Adiponectin and C-Reactive Protein in Obesity, Type 2 Diabetes, and Monodrug Therapy

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To learn more about the factors that regulate adipokines in diabetes, we examined fasting plasma concentrations of adiponectin and C-reactive protein (CRP) in well-characterized groups of age-matched individuals classified as: (1) type 2 diabetes; (2) impaired fasting glucose or mild diabetes (IFG/mild DM); (3) obese, matched for body mass index (BMI); and (4) non-obese. Diabetic subjects were also studied on no phamacologic treatment, after 3 months randomization to metformin or glyburide, and after 3 months crossover to the opposite drug. CRP decreased and adiponectin increased progressively between subjects in groups 1 through 4. CRP was significantly associated with percent ($r = 0.45$) and total ($r = 0.50$) fat, insulin sensitivity as S_I ($r = -0.39$) or homeostasis model assessment of insulin resistance [HOMA (IR)] ($r = -0.36$), and hemoglobin A_{1c} (HbA_{1c}) ($r = 0.41$). The relationship of CRP to percent fat appeared to be logarithmic and log CRP varied with percent fat independent of gender. Adiponectin concentration was significantly associated with insulin sensitivity as S_I ($r = 0.55$) or HOMA (IR) ($r = -0.46$). Adiponectin concentrations were higher among women overall (all groups included) but not in women classified as type 2 diabetes. Although mean adiponectin was higher in subjects classified as non-obese compared to obese, adiponectin, in sharp contrast to leptin (previously reported data) and to CRP, varied markedly when expressed as a function of adiposity. Multiple regression models confirmed the strong relationship of adiponectin to insulin sensitivity, as well as the relationships of CRP to adiposity and insulin sensitivity. Glyburide treatment of diabetes decreased CRP and did so even though body weight increased. We conclude that both CRP and adiponectin correlate strongly to S_I. CRP, in contrast to adiponectin, is far more dependent on adiposity. The relationship between CRP (like leptin) and gender depends on how CRP is expressed relative to adiposity. Our data raise the possibility that gender differences in adiponectin may be lost in diabetes. Finally, pharmacologic treatment of diabetes may modulate CRP independent of adiposity.

CERTAIN ADIPOKINES and C-reactive protein (CRP), which is regulated by proinflammatory adipokines,[1,2] may be important in the pathophysiology of vascular disease in diabetes. Adiponectin and leptin may affect cardiovascular function through affects on fat metabolism, circulating lipids, blood pressure, or other atherogenic factors[3-7] and CRP may play a role in atherogenesis.[8] Circulating concentrations of these substances are altered in diabetes. Therefore, to better understand vascular complications, it is important to understand what factors, related to the diabetic state, regulate plasma concentrations of adipokines.

Circulating adiponectin concentrations are reduced in obesity and negatively correlated to insulin resistance and triglycerides and positively with high-density lipoprotein (HDL).[9,10] Adiponectin may reduce intrahepatic and muscle triglyceride content through increased muscle fat oxidation[11] and induction of genes important in fatty acid transport and oxidation.[10,12]

Plasma CRP concentrations are elevated in obesity, possibly secondary to adipocyte release of factors such as interleukin-6,[1] and higher in insulin-resistant states.[1,13-15] Whether or not CRP is a marker of insulin resistance in type 2 diabetes or involved mechanistically is still unclear.[16] Interestingly, salicylate therapy may improve glycemia and insulin sensitivity,[17,18] although the drug might be detrimental at lower doses.[19,20]

Information is rapidly accumulating regarding the regulation of individual adipokines. However, several issues are still unclear. Little is currently known concerning the relative variation of these substances across individuals with differing degrees of glucose intolerance and adiposity. In addition, there is still uncertainty as to whether factors such as insulin and/or insulin sensitivity or gender may be important per se in regulating adipokines or whether such determinants are dependent on concurrent changes in adiposity. Moreover, it is unclear as to whether treatment of diabetes alters adipokines independent of adiposity.

To address these issues, we examined fasting plasma CRP and adiponectin in highly characterized groups of age-matched subjects on no antihyperglycemic medications classified as: (1) type 2 diabetes; (2) impaired fasting glucose or mild diabetes (IFG/mild DM); (3) obese, matched for body mass index (BMI); and (4) non-obese. Diabetic subjects were also studied prospectively before and after treatment with glyburide or metformin. Fasting plasma leptin concentrations have previously been reported in these subject.[21]

These studies were performed as part of the work of our Veterans Administration/Juvenile Diabetes Research Foundation–sponsored diabetes center directed at vascular disease in diabetes. In the context of this project, all participants underwent metabolic studies and measures of in vivo (forearm) vascular function. The vascular studies are the subject of a separate report.

