Diabetes, Hyperglycemia, and Inflammation in Older Individuals

The Health, Aging and Body Composition study

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OBJECTIVE — The objective of this study was to assess the association of inflammation with hyperglycemia (impaired fasting glucose [IFG]/impaired glucose tolerance [IGT]) and diabetes in older individuals.

RESEARCH DESIGN AND METHODS — Baseline data from the Health, Aging and Body Composition study included 3,075 well-functioning black and white participants, aged 70–79 years.

RESULTS — Of the participants, 24% had diabetes and 29% had IFG/IGT at baseline. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels ($P < 0.001$) were significantly higher among diabetic participants and those with IFG/IGT. Odds of elevated IL-6 and TNF-α (>75th percentile) were, respectively, 1.95 (95% CI 1.56–2.44) and 1.88 (1.51–2.35) for diabetic participants and 1.51 (1.21–1.87) and 1.14 (0.92–1.42) for those with IFG/IGT after adjustment for age, sex, race, smoking, alcohol intake, education, and study site. Odds ratios for elevated CRP were 2.90 (2.13–3.95) and 1.45 (1.03–2.04) for diabetic women and men and 1.33 (1.07–1.69) for those with IFG/IGT regardless of sex. After adjustment for obesity, fat distribution, and inflammation-related conditions, IL-6 remained significantly related to both diabetes and IFG/IGT. CRP in women and TNF-α in both sexes were significantly related to diabetes, respectively, whereas risk estimates for IFG/IGT were decreased by adjustment for adiposity. Among diabetic participants, higher levels of HbA_{1c} were associated with higher levels of all three markers of inflammation, but only CRP remained significant after full adjustment.

CONCLUSIONS — Our findings show that dysglycemia is associated with inflammation, and this relationship, although consistent in diabetic individuals, also extends to those with IFG/IGT.

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Abbreviations: CRP, C-reactive protein; Health ABC, Health, Aging and Body Composition; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-6, interleukin-6; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; TNF-α, tumor necrosis factor-α.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Aging is associated with increased inflammatory activity including proinflammatory and anti-inflammatory cytokines and acute-phase proteins (1). Previous studies suggested that low-grade systemic inflammation plays a role in the pathogenesis of some glucose disorders in adults (2). Several cross-sectional studies showed that insulin resistance and type 2 diabetes are associated with higher levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), markers of subclinical systemic inflammation (3–8). Furthermore, various longitudinal studies have shown that elevated levels of CRP and IL-6 predict the development of type 2 diabetes (9–12). Few studies to date have focused on the association between diabetes and inflammation in older individuals, and to our knowledge none of these have studied the relationship of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) with inflammation in aging.

The underlying mechanism is still unknown. Adipose body mass may be an important mediator to explain these relations. It has been shown that adipocytes express and secrete TNF-α. TNF-α is overexpressed in the adipose and muscle tissues of obese and insulin-resistant nondiabetic subjects, and this overexpression is positively correlated with insulin resistance (13–15). IL-6 is produced in a variety of tissues including adipocytes. Subcutaneous administration of recombinant IL-6 induced dose-dependent increases in fasting blood glucose, probably by stimulating glucagon release and other counterregulatory hormones and/or by inducing peripheral resistance to insulin action (16).

We assessed the association of inflammatory markers with hyperglycemia (IFG/IGT) and diabetes in older individuals. We hypothesized that IFG/IGT and diabetes would be associated with higher levels of inflammation markers and that this relationship would be decreased by the level of body fat and fat distribution. We further hypothesized that poorer glycemic control in diabetic individuals

would be associated with higher levels of inflammation compared with those with better glycemic control.

RESEARCH DESIGN AND METHODS

— Data are from the Health, Aging and Body Composition (Health ABC) study, a 9-year longitudinal cohort study designed to investigate the relationships among health conditions, body composition, social and behavioral factors, and functional decline. The study population consists of 3,075 well-functioning black and white men and women aged 70–79 years and is 48% male. Forty-two percent of the cohort is black. Whites were recruited from a random sample of Medicare beneficiaries residing in designated zip code areas surrounding the Pittsburgh, Pennsylvania, and Memphis, Tennessee, field centers. Blacks were recruited from all age-eligible black community residents in these geographic areas. All potential participants received a mailing, followed by a telephone eligibility screen, with a second eligibility screen at the time of the clinic visit. We excluded *1*) people who reported difficulty walking a quarter mile, walking up 10 steps without resting, or performing basic activities of daily living and those reporting using a cane or other equipment to get around; *2*) those with known life-threatening cancers under active treatment in the past 3 years; and *3*) individuals who planned to leave the area within 3 years. A detailed interview on social demographics, health behaviors, indicators of socioeconomic status, and health service utilization was administered in the home. Participants underwent a clinical examination that included biological and body composition measures and indicators of weight-related health conditions as well as physical performance measures. The baseline home interview and clinic-based examination were carried out between April 1997 and June 1998. All participants gave written informed consent, and all protocols were approved by the institutional review boards at both study sites.

