Association of the T-G Polymorphism in Adiponectin (Exon 2) With Obesity and Insulin Sensitivity

Interaction With Family History of Type 2 Diabetes

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The adipocyte-derived hormone adiponectin seems to protect from insulin resistance, a key factor in the pathogenesis of type 2 diabetes. Genome-wide scans have mapped a susceptibility locus for type 2 diabetes and the metabolic syndrome to chromosome 3q27, where the adiponectin gene is located. A common silent T-G exchange in nucleotide 94 (exon 2) of the adiponectin gene has been associated with increased circulating adiponectin levels. Metabolic abnormalities associated with the G allele have not been reported. We therefore assessed whether this polymorphism alters insulin sensitivity and/or measures of obesity using the Tübingen Family Study database (prevalence of the G allele, 28%). In 371 nondiabetic individuals, we found a significantly greater BMI in GG + GT (25.5 ± 0.7 kg/m^2) compared with TT (24.1 ± 0.3 kg/m^2; $P = 0.02$). Insulin sensitivity (determined by euglycemic clamp, $n = 209$) was significantly lower in GG + GT (0.089 ± 0.007 units) compared with TT (0.112 ± 0.005 units; $P = 0.02$). This difference disappeared completely on adjustment for BMI. Because our population contains a relatively high proportion of first-degree relatives of patients with type 2 diabetes, we stratified by family history (FHD). Much to our surprise, the genotype differences in BMI and insulin sensitivity in the whole population were attributable entirely to differences in the subgroup without FHD, whereas in the subgroup with FHD, the G allele had absolutely no effect. Moreover, individuals without FHD had a significantly lower BMI than individuals with FHD (25.2 ± 0.4 vs. 26.2 ± 0.5 kg/m^2; $P = 0.01$), which was not the case for the GG + GT subgroup without FHD (27.0 ± 0.9 kg/m^2; NS). This suggests that in individuals without familial predisposition for type 2 diabetes, the adiponectin polymorphism may mildly increase the obesity risk (and secondarily insulin resistance). In contrast, in individuals who are already burdened by other genetic factors, this small effect may be very hard to detect. *Diabetes* 51:37–41, 2002

Insulin resistance is an important factor in the development of type 2 diabetes, and multiple mechanisms are thought to contribute to its pathogenesis. Among these, the roles of adipose tissue and obesity are of paramount significance. Recently, a novel adipocyte-derived hormone, adiponectin (also called apM1 [adipose most abundant gene transcript 1] and acrp30 or adipoQ for the murine homologue) was identified and characterized (1,2). With a concentration of ~5 μg/ml in human plasma, adiponectin represents one of the most abundant circulating proteins (0.01% of total protein). It is interesting that in obesity, a condition highly associated with insulin resistance, plasma adiponectin levels are significantly decreased (4.3 vs. 5.8 μg/ml) (3,4). In both Pima Indians and Caucasians, adiponectin concentrations were positively correlated with insulin sensitivity and decreased significantly with deteriorating glucose tolerance (3) while increasing after weight reduction (5). Moreover, intravenous administration of recombinant adiponectin to rodent models of insulin resistance restored normal insulin sensitivity (6). Thus, in contrast to previously discussed peptide hormones released from adipocytes (tumor necrosis factor-α (7,8) and resistin (9), adiponectin seems to protect from insulin resistance and type 2 diabetes.

The adiponectin gene consists of three exons and two introns spanning a 17-kb region and has been located on chromosome 3q27 (4,10). In the same region, genome-wide scans have recently mapped a susceptibility locus for type 2 diabetes and measures of adiposity (11,12). One common and two rare genetic polymorphisms in the adiponectin gene have been identified in nondiabetic populations (4,10): a silent T-G exchange in nucleotide 94 (exon 2) (prevalence ~25%), a T-C exchange in nucleotide 331 (exon 3) resulting in a missense mutation (Tyr111His; prevalence in Germans 4%), and a T-C exchange in nucleotide 383 (exon 3) also resulting in a missense mutation (Arg112Cys; prevalence in Japanese 0.5%). Prevalence of the polymorphisms was ~50% (exon 2) and 0.5% (exon 3). The highly prevalent T/G polymorphism in exon 2, though not resulting in an amino acid exchange, could somehow affect plasma adiponectin levels. Although it did not reach statistical significance, there was a dose-dependent decrease in the mean adiponectin concentration for the G allele in 219 Japanese (4).