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MATERIALS AND METHODS

Design

The protocol was reviewed and approved by our institutional Human Subjects Committee. The study protocol and inclusion and exclusion criteria have been previously reported.[21] No subjects had evidence of vascular disease.

In brief, 3 groups of subjects were initially recruited: (1) type 2 diabetes, defined for the purposes of this study as fasting plasma glucose (FPG) greater than 6.9 mmol/L; (2) obese controls with FPG less than 6.1 mmol/L matched to the diabetic subjects for BMI, age, and gender; and (3) non-obese, nondiabetic controls with FPG less than 6.1 mmol/L matched for age and gender. In the course of screening, some nondiabetic subjects (by history) were found to have FPG $\geq$6.1 mmol/L and $\leq$6.9 mmol/L and were labeled as impaired fasting glucose (IFG). In addition, in the run-in phase of this study (see below), some diabetic subjects (by history) on no oral medications were found to have a FPG $\geq$6.1 mmol/L and $\leq$6.9 mmol/L and, for study purposes, were labeled "mild diabetes." These subjects with IFG or mild diabetes were combined and included as a fourth group labeled "IFG/mild DM." Therefore, the data in this report compare 4 groups of subjects constituting a spectrum from non-obese to obese through IFG to type 2 diabetes. It is important to note the groups were defined a priori for the purposes of this study alone and not to match other classification schemes in clinical use or to match the recent change in the American Diabetes Association classification of clinical IFG to start at 100 mg/100 mL.

At the first screening visit (SV1), overnight fasting (10-hour) blood samples were obtained for measurement of glucose, insulin, hemoglobin A_{1c} (HbA_{1c}), leptin, free fatty acids (FFAs), lipid profile, and for storage at -70°C for potential future biochemical analysis. Subsequently, adiponectin and CRP were assayed. Nondiabetic subjects returned in 2 to 4 weeks and were admitted to our General Clinical Research Center (GCRC) for baseline evaluation (see below). At SV1, diabetic subjects were advised in a weight maintenance meal plan. Oral glycemic medication and/or insulin were discontinued and a run-in period was implemented. Diabetic subjects returned 10 weeks later for screening visit 2 (SV2) if discontinued from antihyperglycemic medication or 4 weeks later if not originally taking antihyperglycemic medication. At SV2, fasting serum glucose was obtained and used in the final classification and assignment of participants. Two to 3 weeks after SV2, subjects were admitted to our GCRC for baseline evaluation.

At baseline evaluation, overnight fasting (10-hour) blood samples were obtained as at SV1. After blood sampling, subjects underwent studies of forearm vascular reactivity using methods we previously described.[22] After lunch, on the same day, body fat and distribution was determined by dual-energy x-ray absorptiometry (DEXA). The next morning, after a 10-hour overnight fast, insulin sensitivity and release were assessed by the frequently sampled intravenous glucose tolerance test (FSIVGTT).

Nondiabetic subjects and subjects with IFG/mild DM completed the protocol at this point. After baseline studies, participants classified as diabetes were randomly assigned to receive open labeled metformin or glyburide for 3 months followed by crossover to the opposite drug. Subjects returned to the GCRC for repeat baseline studies after 3 months of treatment with each drug.

Pharmacologic Treatment

Doses were adjusted until a goal of FPG less than 6.9 mmol/L was achieved or until maximum dosage (20 mg/d glyburide or 2,550 mg/d metformin), following which no additional change was made for the 3-month period and no additional drugs added.[21]

FSIVGTT

Insulin sensitivity (S_I), was determined using the minimal model described by Bergman et al,[23] as we previously reported in these subjects.[21] We also calculated the area under the insulin curve in the first 20 minutes after glucose injection (insulin AUC) as an index of insulin secretory capacity. The insulin modification of the FSIVGTT,[24] needed to accurately fit the data in type 2 diabetes, was used for all subject groups.

The FSIVGTT was completed for only 11 of the 27 non-obese controls because of an unacceptable incidence of hypoglycemia (glucose $<$2.8 mmol/L or symptoms). The FSIVGTT was completed in only 22 of the 25 obese controls because of technical problems (hemolysis or venous access). However, all 27 non-obese and all 25 obese subjects completed the procedure through the first 20 minutes after glucose administration, so we were able to calculate the acute insulin AUC.

Homeostasis Model Assessment for Insulin Resistance

Insulin resistance was also assessed in all subjects as HOMA (IR) calculated from fasting insulin and glucose concentrations using the homeostasis model for insulin resistance as described.[25]

Body Fat Distribution

Regional adipose mass was measured by DEXA using a Hologic QDR 4500 Elite Scanner (Hologic Inc, Bedford, MA). DEXA studies were performed in all obese and non-obese controls but in only 23 of the 26 subjects with type 2 diabetes and 11 of 13 classified as IFG/mild DM as some subjects weighed over 113.6 kg (250 lb), the maximum allowable for the procedure.