Inflammation markers

The inflammatory markers CRP and IL-6 were measured in serum, and TNF-α was measured in plasma that had been drawn after an overnight fast, on average, within 2 weeks of the baseline questionnaire and frozen at −70°C until assayed. IL-6 and TNF-α were measured in duplicate using enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN). The detectable limit for IL-6 (by HS600 Quantikine kit) was 0.10 pg/ml and for TNF-α (by HSTA50 kit) was 0.18 pg/ml. Serum levels of CRP were measured in duplicate by an enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 mg/l. Twenty-six subjects had IL-6 above the upper limit of detection, and their values were set to the limit of 12 pg/ml.

Diabetes and hyperglycemia assessment

Participants were asked whether a doctor had ever told them of a diagnosis of diabetes, excluding the occurrence of diabetes during pregnancy in women. Prescribed and over-the-counter medications used in the preceding 2 weeks were brought to the clinic by the participants. All participants without diabetes underwent a 75-g oral glucose tolerance test (OGTT) performed after at least an 8-h overnight fast. We defined diabetes as *1*) a report of having been told of diabetes and/or *2*) use of oral hypoglycemic medications or insulin or *3*) having a fasting plasma glucose ≥126 mg/dl or *4*) having a 2-h glucose OGTT ≥200 mg/dl (American Diabetes Association criteria). Fasting glucose values were available for 99% of the participants. We used information on reported age at diagnosis to define diabetes duration; only those participants considered diabetic as a result of fasting glucose or OGTT were considered to have new-onset diabetes. Poor glycemic control was defined by the level of HbA_{1c} (A1C) (Bio-Rad). Glucose parameters were measured on a Johnson & Johnson Vitros 950 analyzer. Biological specimens were processed according to standardized protocols by the Laboratory of Clinical Biochemistry at the University of Vermont.

We also defined a hyperglycemic group including participants with IFG or with IGT (IFG/IGT). IFG was defined by fasting glucose between 100 and 126 mg/dl, and IGT was defined by an OGTT between 140 and 200 mg/dl (17,18).

Potential confounders

Covariates included age, sex, race, clinic site, education, body height, total body fat, visceral fat, health status, use of anti-inflammatory drugs, statins, and estrogen, smoking, and alcohol intake. Body height was measured to the nearest millimeter using a wall-mounted stadiometer. Total body fat (kilograms) was measured by dual-energy X-ray absorptiometry (QDR 4500A, software version 8.21; Hologic, Waltham, MA). Visceral fat at the L4-L5 level was quantified from computerized tomography scanning of the abdomen. Scans were performed on a General Electric 9800 Advantage in Pittsburgh and a Siemens Somatron and Picker PQ2000S in Memphis. All data from the computerized tomography scans were analyzed at the University of Colorado Health Sciences Center according to a standardized protocol (19).

Several diseases with a potential association with inflammation or with diabetes were considered in the analysis, including cardiovascular disease, hypertension, peripheral arterial disease, renal insufficiency, arthritis, and respiratory disease. We used a combination of self-reported diagnoses and/or medications to establish the prevalence of cardiovascular disease (heart disease or stroke), arthritis, and pulmonary disease. For hypertension, we used self-report, medications, and measured blood pressure. Peripheral arterial disease was identified by an ankle-to-arm blood pressure ratio <0.9. Serum creatinine levels ≥1.5 mg/dl for men and ≥1.3 mg/dl for women were used to define renal insufficiency (20). Current anti-inflammatory, statin, and estrogen use were assessed at the clinic visit. Smoking status (never, current, or former), pack-years exposure to cigarettes, and average alcohol use during the past year (0, ≤ 1, or >1 drink/day) were assessed at the baseline questionnaire. Education was categorized in two groups: those with <12 and those with ≥12 years of school.