It is not known whether the T/G polymorphism in exon

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FHD, family history of diabetes; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

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TABLE 1
Characteristics of nondiabetic individuals who underwent the OGTT (all individuals)

	TT	GT	GG	GT + GG	P* (3 groups)	P (TT vs GT+GG)
n	268	88	15	103		
Male/female (n)	111/157	32/56	5/10	37/66	0.61†	0.33†
NGT/IGT (n)	249/19	79/9	14/1	93/10	0.64†	0.40†
Age (years)	34 ± 1	35 ± 1	35 ± 2	35 ± 1	0.80	0.44
BMI (kg/m^2)	25.3 ± 0.3	26.7 ± 0.7	27.6 ± 1.3	26.9 ± 0.6	0.47	0.02
Waist-hip ratio	0.84 ± 0.005	0.86 ± 0.01	0.85 ± 0.02	0.86 ± 0.01	0.06	0.03
Body fat (%)	26 ± 1	28 ± 1	31 ± 2	29 ± 1	0.02	0.01
Fasting serum glucose (mmol/l)	4.89 ± 0.03	4.91 ± 0.06	4.83 ± 0.18	4.90 ± 0.05	0.87	0.91
Glucose 120 min (mmol/l, OGTT)	5.51 ± 0.09	5.69 ± 0.16	5.78 ± 0.34	5.70 ± 0.14	0.51	0.25
Fasting serum insulin (pmol/l)	47 ± 2	53 ± 4	64 ± 7	55 ± 4	0.04	0.02
Insulin 120 min (pmol/l, OGTT)	273 ± 14	320 ± 32	478 ± 84	343 ± 30	0.01	0.02

*Analysis of variance; †χ^2 test. NGT, normal glucose tolerance.

2 is associated with insulin sensitivity and whether it influences the relationship between obesity and insulin resistance. Moreover, it has not been examined whether superimposition of absence or presence of family history of type 2 diabetes interferes with any effect of the genotype. In the present studies, therefore, we examined data from the Tübingen Family Study to specifically address the question whether insulin sensitivity is different in carriers of the T/G polymorphism in exon 2 (GG + TG) compared with wild-type controls (TT). For this purpose, we analyzed euglycemic-hyperinsulinemic clamp data (n = 209, normal glucose tolerant) where a direct measure of insulin sensitivity was obtained and data from oral glucose tolerance tests (OGTT) using estimates for insulin sensitivity (n = 371 nondiabetic subjects). The populations were additionally stratified according to presence (FHD) or absence (no FHD) of family history of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects. In the Tübingen Family Study for type 2 diabetes, primarily normal glucose-tolerant individuals with (and without) a family history of type 2 diabetes are recruited and metabolically characterized. Recruitment mechanisms include word-of-mouth, fliers, and newspaper advertisements. In the present analysis, we report data from OGTT (n = 371) and euglycemic-hyperinsulinemic clamps (n = 210; characteristics shown in Tables 1 and 2). In our population, the prevalence of the G allele in adiponectin (exon 2) is ~28%. The OGTT group includes 29 individuals with impaired glucose tolerance (IGT). This proportion represents the population's prevalence of IGT (13). To ensure that we did not miss an effect of the polymorphism on glucose tolerance, we left this subgroup in the analysis. The characteristics of the subgroups that underwent the different protocols are shown in Tables 1 and 2. We additionally stratified the groups by presence or absence of family history of diabetes, which was known in 360 individuals (characteristics shown in Tables 3 and 4). Assessment of family history status depended solely on self-reports using a standardized questionnaire.

The genotype distribution of the study population (72.2% TT, 23.7% GT, 4% GG) was essentially in Hardy-Weinberg equilibrium (P = 0.09, χ^2 test). The statistical trend is due to an overrepresentation of the homozygotes by one or two individuals, who were not related. The protocols were approved by the local ethical committee, and all individuals gave informed written consent.

OGTT. After a 10-h overnight fast, individuals ingested a solution that contained 75 g dextrose, and venous blood samples were obtained at 0, 30, 60, 90, and 120 min for determination of plasma glucose and plasma insulin. Stages of glucose tolerance were classified according to World Health Organization criteria (14).

