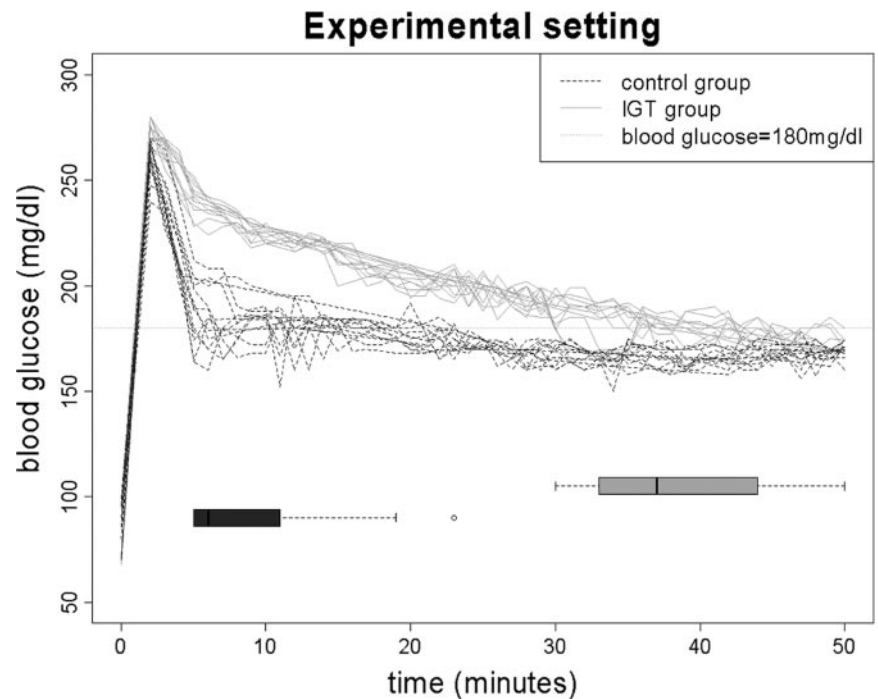
Figure 1—*Experimental setting and course of blood glucose (mg/dl) during hyperglycemic stress testing by intravenous glucose infusion for each group without ARB. A bolus (1.5 ml 20% glucose solution/kg) was given to raise blood glucose acutely. Subsequently, as blood glucose reached a level of 180 mg/dl, the desired hyperglycemic plateau of >160 mg/dl and <180 mg/dl was maintained by the start of an adjusted continuous infusion of 20% glucose. There is a significant difference of the time duration to undercut a blood glucose value of 180 mg/dl with a significantly shorter time in the NGT group (Mann-Whitney U test; presented as box plots, P < 0.001, Bonferroni-adjusted P values).*

1/fasting serum insulin × fasting serum glucose (9).

Statistical analysis
Data are given as means ± SD for continuous variables or as a percentage in categorical variables. Normal data distribution was confirmed by the Kolmogorov-Smirnov test. Normally distributed data were analyzed using the Student's *t* test for comparisons at baseline and after treatment with ARB. We used the Mann-Whitney *U* test to analyze the differences of time spent to undercut the target limit of 180 mg/dl blood glucose for both groups. All statistical analyses were performed using the SPSS version 16.0 for Windows.

RESULTS — Baseline characteristics are shown in Table 1. There was no significant difference in age, BMI, waist circumference, systolic and diastolic blood pressure, fasting serum glucose, triglycerides, and HDL cholesterol. A total of 13 participants were treated

Table 1—*Baseline characteristics of the subjects according to the study groups*

	IGT group	NGT group
n	13	13
Age (years)	50.0 ± 13	50.6 ± 10
BMI (kg/m²)	31.1 ± 6	33.5 ± 4
Waist circumference (cm)	110.3 ± 11	111.9 ± 9
Office systolic blood pressure (mmHg)	137 ± 10	136 ± 16
Office diastolic blood pressure (mmHg)	85 ± 6	88 ± 13
Fasting serum glucose (mg/dl)	89 ± 13	85 ± 8
Serum triglycerides (mg/dl)	111 ± 37	102 ± 37
Serum HDL (mg/dl)	45 ± 14	44 ± 16

Data are means ± SD.