Statistical methods

Of the Health ABC participants, 2,683 had complete information on inflammation markers and glucose parameters and constituted the study sample for the analysis. For all the other categorical variables with missing data, a separate category for those with missing data within each variable was used so that all observations remained in the analysis. Baseline descriptive characteristics were compared between the normal glucose tolerance (NGT) and IFG/IGT groups and between the NGT and diabetic groups, respectively. A χ^2 test for categorical variables and the GLM procedure for continuous variables were used to compare prevalence and means differences between the

Table 1—*Baseline characteristics by diabetes and hyperglycemic status*

Characteristic	Diabetes	IFG/IGT	NGT	*P*
n (%)	650 (24.2)	787 (29.3)	1,246 (46.4)	
Sociodemographic				
Age (years)	73.7 ± 2.8	73.7 ± 2.9	73.5 ± 2.9	NS
Male sex (%)	55.1	46.3	48.1	—*
Blacks (%)	52.2	37	36.4	—*
Education <12 years	32.3	22.6	23.4	—*
Health status (%)				
Hypertension	68.4	59.0	51.4	—*†
Coronary heart disease	27.7	20.0	17.7	—*
Cerebrovascular disease	10	7.6	7.4	—*
Peripheral arterial disease	20.5	13.4	11.9	—*
Renal insufficiency	11.4	7.4	7.0	—*
Arthritis	13.3	19.8	17.3	—*
Systolic blood pressure (mmHg)	138.8 ± 21.5	136.5 ± 21.3	134.0 ± 20.8	—*†
Diastolic blood pressure (mmHg)	70.5 ± 11.7	72.4 ± 11.5	71.3 ± 11.6	—†
Ankle arm index (AAI)				
Lowest AAI	1.03 ± 0.19	1.07 ± 0.19	1.08 ± 0.18	—*
Smoking status				
Never	41.8	44.7	45.3	
Current	8.8	9.2	11.3	
Former	49.4	46.1	43.4	—*
Pack-years of cigarettes	5 (0–32)	4 (0–32)	3 (0–27)	—*‡
Alcohol intake				
0	60.5	46.4	47.2	
≤1 drink/day	33.7	45	46.2	
>1 drink/day	5.9	8.6	6.6	—*
Medications (%)				
Anti-inflammatory drugs	53.4	54.0	52.9	NS
Estrogen	8.5	11.3	12.4	—*
Statins	14.8	15.4	10.4	—*†
Blood glucose				
Fasting glucose (mg/dl)	141.8 ± 51.5	99.2 ± 9.9	88.6 ± 6.3	—*†
2-h glucose test (mg/dl)	233 (*n* = 263) (209–282)	150 (133–168)	104 (90–120)	—*†‡
A1C (%)	7.6 ± 1.5	6.1 ± 0.6	5.9 ± 0.5	—*†
Body composition				
Weight (kg)	80.6 ± 14.8	76.4 ± 14.9	73.2 ± 14.3	—*†
BMI (kg/m^2)	28.9 ± 4.8	27.9 ± 4.9	26.4 ± 4.4	—*†
Total fat (kg) (DXA)	27.5 ± 8.8	27.1 ± 8.8	24.4 ± 8.0	—*†
Visceral fat (cm^2)	167.2 ± 72.6	152.4 ± 64.7	127 ± 60.4	—*†

Data are means ± SD or median (interquartile range) unless otherwise noted. *$P < 0.05$, comparison between diabetic and NGT population. †$P < 0.05$, comparison between IFG/IGT and NGT population. ‡Wilcoxon rank-sum test. DXA, dual-energy X-ray absorptiometry.

NGT and IFG/IGT participants and NGT and diabetic participants, respectively. Because the distributions of CRP, IL-6, and TNF-α were skewed, median values with 25th–75th percentile ranges were reported, and we used the *t* test on log-transformed values to compare the different groups. The distribution of 2-h glucose was not normal, and the nonparametric Wilcoxon's rank-sum test was used for comparison.