Plasma Determinations

Free insulin concentrations were determined by Abbott Microparticle Enzyme Immunoassay (Abbott Diagnostics, North Chicago, IL) automated on the Abbott IMx after precipitation by polyethylene glycol. Human adiponectin was determined by radioimmunoassay using kits purchased from Linco, Inc (St Louis, MO) on plasma diluted 1:500. CRP was determined by enzyme-lonked immunosorbent assay (ELISA0 using a kit purchased from ALPCO Diagnostics (Windham, NH). The assay required a 1:100 dilution of the plasma sample. FFAs were measured using a colorimetric kit purchased from Roche Diagnostics (Mannheim, Germany). Total cholesterol, low-density lipoprotein (LDL), HDL, triglycerides, and glucose were determined by the clinical chemistry laboratory at our institution on plasma obtained in our GCRC.

Data Analysis

Differences between groups by analysis of variance (ANOVA), linear correlations, differences in linear slopes and elevations, and multiple regression analyses were performed using commercial software (GraphPad Prism, GraphPad Software, San Diego, CA and Sigma Stat, Statistical Solutions, Saugus, MA).

RESULTS

Table 1 lists characteristics of the study participants. Diabetic subjects had been advised in a weight maintenance diet and body weights were stable at the time of GCRC admission (92.3 $\pm$ 3.1 kg at the initial GCRC admission and 92.4 $\pm$ 3.1 when determined at SV2, 2 to 3 weeks before admission).

As shown in Fig 1, adiponectin concentrations were highest in non-obese controls and progressively decreased when compared to obese subjects, IFG/mild diabetes, and type 2 diabetes. CRP concentrations varied in opposite fashion. Previously re-

Table 1. Characteristics of Subjects by Group

	Type 2 DM	IFG/Mild DM	Obese	Non-obese
n	26	13	25	27
Age (yr)	58.5 ± 1.4	51.9 ± 2.8	55.4 ± 1.6	54.1 ± 1.5
BMI (kg/m^2)	33.8 ± 1.0	33.4 ± 1.2	31.8 ± 0.7	24.5 ± 0.5†
HbA_{1c} (%)	7.93 ± 0.26†	6.04 ± 0.11	5.60 ± 0.07	5.60 ± 0.05
Fasting glucose (mmol/L)‡	10.45 ± 0.47†	6.49 ± 0.26*	5.23 ± 0.10	5.14 ± 0.10
Fasting insulin (pmol/L)‡	106 ± 10	118 ± 25	89.7 ± 10.1	41.6 ± 3.6†
Cholesterol (mmol/L)	4.96 ± 0.15	4.78 ± 0.20	5.10 ± 0.19	5.07 ± 0.18
HDL (mmol/L)	1.12 ± 0.05*	1.27 ± 0.10	1.41 ± 0.08	1.73 ± 0.08†
Triglycerides (mmol/L)	2.41 ± 0.29*	1.69 ± 0.15	1.67 ± 0.17	1.15 ± 0.11
S_1 ($min^{-1} \cdot \mu U^{-1} \cdot mL$)§	0.91 ± 0.11†	1.79 ± 0.35	2.31 ± 0.33	3.21 ± 0.42
Insulin AUC (nmol/L/20 min)	2.35 ± 0.23†	6.01 ± 1.16*	9.75 ± 1.23	4.43 ± 0.59†
Percent fat‖	37.9 ± 2.0	37.7 ± 1.9	35.7 ± 1.5	27.4 ± 1.6†
Total fat (kg)‖	35.0 ± 2.2	35.1 ± 2.3	32.5 ± 1.7	19.5 ± 1.1†
No. female	14	7	16	15

*$P < .05$ compared to obese by ANOVA with Dunnett's post test.

†$P < .01$ compared to obese by ANOVA with Dunnett's post test.

‡Average of 4 values for each subject over time −15 to 0 minutes of FSIVGTT.

§Determined in only 22 obese and 11 non-obese subjects.

‖Determined in only 23 of the 26 subjects with type 2 diabetes and 11 of 13 classified as IFG/mild DM.

ported leptin concentrations were included for comparison. These parameters were also evaluated in relation to gender (Table 2). Adiponectin and CRP concentrations followed the same pattern in female subjects considered alone. Moreover, the same pattern was observed in male subjects, although significant differences are not evident, likely because of the limited overall sample size. These data also reveal an interesting contrast in adiponectin by gender and group. Analysis by 2-factor (gender and group) reveals an overall gender difference between males and females ($P < .01$ for gender, $P < .0001$ for group, interaction nonsignificant). However, Table 2 shows essentially no gender difference among the subjects with type 2 diabetes.