Hyperinsulinemic-euglycemic clamp. After the baseline period, individuals received a primed insulin infusion at a rate of 1.0 mU · kg^{-1} · min^{-1} for 2 h as previously described (15). Blood was drawn every 5–10 min for determination of blood glucose, and the infusion rate of exogenous glucose was adjusted appropriately to maintain the baseline glucose level.

Analytical procedures. Blood glucose was determined using a bedside glucose analyser (glucose-oxidase method; Yellow Springs Instruments, Yellow Springs, CO). Plasma insulin was determined by microparticle enzyme immunoassay (Abbott Laboratories, Tokyo, Japan), and plasma C-peptide was determined by radioimmunoassay (Byk-Sangtec, Dietzenbach, Germany). The T-G polymorphism in exon 2 of the adiponectin gene was determined by sequencing the polymerase chain reaction product (primer sequence as previously described [4]) using an automated sequencer (ABI prism 310, Perkin-Elmer, Foster City, CA).

Calculations. The insulin sensitivity index (in µmol · kg^{-1} · min^{-1} · [pmol/l]$^{-1}$) for systemic glucose uptake was calculated as mean infusion rate of exogenous glucose necessary to maintain euglycemia during the last 60 min of the standard clamp divided by the steady-state serum insulin concentration.

Statistical analysis. Data are given as mean ± SE unless otherwise stated. Differences were assessed by analysis of variance for three groups in the OGTT database. In addition, comparison between two groups (individuals heterozygous and homozygous for the polymorphism were pooled, GT + GG) was analyzed using an unpaired Student's t test on log-transformed data. For

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TABLE 2
Characteristics of normal glucose-tolerant individuals who underwent the hyperinsulinemic-euglycemic clamp (all individuals)

	TT	GT + GG	P
n	160	49	
Male/female (n)	80/80	22/27	0.53*
Age (years)	32 ± 1	32 ± 2	0.63
BMI (kg/m^2)	24.1 ± 0.3	25.5 ± 0.7	0.02
Waist-hip ratio	0.83 ± 0.01	0.85 ± 0.01	0.06
Body fat (%)	23 ± 1	25 ± 1	0.06
Fasting serum glucose (mmol/l)	4.72 ± 0.04	4.80 ± 0.07	0.29
Glucose 120 min (mmol/l, OGTT)	5.13 ± 0.10	5.33 ± 0.15	0.29
Fasting serum insulin (pmol/l)	41 ± 2	52 ± 5	0.04
Insulin 120 min (pmol/l, OGTT)	223 ± 15	326 ± 37	0.02
Insulin sensitivity index (µmol · kg^{-1} · min^{-1} · [pmol/l]$^{-1}$)	0.112 ± 0.005	0.089 ± 0.007	0.02 (0.13†)

*χ^2 test; †adjusted for BMI and % body fat.

TABLE 3
Characteristics of nondiabetic individuals who underwent the OGTT (stratified by FHD)

	No FHD				FHD					
	All	TT	GT + GG	*P**	All	TT	GT + GG	*P**	*P*‡	*P*†
n	200	147	53		160	114	46			
Male/female (*n*)	86/114	81/66	33/20	0.34§	105/55	75/39	16/30	0.95§	0.10§	
NGT/IGT (*n*)	191/9	142/5	49/4	0.24§	143/17	162/12	41/5	0.95§	0.02§	
Age (years)	32 ± 1	32 ± 1	32 ± 2	NS	38 ± 1	38 ± 1	38 ± 1	NS	<0.001	<0.001
BMI (kg/m^2)	25.2 ± 0.4	24.5 ± 0.4	27.0 ± 0.9	<0.05	26.2 ± 0.05	26.0 ± 0.6	26.6 ± 0.8	NS	0.05	0.01
Waist-hip ratio	0.84 ± 0.01	0.84 ± 0.01	0.85 ± 0.01	NS	0.85 ± 0.01	0.84 ± 0.01	0.87 ± 0.01	NS	0.16	0.04
Body fat (%)	26 ± 1	24 ± 1	29 ± 1	<0.05	28 ± 1	28 ± 1	29 ± 1	NS	0.02	0.05
Fasting serum glucose (mmol/l)	4.78 ± 0.04	4.76 ± 0.05	4.83 ± 0.08	NS	5.03 ± 0.04	5.05 ± 0.05	4.97 ± 0.08	NS	<0.001	<0.001
Glucose 120 min (mmol/l, OGTT)	5.28 ± 0.09	5.17 ± 0.11	5.56 ± 0.14	NS	5.93 ± 0.12	5.94 ± 0.18	5.90 ± 0.24	NS	<0.001	<0.001
Fasting serum insulin (pmol/l)	49 ± 3	46 ± 3	57 ± 5	<0.001	49 ± 3	47 ± 3	53 ± 5	NS	0.10	0.07
Insulin 120 min (pmol/l, OGTT)	294 ± 20	255 ± 18	404 ± 52	<0.01	287 ± 15	291 ± 19	279 ± 28	NS	0.08	0.02