Multivariate logistic regression analyses were used to test the association between diabetes or IFG/IGT with high levels of inflammatory markers. A high inflammation level was defined as a level >75th percentile (CRP >3.11, IL-6 >2.84, and TNF-α >4.11). Odds ratios (ORs) and 95% CIs for high CRP, IL-6, or TNF-α in relation to diabetes and IFG/IGT were calculated. Two separate analyses were performed for diabetes and IFG/IGT, respectively; we also ran the analysis including diabetes and IFG/IGT as dummy variables in the same model and the results were similar. Comorbidities and body composition measures hypothesized to be either potential confounders or potential mediators in the pathway of the association between diabetes or IFG/IGT and inflammation were progressively added to the models. The first model was adjusted for age, race, sex, education, smoking, alcohol intake, and clinic site. The second model was adjusted additionally for total body fat and visceral fat. When total body fat was included in the models, an additional adjustment was made for body height to normalize total body fat. The fully adjusted model took into account the comorbidities and medication use. We tested for an interaction of sex and race with diabetes and IFG/IGT for the different inflammatory markers. Because high levels of two or more inflam-

Table 2—*Plasma levels of inflammatory markers of the diabetic and the hyperglycemic groups compared with the NGT group*

Inflammatory marker	Diabetes	IFG/IGT	NGT	*P* value
n	650	787	1,246	
CRP (mg/l)				
Quartiles (%)				
≤1.0	20.0	24.5	28.2	—*†‡
1.1–1.67	21.4	23.8	27.8	
1.68–3.11	24.2	26.7	24.1	
>3.11	34.5	25.0	20.0	
Median (25th–75th percentile)	2.15 (1.15–3.81)	1.74 (1.02–3.13)	1.47 (0.95–2.69)	—*†§
IL-6 (pg/ml)				
Quartiles (%)				
≤1.28	15.4	24.0	30.7	—*†‡
1.29–1.85	23.1	25.3	25.8	
1.86–2.84	28.6	23.8	23.9	
>2.84	32.9	26.9	19.6	
Median (25th–75th percentile)	2.18 (1.5–3.23)	1.87 (1.3–2.98)	1.7 (1.15–2.51)	—*†§
TNF-α (pg/ml)				
Quartiles (%)				
≤2.45	20.3	26.3	26.7	—*‡
2.46–3.17	22.3	22.6	27.9	
3.18–4.11	24.6	26.7	24.1	
>4.11	32.8	24.4	21.3	
Median (25th–75th percentile)	3.42 (2.58–4.46)	3.2 (2.41–4.08)	3.05 (2.38–3.92)	—*†§

*$P < 0.05$, comparison between diabetic and NGT populations. †$P < 0.05$, comparison between IFG/IGT and NGT populations. ‡χ^2 test for categorical inflammatory markers. §*t* test based on log-transformed values.

matory markers represent a more specific indicator of systemic inflammation (21) than a high level of just one, a composite inflammation index was calculated. The high extreme group included those who had at least two of the inflammatory markers in the highest quartile. The low extreme group, considered as the reference category in the analysis, included participants with all three inflammation markers below or equal to the median, and the intermediate group included individuals with all other possible combinations of cytokine levels. A polytomous logistic regression was used to test the relationship between diabetes and IFG/IGT with the inflammation index.

To test whether poorer glycemic control in diabetic participants ($n = 637$, all with A1C values) was associated with higher levels of inflammatory markers, we performed multivariate logistic regression analyses using A1C level and high inflammation level as described above. A value of $P < 0.05$ was accepted as statistically significant. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS — Among the 2,683 participants with complete information, 650 (24.2%) were diabetic at baseline and 787 (29.3%) had IFG or IGT. Participants with diabetes were more likely to be male and black and had a lower level of education (Table 1). Participants in the diabetic and the IFG/IGT group had a higher prevalence of hypertension, higher levels of indicators of glucose metabolism, and greater total body fat mass and visceral fat area compared with the NGT participants. Diabetic individuals had more cardiovascular diseases and peripheral arterial disease than their counterparts with NGT.

Plasma levels of inflammatory markers were moderately correlated. The highest correlation was observed for CRP and IL-6 (Pearson $r = 0.40$, $P < 0.0001$). The correlation between IL-6 and TNF-α was 0.19 ($P < 0.0001$) and between CRP and TNF-α was 0.09 ($P < 0.0001$). Table 2 shows the plasma concentrations of the inflammatory markers by diabetes and hyperglycemic status. Levels of CRP, IL-6, and TNF-α, using either quartile levels or continuous levels, were significantly higher in the IFG/IGT and diabetic group compared with the NGT group.