We also determined the effect of treating type 2 diabetes with metformin or glyburide on CRP and adiponectin concentrations. Table 3 lists the characteristics and effects of treatment of the 26 diabetic subjects at screening, baseline (before drug treatment) and after 3 months of each drug. Since these studies involved repeated measures in the same individual subjects, gender was not at issue. Treatment with either metformin or glyburide reduced glycemia to approximately the same extent. Both drugs reduced CRP concentrations; however, the reduction in CRP was significant only for glyburide. To test for the impact of the crossover design we examined the CRP data in a 2-factor ANOVA model, the factors including treatment group and the initial drug (Fig 2). Glyburide appeared to reduce CRP whether administered as the first or second drug, but the effect achieved statistical significance only when glyburide was administered first. Interaction between treatment group and drug was not significant ($P = .80$) in this analysis. Glyburide had approximately the same effect in male and female subjects (data not shown).

We further assessed the interrelationship between adiponectin and CRP with several other parameters by Pearson corre-

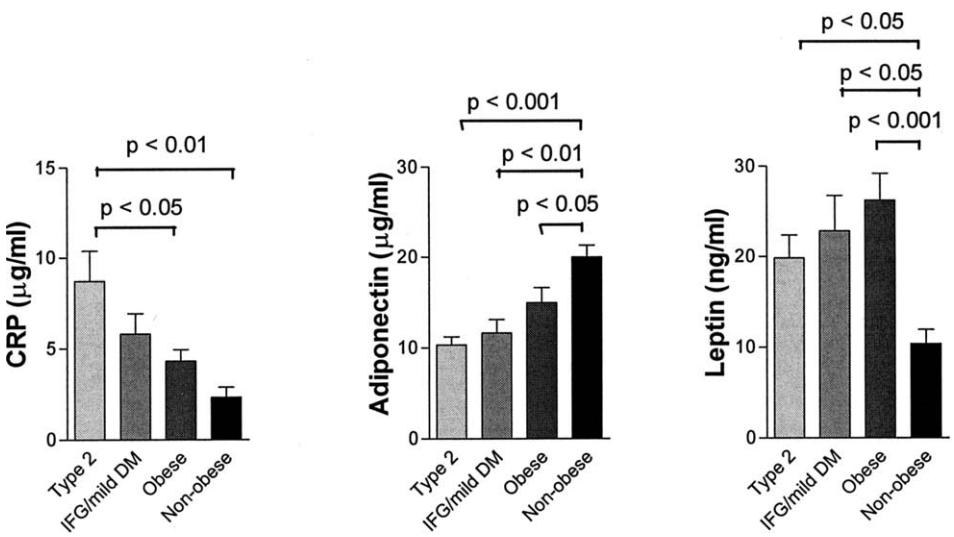

Fig 1. Fasting CRP, adiponectin, and leptin concentrations in subjects classified as type 2 diabetes, IFG/mild diabetes, obese, or non-obese.

Table 2. CRP and Adiponectin by Gender in Participants Classified as Non-obese, Obese, IFG/Mild DM, and Type 2 DM

	Type 2 DM	IFG/mild DM	Obese	Non-obese
Males				
n	12	6	9	12
CRP (μg/mL)	6.0 ± 2.5	4.9 ± 1.3	2.6 ± 0.9	0.7 ± 0.2
Adiponectin (μg/mL)	10.1 ± 1.3	8.9 ± 1.2	12.8 ± 2.4	15.7 ± 2.0
Females				
n	14	7	16	15
CRP (μg/mL)	11.1 ± 2.1	6.6 ± 1.8	4.8 ± 0.7*	3.6 ± 0.8*
Adiponectin (μg/mL)	10.6 ± 1.3	13.9 ± 2.4‡	16.3 ± 2.2‡	23.4 ± 1.3†

NOTE. Data were analyzed by 1-way ANOVA with Tukey's post test.
*$P < .01$, or †$P < .001$ compared to type 2 DM.
‡$P < .05$ compared to non-obese controls.

lation analysis (Table 4). Of particular interest is the strong relationships between CRP and adiposity (percent fat or total fat) in contrast to the lack in correlations of adiponectin to adiposity. Of additional note is the strong correlation between adiponectin and HDL cholesterol and the relationships of both CRP and adiponectin to insulin sensitivity determined either as S_I or as HOMA (IR). LDL cholesterol did not significantly correlate to any of these factors (data not shown).