Experimental setting under ARB
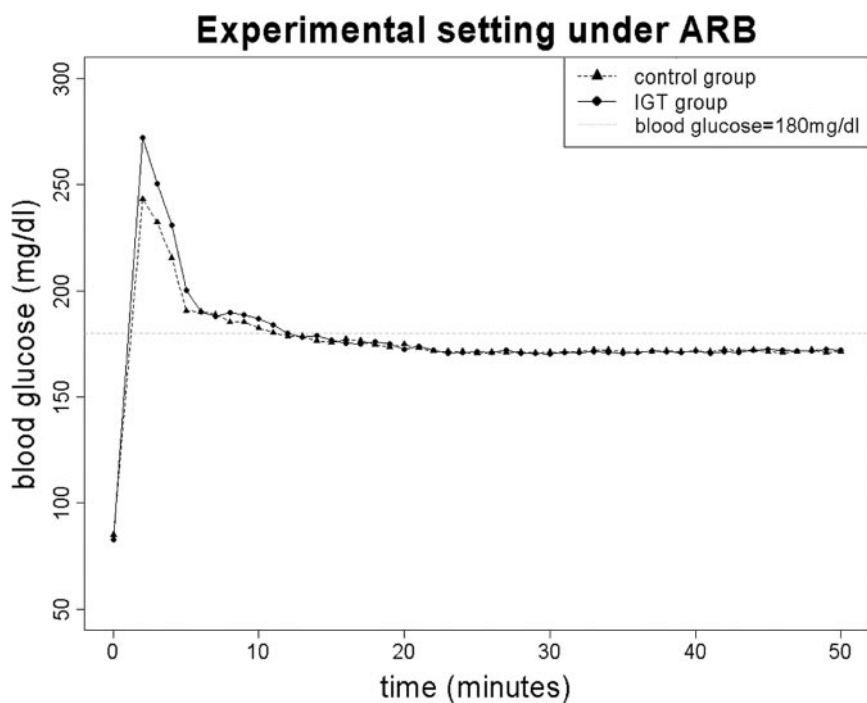
Figure 2—*Blood glucose (mean values) (mg/dl) during hyperglycemic stress testing for each group after 4-week treatment with valsartan.*

with antihypertensive agents (calcium antagonists: four IGT; three NGT; β-blockers: three IGT, three NGT). During hyperglycemia, mean blood glucose values of 170 ± 9 mg/dl (IGT) and 171 ± 7 mg/dl (NGT) were held over 90 min. The time required to reach steady-state conditions within the targeted blood glucose plateau was longer in the IGT group (IGT 37.2 ± 3 vs. NGT 15.8 ± 2 min, $P < 0.05$, Fig. 1). Under ARB, there was no significant difference in the blood glucose profiles of both study groups under clamp testing (Fig. 2). At baseline, HOMA-IR, RBP4, and high-sensitive (hs)-CRP serum levels

were significantly higher, whereas insulin sensitivity index and plasma adiponectin were significantly lower for the IGT group (Table 2). At baseline, in both groups, there were no significant differences in ambulatory systolic (IGT 125 ± 6 vs. NGT 123 ± 1 mmHg, $P = 0.86$) and diastolic (IGT 77 ± 2; NGT 77 ± 3 mmHg, $P = 0.95$) blood pressure. However, there was a significantly higher reduction of systolic blood pressure in the IGT group compared with the NGT group (IGT 118 ± 3 vs. NGT 121 ± 4 mmHg, $P < 0.05$) under ARB. There was no significant difference between diastolic blood pressure re-

duction in either group (IGT 73 ± 3 vs. NGT 74 ± 5 mmHg, $P = 0.11$) (Table 2).

Effects of ARB on insulin sensitivity

Under 4-week treatment with valsartan, insulin sensitivity index increased significantly in both groups (IGT 1.5 ± 1 vs. 2.3 ± 1, $P < 0.05$; NGT 1.8 ± 1 vs. 2.5 ± 2, $P < 0.05$). HOMA-IR decreased significantly in the IGT group under ARB (IGT 4.1 ± 3 vs. 2.6 ± 2, $P < 0.01$; NGT 2.3 ± 1 vs. 1.6 ± 1, $P = 0.016$, Fig. 3). There was a significant reduction in A1C in the IGT group (5.58 ± 0.15 vs. 5.2 ± 0.25%, $P < 0.05$), whereas no A1C changes were noted in the control group (Table 2). RBP4 decreased significantly in the IGT group (IGT 27.1 ± 2.1 vs. 22.1 ± 1.8 ng/ml, $P < 0.01$; NGT 24.0 ± 2.0 vs. 22.0 ± 1.9, $P = 0.98$). Fasting insulin levels were reduced under valsartan in both groups (IGT 16.6 ± 11 vs. 13.2 ± 8 mU/l, $P < 0.05$; NGT 16.1 ± 10 vs. 12.3 ± 6, $P < 0.05$). There was no difference in C-peptide levels in all groups (Table 2).

Effects of ARB on inflammatory risk markers

Plasma adiponectin levels increased significantly in both groups (IGT 3.2 ± 1.0 vs. 4.1 ± 1.9 μg/ml, $P < 0.05$; NGT 5.2 ± 2.4 vs. 6.3 ± 2.9, $P < 0.05$). hsCRP levels decreased significantly in the IGT group (IGT 3.9 ± 1.9 vs. 1.8 ± 0.9 mg/l, $P < 0.05$; NGT 1.8 ± 0.9 vs. 2.2 ± 1.9, $P = 0.89$).