Multivariate analyses

Multivariate analyses on the risk of high inflammation associated with diabetes and hyperglycemic status are shown in Table 3. Compared with those without diabetes, after adjustments for age, sex, race, smoking status, alcohol intake, education, and site, diabetic individuals continued to exhibit higher inflammation levels with an OR of 1.95 (95% CI 1.56–2.44) of higher IL-6 and an OR of 1.88 (1.51–2.35) of higher TNF-α. As we found an interaction for sex with diabetes in the association with high CRP ($P = 0.006$), we then stratified the analysis by sex for the association between diabetes and high CRP. Diabetic women compared with those without diabetes had an OR of 2.90 (2.13–3.95) of higher CRP and diabetic men an OR of 1.45 (1.03–2.04). The association between diabetes and higher inflammation level was weakened by adjustments for body fat and visceral fat, inflammation, and diabetes comorbidities and potential confounders (Table 3, models 2 and 3) but still remained significant, except for high CRP in men. Total body fat and visceral fat accounted for most of the attenuation of the association between diabetes and higher inflammation.

In the IFG/IGT group, after adjustments for age, sex, race, smoking, alcohol intake, education, and study site, the ORs for elevated CRP, IL-6, and TNF-α were, respectively, 1.33 (95% CI 1.07–1.69), 1.51(1.21–1.87), and 1.14 (0.92–1.42).

Table 3—*Multivariate analyses for the association of hyperglycemia and diabetes with inflammation*

	Risk of high inflammation level associated with diabetes and hyperglycemic status			
	n	Model 1	Model 2	Model 3
Diabetes				
High IL-6	458	1.95 (1.56–2.44)	1.69 (1.33–2.13)	1.59 (1.25–2.03)
High TNF-α	478	1.88 (1.51–2.35)	1.6 (1.26–2.02)	1.51 (1.19–1.93)
High CRP				
Men	186	1.45 (1.03–2.04)	1.17 (0.82–1.68)	1.10 (0.76–1.61)
Women	287	2.90 (2.13–3.95)	2.25 (1.60–3.16)	2.21 (1.54–3.17)
Inflammation index				
≥2 high	388	4.41 (3.16–6.16)	2.85 (2.01–4.05)	2.58 (1.79–3.72)
Intermediate	1,125	1.99 (1.49–2.65)	1.50 (1.11–2.03)	1.40 (1.03–1.91)
Low	383	1	1	1
IFG/IGT				
High IL-6	456	1.51 (1.21–1.87)	1.38 (1.11–1.73)	1.37 (1.09–1.72)
High TNF-α	457	1.14 (0.92–1.42)	1.09 (0.88–1.36)	1.07 (0.85–1.34)
High CRP	446	1.33 (1.07–1.66)	1.13 (0.89–1.42)	1.10 (0.87–1.39)
Inflammation index				
≥2 high	349	1.66 (1.24–2.22)	1.28 (0.95–1.74)	1.26 (0.92–1.72)
Intermediate	1,219	1.20 (0.96–1.51)	0.98 (0.78–1.25)	1.00 (0.78–1.27)
Low	465	1	1	1

	Relationship between glycemic control (A1C) and inflammation in diabetes		
	Model 1	Model 2	Model 3
High CRP	1.17 (1.04–1.32)	1.16 (1.03–1.32)	1.15 (1.01–1.32)
High IL-6	1.12 (1.00–1.26)	1.11 (0.99–1.25)	1.07 (0.94–1.23)
High TNF-α	1.13 (1.01–1.27)	1.11 (0.98–1.25)	1.10 (0.97–1.26)

Data are OR of high levels of inflammatory marker (95% CI). For risk of high inflammation level associated with diabetes and hyperglycemic status, model 1 is adjusted on age, sex, race, smoking status, alcohol intake, education, and site. Model 2 adds total body fat, visceral fat, and height. Model 3 adds cardiovascular diseases, hypertension, peripheral arterial disease, renal insufficiency, arthritis, pulmonary disease, anti-inflammatory, statin, and estrogen use. For relationship between glycemic control and inflammation in diabetes, models 1 and 2 are the same and model 3 adds diabetes duration.

Adjustment for body fat and visceral fat attenuated these associations so that only IL-6 remained statistically significant. A higher IL-6 level was associated with IFG/IGT even after further adjustment for comorbidities and confounders. Diabetes but not IFG/IGT was also associated with the inflammation index for both the high and intermediate groups, when adjustments were made for body composition measures.

Diabetic participants with poorer glycemic control also showed higher inflammatory levels of CRP with an OR of 1.17(95% CI 1.04–1.32) after adjustments for age, sex, race, smoking status, alcohol intake, education, and clinic site (Table 3). Adjustment for body fat and visceral fat attenuated the relationships, but they still remained statistically significant even with further adjustment for comorbidities and potential confounders.