The regressions of leptin, CRP, and adiponectin on percent fat are illustrated in Fig 3A through C. Given the wide scatter in the relationship between adiponectin and percent fat, we also examined adiponectin in relation to other indices of adiposity including total fat (Fig 3D) and BMI (not shown) and, likewise, observed nonsignificant relationships with wide scatter. To avoid confounding effects of diabetes or glucose intolerance, the data of Fig 3 include only the nondiabetic control groups. Given the appearance of the data for leptin and CRP versus percent fat, we also examined log leptin (previously reported)[21] and log CRP as a function of percent fat (Fig 3E and F) and showed an improvement in the linear relationships. The slopes and elevations of the regression lines of log leptin versus percent fat did not differ by gender.[21] Since the regression of log CRP to percent fat resembled that for leptin, we also examined that relationship by gender (Fig 3F) and found no significant difference in the slopes or elevations. We note that, as we previously observed for leptin,[21] this apparent gender independent relationship for CRP holds only for percent fat but not total fat or BMI, wherein male subjects have lower log CRP for given fat mass (Fig 3G) or BMI (not shown) and the slopes differ significantly by gender.

In multiple regression models using backwards stepwise regression, we examined the relationships of adiponectin and log CRP (as dependent variables) to percent fat, HOMA (IR), FFAs, HbA_{1c}, age, and gender (coded as 1 or 0) including all subjects over all 4 groups. The dependent variable, adiponectin, was predicted by HOMA (IR) ($P < .001$) and gender ($P = .005$). Log CRP was predicted by percent fat ($P < .001$), HOMA (IR) ($P < .01$), and FFAs ($P = .026$). Other multiple regression models including triglycerides and HDL were considered but confounded by strong correlations between independent variables. We also used backwards stepwise regression to examine the relationship of log CRP (dependent variable) to percent fat and gender among the nondiabetic subjects. By this analysis log CRP was dependent on percent fat ($P < .001$) independent of gender, as anticipated based on the data of Fig 3F.

DISCUSSION

Previous studies show that adiponectin is reduced,[9,10] while CRP is elevated[2,13-15] in subjects with features of the metabolic

Table 3. Parameters Determined in 26 Subjects Classified as Type 2 DM at Screening, Baseline, and After Three Months of Treatment With the Indicated Drug

	Screening	Baseline	Metformin	Glyburide
BMI (kg/m^2)	34.6 ± 0.9†	33.8 ± 1.0	33.5 ± 1.0	34.5 ± 1.0*
CRP (μg/mL)	8.07 ± 1.36	8.73 ± 1.66	6.97 ± 1.34	5.95 ± 0.98*
Adiponectin (μg/mL)	10.6 ± 1.0	10.4 ± 0.9	11.1 ± 1.1	10.8 ± 1.0
HbA_{1c} (%)	7.04 ± 0.16†	7.93 ± 0.26	7.01 ± 0.17†	7.10 ± 0.24†
Fasting glucose (mmol/L)‡	8.79 ± 0.34†	10.45 ± 0.47	7.93 ± 0.37†	8.00 ± 0.43†
Fasting insulin pmol/L)‡	120 ± 13	106 ± 10	111 ± 14	132 ± 13
Cholesterol (mmol/L)	4.95 ± 0.15	4.96 ± 0.15	4.68 ± 0.14*	4.74 ± 0.15
HDL (mmol/L)	1.12 ± 0.05	1.12 ± 0.05	1.16 ± 0.05	1.14 ± 0.05
Triglycerides (mmol/L)	2.24 ± 0.29	2.41 ± 0.29	2.28 ± 0.36	2.14 ± 0.22
S_1 ($min^{-1} \cdot \mu U^{-1} \cdot mL$)§		0.91 ± 0.11	1.14 ± 0.16*	1.05 ± 0.19
Insulin AUC (nmol/L/20 min)§		2.35 ± 0.23	3.32 ± 0.46*	3.73 ± 0.40†

*$P < .05$ or †$P < .01$ compared to baseline by repeated measure ANOVA with Dunnett's post test.
‡Baseline, metformin, and glyburide values represent the average of 4 determinations for each subject over time −15 to 0 minutes of FSIVGTT; screening values determined on single samples.
§Not determined at screening.