CONCLUSIONS — In obese males with IGT, we found increased inflammatory markers associated with a higher degree of insulin resistance compared with

Table 2—*Insulin resistance parameters, inflammatory markers, and 24-h systolic and diastolic blood pressure of the subjects according to the study groups with and without ARB*

	IGT group	NGT group	P	IGT group + ARB	NGT group + ARB
n	13	13		13	13
Adiponectin (μg/ml)	3.2 ± 0.9	5.2 ± 2.4	<0.05	4.1 ± 1.9*	6.3 ± 2.9*
HOMA-IR	4.1 ± 3	2.3 ± 1	<0.01	2.6 ± 2†	1.6 ± 1
Insulin sensitivity index	1.5 ± 0.9	1.8 ± 1.2	<0.05	2.3 ± 1*	2.5 ± 2*
Fasting (insulin) (mU/l)	16.6 ± 11.2	16.1 ± 10	<0.05	13.2 ± 8*	12.3 ± 6*
C-peptide (nmol/l)	1.2 ± 0.4	1.5 ± 1	0.78	1.0 ± 0.4	1.2 ± 0.4
hsCRP (mg/l)	3.9 ± 1.9	1.8 ± 1	<0.05	1.8 ± 0.9*	2.2. ± 1.9
A1C (%)	5.58 ± 0.2	5.29 ± 0.2	<0.01	5.20 ± 0.3*	5.30 ± 0.3
RBP4 (ng/ml)	27.1 ± 2.1	24.0 ± 2.0	<0.05	22.1 ± 1.8†	22.0 ± 1.9
24-h systolic blood pressure (mmHg)	125 ± 6	123 ± 1	0.86	118 ± 3*	121 ± 4
24-h diastolic blood pressure (mmHg)	77 ± 2	77 ± 3	0.95	73 ± 3	74 ± 5

Data are means ± SD, unless otherwise indicated. *$P < 0.05$. †$P < 0.01$.
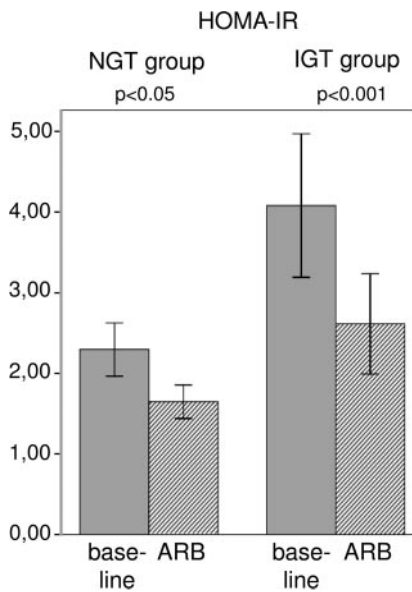
HOMA-IR

Figure 3—*Insulin resistance defined by HOMA-IR with and without ARB separately for the NGT and IGT group.*

matched obese subjects with NGT. Treatment with valsartan improved insulin sensitivity, RBP4, and A1C as chemical features of insulin resistance. hsCRP and adiponectin improved in the group of subjects with IGT.

Improvement of insulin sensitivity
In IGT, defective early-phase and late insulin secretion combined with muscle and hepatic insulin resistance results in prolonged hyperglycemia after a glucose load. Our data confirm pathophysiological mechanisms, where the timeframe after glucose bolus averages about 20 min longer than for the control group. After treatment with valsartan, metabolic changes are indicated by a decrease in insulin resistance and an increase in adiponectin. The reduction of time to reach the targeted blood glucose <180 mg/dl after glucose bolus within the IGT group under ARB demonstrates an improvement in early-phase insulin secretion and reduction of insulin resistance. A sequential insulin scan between glucose bolus and target value is advisable but was not part of this study. Jin and Pan (10) showed an improvement in glucose homeostasis in type 2 diabetic patients by lorsartan. The results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial indicated favorable effects of RAS blockade with ramipril on glucose metabolism (11). Mechanisms for the improvement of glucose tolerance are complex. The inter-