CONCLUSIONS — In our study of well-functioning black and white older individuals, we found that diabetic participants and those with IFG/IGT have higher levels of inflammatory markers compared with the nondiabetic population. The association between diabetes and a high level of inflammation remained even after adjustments for possible confounders, such as demographics, lifestyle habits, total body fat, visceral fat, and comorbidities. We also found that the association between diabetes and inflammation was stronger when we used a composite inflammation index of the three inflammatory markers, which is a more specific indicator of systemic inflammation (21). Older diabetic individuals have a 2.58-fold increased odds of having higher levels of at least two inflammatory markers than those with normal glucose values. For the association between diabetes and CRP, we observed a sex difference; the association was stronger in women and not statistically significant in men. This sex difference was not found with any of the other inflammatory markers.

Our results are consistent with those for other cross-sectional studies in younger populations in which an increase of CRP was found with diabetes (5,7,8) and increases of CRP, IL-6, and TNF-α were found with IGT (22,23). It has also been shown in several longitudinal studies that inflammation is a predictor of development of diabetes (9,10,12,24). Thus, the link between diabetes and inflammation could be due to a reciprocal process, in that inflammation may contribute to diabetes onset and diabetes may then contribute to continued inflammation. In addition, hyperglycemia is known to mediate formation of advanced glycosylation end products. These advanced glycosylation end products may also contribute to inflammation, producing a chronic stimulation for secretion of cytokines (25).

Adipose tissue could be a mediator in the relationship. Obesity, particularly visceral fat, contributed the most to the attenuation of the association between diabetes or IFG/IGT and inflammation and could explain the relationship be-

tween diabetes and CRP in men and between IFG/IGT and CRP in both men and women. Data emerging over the past several years have established the fact that adipocytes express and secrete the cytokine TNF-α and that enlarged adipocytes from obese animals and humans overexpress this factor (26). The findings from the Third National Health and Nutrition Examination Survey showed a higher prevalence of increased levels of CRP in both overweight and obese participants (27). Adiposity, in particular visceral adipose tissue, has been found to be a key promoter of low-grade chronic inflammation (28,29). Obesity appears to be a state of chronic inflammation with increased production of cytokines and other acute-phase reactants that play a crucial role in regulation of systemic insulin action; it has been shown that TNF-α–deficient mice show increased insulin action (30).

Is the elevation of inflammatory markers the result of vascular and renal disease due to diabetes or a causal pathway? Numerous studies showed an association between cardiovascular diseases with inflammation, and a higher CRP level is associated with increased risk of development of vascular disease (31–34). CRP and IL-6 are also known to increase with declining kidney function, even before end-stage renal disease occurs (35–37). Trials to study decreases of inflammation in diabetes or cardiovascular disease events are still lacking. A better understanding of the actions of cytokines with other factors in the pathogenesis of diabetes may lead to improved understanding of its cause and open new approaches for its prevention.

We found an association between poor glycemic control and an increased level of CRP. Several studies showed that cytokine levels (CRP, IL-6, and TNF-α) are related to glycemic control (38–40). Improvement of glycemic control has an inconsistent beneficial impact on the level of inflammatory markers. No significant effect was found on the levels of IL-6 and TNF-α with sulfonylureas or insulin therapy, but a significant decrease in CRP was observed with insulin (41). Troglitazone with an improvement in glycemic control reduces CRP (42) and decreases plasma levels of TNF-α in obese diabetic patients (43). One weight loss study showed that moderate-intensity regular exercise decreases the TNF-α level (44). A high inflammation level might contribute to the worsening of progression of type 2 diabetes in addition to glycemic control.

Our study has several strengths. First, we have several measures of inflammatory markers and can create an inflammatory index. Second, the study includes a large sample size and a biracial population with a high percentage of blacks.

One limitation of our study is that because of the study design (cross-sectional study), the direction of these associations cannot be conclusively determined and a causal relationship cannot be inferred. Additionally, the study population includes well-functioning relatively healthy participants; our findings may not be generalized to a frail older population.

In summary, diabetes is associated with increased levels of three inflammatory markers and IFG/IGT with increased IL-6 in this well-functioning older population. Among those with diabetes, poorer glycemic control was associated with higher levels of CRP. Whether baseline levels of inflammatory markers in those without pre-diabetes or diabetes would be predictors of the onset of pre-diabetes and diabetes should be determined, and we plan to explore this in our longitudinal data.

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