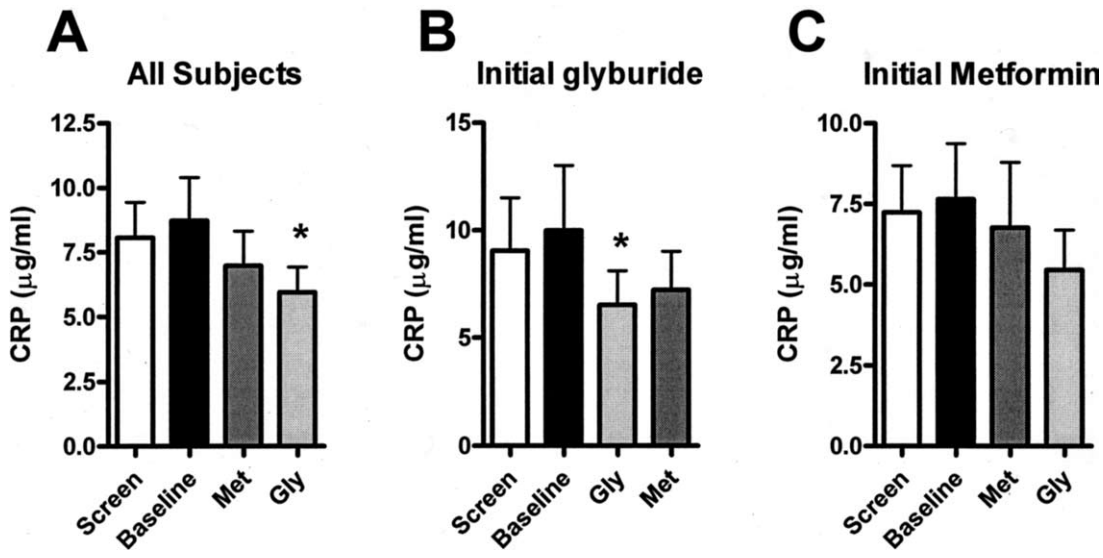

Fig 2. Effect of glyburide and metformin on fasting CRP concentrations at screening, baseline, and after 3 months of treatment with metformin or glyburide. (A) Data from all subjects irrespective of the order of administration of the 2 drugs; (B) subjects who received glyburide for the first 3 months followed by metformin; (C) subjects who received metformin for the first 3 months followed by glyburide. *$P < .05$ by 1-way ANOVA (A) or 2-factor (drug and order of administration) ANOVA (B and C).

syndrome. While confirming these general concepts, our current work examines both of these parameters concurrently over a spectrum of age-matched subjects with varying glucose tolerance and adiposity from normal, through IFG, to type 2 diabetes. We also report the effect of 2 forms of monotherapy on adiponectin and CRP in subjects off drug treatment at the onset and on a consistent dietary regimen.

CRP appears to progressively increase when glucose metabolism deteriorates, as evident in subjects with impaired fasting glucose and type 2 diabetes (Fig 1). This relationship between worsening glycemia and CRP is independent of obesity as the subjects in the groups with type 2 diabetes, IFG/mild DM, and obesity were adiposity matched. This independence from adiposity is consistent with data by McLaughlin et al,[26] who measured CRP before and after calorie restriction in obese women classified as insulin-resistant or insulin-sensitive. In that report, the relation between CRP concentrations and insulin resistance did not depend on obesity.

Our treatment data (Fig 2) also show that CRP may be regulated independent of concurrent changes in adipose mass. Glyburide decreased CRP even though BMI did not improve, but, in fact, increased (Table 3). Thus, improved glycemia or some effect of the sulfonylurea drug decreased CRP independent of adiposity. Metformin also decreased CRP but the data did not achieve significance in the sample size (N = 26) examined. We previously found[21] that glyburide treatment increased leptin concentrations in these subjects, so, under these conditions, an increase in adiposity resulted in divergent

Table 4. Interrelations Between Several Parameters Related to Adipose Mass and Glycemia

	Leptin	CRP	% Fat	Total Fat	S_1	I_{AUC}	A_{1c}	FFA	TG	HDL	HOMA	Age
Adipo	.01	−.34†	−.03	−.20	.55†	.00	−.33†	−.09	−.28†	.57†	−.46†	.08
Leptin		.28†	.79†	.76†	−.30*	.26*	.04	.15	.22*	.00	.28*	.05
CRP			.45†	.50†	−.39†	−.13	.41†	.29†	.35†	−.20	.36†	.08
% fat				.87†	−.29*	.02	.26*	.26*	.33†	.02	.37†	.07
Total fat					−.41†	.15	.26*	.25*	.38†	−.27*	.52†	.02
S_1						.04	−.48†	−.14	−.36†	.52†	−.66†	−.08
I_{AUC}							−.36†	−.16	−.03	−.10	−.04	−.25*
A_{1c}								.28†	.41†	−.38†	.69†	0.23*
FFA									.12	.03	.14	0.25*
TG										−.47†	.48†	.27*
HDL											−.51†	.01
HOMA												.12

NOTE. Data represent Pearson correlation coefficients across the spectrum of all subjects (non-obese, obese, IFG/mild DM, and type 2 DM).

*$P < .05$.

†$P < .01$.

Abbreviations: Adipo, adiponectin; I_{AUC}, acute insulin release as area under the curve from 0 to 20 minutes; A_{1c}, hemoglobin A_{1c}; TG, triglycerides, HOMA, HOMA (IR).