*TT versus GT + GG (Tukey-Kramer); †analysis of variance (four groups); ‡no FHD versus FHD (all); §χ^2 test. NGT, normal glucose tolerance.

analyses in the substantially smaller clamp group only, the pooled (GT + GG) genotypes were used. The nonparametric Wilcoxon test was used for nonnormally distributed parameters. For the comparison of subgroups stratified by presence or absence of family history of type 2 diabetes, analysis of variance followed by a Tukey-Kramer test was used. The interaction effect of family history and genotype was assessed using factorial multivariate analysis of variance. $P < 0.05$ was considered to be statistically significant. The statistical software package JMP (SAS Institute, Cary, NC) was used for the statistical analyses.

RESULTS

In the 371 nondiabetic individuals who underwent the OGTT, we found a significantly greater BMI in GG + GT (25.5 ± 0.7 kg/m^2) compared with TT (24.1 ± 0.3 kg/m^2; $P = 0.02$; Table 1). A parallel difference for percentage body fat was observed. Stratification by FHD revealed that the difference observed in the whole population was entirely attributable to even more pronounced differences in the subgroup without FHD, whereas in the subgroup with FHD, the G allele had absolutely no effect (Table 3). Regardless of the genotype, individuals without FHD had a significantly lower BMI than individuals with FHD (25.2 ± 0.4 vs. 26.2 ± 0.5 kg/m^2; $P = 0.01$). It is interesting that the BMI in the GG + GT genotype without FHD (27.0 ± 0.9 kg/m^2) was not significantly different than in the whole group with FHD (Fig. 1). The significantly greater basal and postload insulin concentrations in the GT + GG group suggests that the BMI difference, not unexpectedly, leads to differences in insulin sensitivity.

In the subgroup that underwent the hyperinsulinemic-euglycemic clamp ($n = 209$), the findings regarding obesity parameters were reproducible (Tables 2 and 4). Insulin sensitivity was significantly lower in GG + GT (0.089 ± 0.007 units) compared with TT (0.112 ± 0.005 units; $P = 0.02$). This statistical difference disappeared completely on adjustment for BMI and percentage body fat. The relationships among family history of diabetes, BMI, insulin sensitivity, and genotype are shown in Fig. 2.

DISCUSSION

The purpose of the present studies was to examine the effect of the common T-G polymorphism in the adiponectin gene on measures of obesity and insulin sensitivity. The most interesting finding was the difference in BMI, percentage body fat, and insulin sensitivity, especially in the group without FHD. The G allele was significantly associated with obesity. The decreased insulin sensitivity associated with the G allele was entirely accounted for by the difference in BMI. These associations with the G allele were entirely absent in the subgroup with FHD.

Our findings suggest that in individuals without familial predisposition for type 2 diabetes, the adiponectin polymorphism may mildly increase obesity risk and secondarily cause insulin resistance. A possible interpretation for the absence of such an association in the subgroup with FHD could be as follows: the familial predisposition represents a much stronger genetic load than the presence of single polymorphism, with a weak effect on the individual's phenotype. The latter effect may thus be buried by sum effects of other, unidentified genetic factors. Our observation of a significantly greater BMI in the subgroup with FHD compared with the subgroup without FHD but not compared with the GT + GG (without FHD) cohort supports this hypothesis.