action of RAS with peroxisome proliferator–activated receptor (PPAR)-γ affects insulin sensitivity (12). Angiotensin II inhibits adipogenic differentiation of human adipocytes via the AT1 receptor (13). Expression of angiotensin II–forming enzymes in adipose tissue correlates inversely with insulin sensitivity by decreased circulating adiponectin (14). In vivo, the activation of the angiotensin 2 receptor and certain ARB induce adiponectin in adipocytes, which is associated with improvement in insulin sensitivity in murine adipocytes and obese Zucker rats. ARB-induced adiponectin stimulation is likely to be mediated via PPAR-γ activation involving a posttranscriptional mechanism (15). ARB induce adipogenesis and PPAR-γ target gene expression in human adipocytes and increase adiponectin, which contributes to the metabolic impact of this class of drug. In humans, it is unclear whether larger doses of ARB or longer treatments, or both, may be required to activate PPAR-γ in adipose cells. The relevance for the glucose metabolism of the PPAR-γ agonist actions of the ARB on insulin sensitivity in patients with IGT is unclear, noting that effects are much greater in cell-free systems than in intact cells or in vivo (16). Another mechanism to discuss is improvement of intra-islet blood flow regulated by local activity of the RAS (17). We have no knowledge of any upregulation of the RAS through the temporary hyperglycemia in patients with IGT. In animal testing by the Zucker obese (*fa/fa*) model of type 2 diabetes, an upregulation after glucose load was noted. After administration of an ARB, islet blood flow increased insulin secretion and increased β-cell mass and normalization of islet morphology (18). Changes in islet perfusion may contribute to the delayed first phase of insulin response to glucose. The enhancement of insulin signaling, possibly additionally disturbed by angiotensin II receptor cross-talk and insulin secretion by the β-cells, supports glucose delivery to insulin-sensitive tissue by inhibiting the RAS, which may improve intra-islet blood flow and microcirculation in skeletal muscle.

While in rats Juan et al. (19) demonstrated increased insulin sensitivity upon chronic angiotensin II infusion, we found in contrast increased insulin sensitivity by ARB treatment in human subjects with IGT. We know that angiotensin II exerts its effects through two different receptors, the angiotensin type 1 receptor (AT1R)

and angiotensin type 2 receptor (AT2R). We know that the AT1 receptor is the predominant receptor in the cardiovascular system and mediates most of the deleterious effects of angiotensin II, such as vasoconstriction, endothelial damage, and cell proliferation. The AT2 receptor is now recognized as the counter-regulator of the AT1 receptor, exerting mostly beneficial actions such as vasodilation, antiproliferation, and anti-inflammatory effects. Apart from species differences, these contradicting results may be explained by the AT2R stimulation during selective AT1 receptor blockade under certain pathological conditions in which the available angiotensin II is redirected to the AT2 receptor.

Improvement of inflammatory risk markers
Subclinical low-grade inflammation plays an important role in the pathogenesis of insulin resistance. Angiotensin II adversely affects glucose metabolism by increasing reactive oxygen species and inducing subclinical inflammation. Elevated CRP serum levels have been associated with cardiovascular disease and insulin resistance (20). Adiponectin inhibits production and action of tumor necrosis factor (TNF)-α, which may influence interleukin-6 and CRP production (21). It has been shown that CRP suppresses adiponectin gene expression partially through the phosphatidylinositol 3-kinase pathway, and decreased production of adiponectin might represent a mechanism by which CRP regulates insulin sensitivity (22). Yuan et al. (23) showed an elevation of hsCRP in patients with IGT accompanied by the opposite changes of adiponectin. In our study, treatment with valsartan improved hsCRP and adiponectin concentrations. RBP4 has been shown to correlate with the magnitude of insulin resistance in lean, obese, and diabetic subjects identifying associated cardiovascular risk factors (6). Our data confirm these findings for subjects with IGT with significantly higher RBP4 levels compared with matched control subjects with NGT, indicating possible beneficial effects for the prevention of diabetes.

Effect of RAS blockade on blood pressure in IGT
Obesity is a major etiological factor in prehypertension in which adipose tissue activates the RAS. The Trial of Prevention of Hypertension demonstrated

that angiotensin receptor blockade delays blood pressure exaggeration in prehypertensive patients (24). Our study included prehypertensive individuals, defined as having a systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg, and hypertensive individuals. The mean reduction in ambulatory systolic blood pressure under valsartan treatment was considerably higher in the IGT group than the NGT group. These changes may reflect an activated RAS in subjects with insulin resistance.

We acknowledge the following limitation of our experimental study: In isolated IGT, the primary pathomechanism is defective early-phase and late insulin secretion combined with muscle and hepatic insulin resistance. An important additional pathomechanism is also the reduced glucagon-like peptide (GLP)-1 serum level (25). In our patient group, we cannot exclude to a certain extent a variance of the low GLP-1 levels. In addition, since we investigated insulin resistance during intravenous glucose stress testing, the effects of incretins (GLP-1, glucose-dependent insulinotropic peptide) on intravenous glucose load were not retrieved. This important and interesting incretin effect has to be taken into account in interpreting our results.

In conclusion, in patients with impaired glucose tolerance, insulin sensitivity and associated low-grade inflammation improve after treatment with ARB. These effects may provide a rationale for early pharmacological intervention aimed at ameliorating diabetic and cardiovascular risk in subjects with metabolic disease.

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