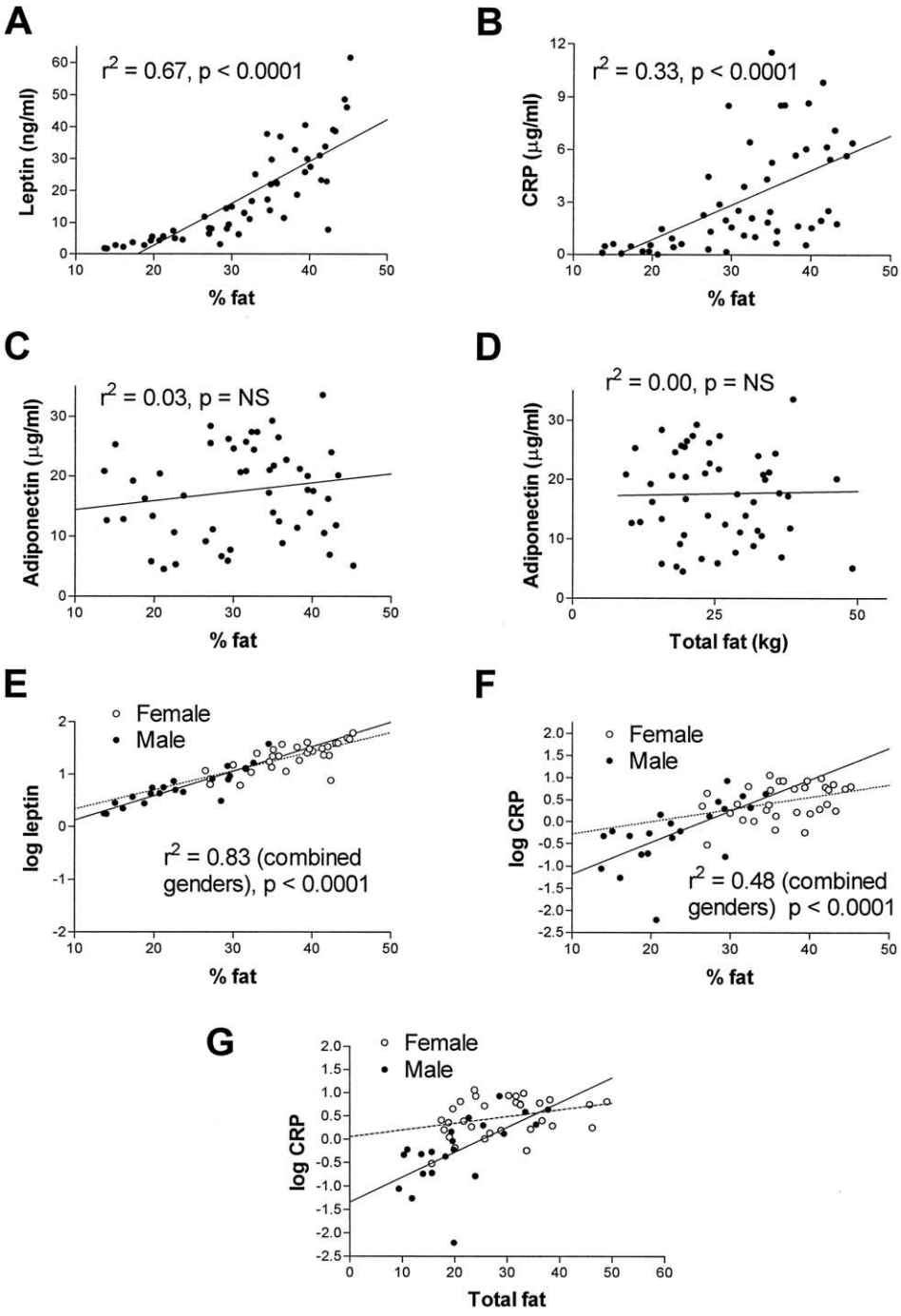

Fig 3. Linear regression analyses of selected parameters on percent fat or total fat mass in subjects classified as obese and non-obese controls: (A) Leptin *v* percent fat; (B) CRP *v* percent fat; (C) adiponectin *v* percent fat; (D) adiponectin *v* fat mass; (E) log leptin *v* percent fat by gender (no differences in slope or elevation by gender); (F) log CRP *v* percent fat by gender (no differences in slope or elevation by gender); (G) log CRP versus fat mass by gender (slopes differed by gender, *P* = .02; elevation cannot be compared).

changes in leptin and CRP. It follows that, although the increase in CRP in obesity is hypothetically secondary to fat tissue adipokines,[1] the adipokine, leptin, is not likely a factor, and clearly not a sole factor, regulating CRP.

Adiponectin was not altered by glyburide or metformin (Table 3). These findings differ from a report[27] that adiponectin increased in subjects treated with glimeperide for 12 weeks. In that report, the HbA_{1c} decreased form 8.4 to 6.9, more than in our study, and glimeperide improved insulin resistance as assessed by the homeostasis model. In our subjects, both metformin and glyburide increased S_I; however, the effect was significant only for metformin.