It is unclear how a silent polymorphism (i.e., one not resulting in an amino acid exchange) can affect metabolism and/or alter the risk of obesity. Generally, a polymorphism need not be functionally relevant itself but can be in complete or near-complete linkage disequilibrium with a yet unidentified second polymorphism that has functional relevance, for example in the promoter region. However, sequencing of the promoter region of the human adiponectin gene in reasonably sized populations did not reveal common polymorphisms, let alone one in linkage disequilibrium with the T-G polymorphism in exon 2 (4,10). Alternatively, the polymorphism can be in linkage disequilibrium with polymorphism in introns that, in analogy to the UCSNP-43 polymorphism in calpain-10 (16), would destabilize pre-mRNA and result in reduced mRNA levels. Because intronic regions of the adiponectin gene have not yet been systematically screened for single nucleotide polymorphisms, this scenario remains a possibility. Pro-

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TABLE 4
Characteristics of NGT individuals who underwent the hyperinsulinemic-euglycemic clamp (stratified by FHD)

	No FHD				FHD					
	All	TT	GT + GG	P*	All	TT	GT + GG	P*	P‡	P†
n	126	100	26		83	59	24			
Male/female (n)	69/57	54/46	15/11	0.45§	29/54	22/37	7/17	0.95§	0.56§	
Age (years)	30 ± 1	30 ± 1	29 ± 1	NS	35 ± 1	34 ± 1	36 ± 1	NS	<0.001	<0.001
BMI (kg/m^2)	23.9 ± 0.4	23.5 ± 0.4	25.4 ± 1.0	NS	25.6 ± 0.6	25.1 ± 0.6	26.8 ± 1.2	NS	0.01	0.06
Waist-hip ratio	0.83 ± 0.01	0.82 ± 0.01	0.84 ± 0.01	NS	0.84 ± 0.01	0.83 ± 0.01	0.87 ± 0.02	NS	0.21	0.07
Body fat (%)	22 ± 1	22 ± 1	25 ± 2	NS	27 ± 1	26 ± 1	28 ± 1	NS	<0.001	<0.001
Insulin sensitivity index μmol · kg^{-1} · min^{-1} · [pmol/l]$^{-1}$	0.108 ± 0.005	0.116 ± 0.006	0.082 ± 0.008	<0.05 (NS‖)	0.094 ± 0.006	0.096 ± 0.006	0.089 ± 0.011	NS	0.07 (NS‖)	0.01 (NS‖)

*TT versus GT + GG (Tukey-Kramer); †analysis of variance (four groups); ‡no FHD versus FHD (all); §χ^2 test; ‖adjusted for BMI and % body fat.

FIG. 1. BMI in individuals with (GT + GG) and without (TT) the T-G polymorphism in adiponectin (exon 2), stratified by FHD. The complementary subgroups were analyzed using the Tukey-Kramer test for multiple comparisons.

viding a final answer to this question is beyond the capabilities of our laboratory. The strong linkage disequilibrium with type 2 diabetes, measures of adiposity, and insulin levels found in the chromosomal region where the adiponectin gene is located (11,12) suggests that somewhere on this locus a common genetic variant, such as the T-G polymorphism in the adiponectin gene, must have a measurable effect on obesity, glucose homoeostasis, or both.

It may be of interest that circulating adiponectin concentrations were significantly lower in Japanese carriers of the G allele (4). Although this did not quite reach statistical significance, it may point to a possible link among the GG genotype, reduced circulating adiponectin levels, and reduced insulin sensitivity. A conclusive assess-

FIG. 2. Relationship between BMI and insulin sensitivity in individuals with (GT + GG) and without (TT) the T-G polymorphism in adiponectin (exon 2), stratified by FHD (for clarity, the subgroup with FHD was not divided into genotype groups that were essentially superimposable). The insert depicts the means ± SE of the two genotype subgroups without FHD and the whole group with FHD on a magnified scale (BMI and insulin sensitivity are on a logarithmic scale).

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ment of these relationships probably requires larger sample sizes and the advent of a commercially available adiponectin assay.

Our findings are clearly at variance with reports from a Japanese (4) and a German population (10) in which no effect of G allele on measures of obesity were observed. Possible explanations for this divergence include differences in family history status by which we had stratified and a selection bias due to recruitment of individuals through an endocrinological outpatient clinic (10).

In conclusion, we found a significantly greater BMI in GG + GT accompanied by reduced insulin sensitivity compared with TT. This difference was attributable entirely to differences in the subgroup without FHD, whereas in the subgroup with FHD, the G allele had absolutely no effect. This suggests that in individuals without FHD, the adiponectin polymorphism may mildly increase the obesity risk (and secondarily insulin resistance). In contrast, in individuals who are already burdened by other genetic factors, this small effect may be very hard or impossible to detect.

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