Whether the above effects of sulfonylurea treatment on CRP and adiponectin translate to vascular protection is unclear. In this regard a controversial early trial in the 1970s[28] suggested the opposite, that is, increased vascular risk. However, the United Kingdom Prospective Diabetes Study,[29,30] which involved a much larger population, showed no effect or a non-

significant decrease in vascular events in subjects treated to improve glycemia with sulfonylureas. In any case, it seems clear that more work is needed before concluding that sulfonylureas offer any vascular benefit based solely on changes in CRP or any specific adipokine.

Our data provide a head to head comparison between monodrug therapy with metformin and glyburide in subjects on no antidiabetic drugs at onset. Data derived in this way are currently lacking. In this regard, the recently initiated ADOPT (A Diabetes Outcome Progression Trial) trial[31] will compare monodrug treatment with metformin, a sulfonylurea, and a thiazolidinedione, in a very large multicentered population over 4 years. This study will examine several outcome parameters, including inflammatory markers.

While adiponectin, over the spectrum of subjects in Table 1, varied in opposite fashion to CRP, adiponectin appeared much less sensitive to adipose mass and, in fact, did not significantly correlate with percent fat or total fat (Table 4 and Fig 3). Hence, adiponectin, like CRP, varies with insulin sensitivity but apparently in a manner less dependent on fat mass. In this regard our data agree with a recent report suggesting that adiponectin concentrations are most closely related to insulin sensitivity, measured by insulin-mediated glucose disposal, than obesity.[32] In that report, obesity was measured only as BMI.

Overall, the relationship of adiponectin to adiposity has been controversial with some studies supporting[33-36] and others not supporting[32,37-39] an association. As seen in Figs 3C and 3D, there is wide scatter in plots of adiponectin versus adiposity. Thus, the controversy may be due to variability in the data. Clearly Fig 3 shows that adiposity per se is not nearly as strong a predictor of adiponectin as compared to leptin and CRP.

CRP, as we previously observed for leptin,[21] appears to vary in logarithmic fashion with percent fat. In fact, when log CRP (Fig 3F), similar to log leptin (Fig 3E), is expressed relative to percent fat, there is no significant difference in the slopes or elevations of the lines by gender. This is not the case for log leptin, as we previously reported,[21] or log CRP when the data are expressed relative to total fat (Fig 3G) or to BMI (not shown). These considerations suggest that the higher concentrations of CRP and leptin in females is due to higher percent fat rather than gender differences in the production of adipokines per unit fat. This also provides an explanation as to why gender dropped from the multiple regression analysis relating log CRP to percent fat, S_I, FFAs, HbA_{1c}, age, and gender (see "Results").

There is reason to think that expressing log leptin or log CRP relative to percent fat (as opposed to total fat or BMI) may be a physiologically important way to view this data. First, biologic dose-response curves do not tend to be linear, but often logarithmic in nature. Second, these are measures of concentration and not secretion rate. Since plasma concentration would depend on distribution volume, a higher percent fat at a given total fat mass would imply a smaller distribution volume, and, concentration, for a given amount secreted, would be greater at higher percent fat. Of course, this is speculative and does not consider the effect of clearance on concentration. In any case, we can conclude that for CRP and leptin, gender differences are complex and depend on how the data are expressed. These considerations, along with the relationships of adiponectin to adiposity (above paragraph), suggest a need for common ground in quantifying of substances released from or influenced by fat tissue.

The data in Table 2 raise the interesting possibility that lack of a gender difference in adiponectin in diabetes may, in part, explain the well-known loss of protection from atherogenesis (normally afforded by female gender) in individuals with diabetes. We must acknowledge, however, that this finding should be verified over larger numbers of subjects. Moreover, another study[40] reported reduced adiponectin for both genders in diabetic subjects versus controls. This study did not address the issue of possible treatment effects (of diabetes) that could impact these comparisons. In contrast, we can emphasize that our diabetic subjects were not on drugs and were on weight maintenance diet regimens at the time of study, so that diabetic treatment effects do not confound our data.

In summary, our data support the concept that the development of obesity and type 2 diabetes are accompanied by progressively elevated CRP and reduced adiponectin. We provide new information suggesting that treatment of diabetes with sulfonylureas may reduce CRP in the absence of weight loss or even with an increase in weight. We also provide novel information concerning the relationships of CRP and adiponectin to insulin sensitivity and measures of body fat. We show that CRP and adiponectin correlate strongly to insulin sensitivity, but CRP, in contrast to adiponectin, is far more dependent on adiposity. Our data suggest that gender differences in CRP may depend on the means of expressing the data. Our results at least raise a question that gender differences in adiponectin may be lost in diabetes. Finally, we draw attention to certain difficulties in expressing adipose-related proteins relative to adiposity and suggest the need for common ground.

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