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Resistin levels decrease as insulin resistance increases in a Mexican-American cohort

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Abstract

Aims: Links between resistin, insulin resistance (IR), and resistin-stimulated cytokine signaling remain unknown in Mexican-Americans. A Mexican-American cohort was examined to determine (1) relationships between circulating resistin and IR, (2) resistin's associations with cytokines and demographic and anthropometric variables, and (3) similar measurements with other adipokines.

Methods: For cross sectional analyses, 953 adults (367 males and 586 females) in the Cameron County Hispanic Cohort (CCHC) were stratified into three groups: normal glucose tolerance, prediabetes, and diabetes mellitus. Differences in resistin and other adipokine levels were examined using linear regression via unadjusted model (Model 1), model adjusted for cytokines (Model 2), and model further adjusted for demographic and anthropometric variables (Model 3).

Results: HOMA-IR increased with worsening glucose tolerance ($p < 0.0001$). In all models, resistin significantly decreased as glucose tolerance deteriorated. Model 3 resistin was positively associated with IL-1β ($p = 0.0252$) and IL-8 ($p < 0.0001$), inversely associated with TNF-α ($p =$

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CRediT authorship contribution statement

Absalon D. Gutierrez: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Supervision. **Carlos A. Flores:** Conceptualization, Investigation, Writing – review & editing. **Sapna Naik:** Conceptualization, Investigation, Writing – review & editing. **MinJae Lee:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing. **Parisa Asgarisabet:** Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. **Masha Resman:** Conceptualization, Investigation, Writing – review & editing. **Miryoung Lee:** Investigation, Data curation, Writing – review & editing. **Joseph B. McCormick:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition. **Susan P. Fisher-Hoch:** Conceptualization, Methodology, Resources, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

0.0352), but nonsignificantly associated with IL-6 ($p = 0.8671$). Model 3 leptin was significantly lower in diabetes mellitus compared to other groups ($p < 0.005$) and positively associated with female sex ($p < 0.0001$), age ($p = 0.024$), and BMI ($p < 0.0001$), without significant cytokine associations. Adiponectin displayed no significant associations with glucose tolerance, but was significantly associated with sex, BMI, and lipids (Model 3).

Conclusions: Resistin unexpectedly decreased as IR increased while supporting evidence of a resistin-stimulated cytokine pathway in this Mexican-American cohort. Leptin fell with elevated IR after adjusting for cytokines, demographic and anthropometric variables. Adiponectin nonsignificantly decreased as IR increased while showing significant associations with sex, BMI, and lipids.

Keywords

Resistin; Insulin resistance; Leptin; Adiponectin; Mexican-American

1. Introduction

Diabetes mellitus and its complications are widespread. Among Hispanics living in the United States, there is an approximately 50% increased lifetime risk of developing diabetes mellitus, compared to non-Hispanic Whites [1]. Type 2 diabetes mellitus (T2DM) develops via a transition from normal glucose tolerance to prediabetes to T2DM. This transition accompanies an increase in insulin resistance (IR), which is a key factor in the development of diabetic microvascular complications and atherosclerotic cardiovascular disease [2,3].

Resistin is a key adipokine implicated in the development of increased IR, as shown in many murine studies and an increasing number of human studies. Some studies show positive associations between increased resistin level and increased IR [4–7] but other studies reveal no such differences [8–10]. Notably resistin levels vary across different ethnic groups, but Mexican-Americans are underrepresented in these studies [11].

Of particular interest is a proposed mechanism of resistin-mediated stimulation of four proinflammatory cytokines (IL-1β, IL-6, TNF-α, and IL-8) through a collaborative pathway, recently observed in Italian cohorts of healthy and insulin-resistant subjects [12]. Poorly controlled T2DM manifests as a chronic low grade inflammatory state [13], so the presence of this relationship is not surprising. What is less known is the role that resistin plays on the surrounding milieu of cytokines during the progression from normal glucose tolerance (NGT) to prediabetes to diabetes mellitus - along with concurrent IR deterioration - amongst Mexican-Americans.

Other than resistin, the adipokines leptin and adiponectin are implicated in the progression of IR. In non-obese insulin-resistant humans, leptin administration ameliorates IR and lowers blood glucose [14]. However in obese insulin-resistant humans, leptin levels are elevated; this represents a concurrent state of leptin resistance [15]. Data are conflicting regarding the association of circulating leptin levels with IR in Mexican-Americans [13,16] and other ethnic groups [17–19]. Adiponectin is a mediator of insulin sensitivity; lower

levels are reported in insulin-resistant states in some Mexican-Americans [20,21], though this may not be true of all ethnicities [22].

The Cameron County Hispanic Cohort, which is a Mexican-American population living along the south Texas-Mexico border [23], provides a unique opportunity to study relationships between these adipokines and IR. Our prior studies show that this population exhibits unusually high insulin resistance compared to other ethnic groups [24], which is highly associated with the percentage of Amerindian ancestry markers [25]. T2DM in this population is associated with multiple elevated inflammatory markers [13].

The primary goal of this study is to define relationships between circulating resistin levels and IR in a homogeneous Mexican-American cohort. We concurrently delineate the effects of cytokines (IL-1β, IL-6, TNF-α, and IL-8) and demographic and anthropometric variables on resistin levels. The same assessments are repeated to comparatively explore associative patterns between other adipokines (leptin and adiponectin) and IR.

2. Methods

The study was approved by the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston. All work was carried out in accordance with the Declaration of Helsinki.

2.1. Study Participants

This cross-sectional analysis uses baseline data from the Cameron County Hispanic Cohort (CCHC), an ongoing randomly ascertained community cohort study recruited from households in a homogeneous Mexican-American population living along the southern Texas border. Participants enroll in the cohort by signing a written informed consent. This is followed by the completion of questionnaires (addressing anthropometric and socio-demographic characteristics), clinical examinations, and collection of laboratory specimens as previously described [23]. At the time of this analysis, the cohort consisted of 4,258 subjects recruited between 2004 and 2018 in Brownsville TX. Of these, 3,929 subjects were adults (18 years or older).

Only adult subjects with measurements of plasma resistin, leptin, and adiponectin were included in the analysis; these measurements were available in 1,834 of the 3,929 adult subjects. Participants were categorized into normal glucose tolerance, pre-diabetes, or diabetes mellitus based on American Diabetes Association criteria using fasting blood glucose (FBG) and or hemoglobin A1c (HbA1c) levels. Further information includes age, gender, blood pressure, and body mass index (BMI).

Subjects were excluded for history of ischemic heart disease, stroke, malignancy, hyperthyroidism, or hypothyroidism from the analysis. As nicotine influences adipokine levels [26,27], current smokers (at time of visit) were excluded. Subjects were also excluded for use of medications which alter adipokine levels: statins [26,28], NSAIDs [28], thiazolidinediones [26,28,29], glucagon-like peptide-1 receptor agonists (GLP-1RAs) [30,31], dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) [32], sodium-

glucose cotransporter-2 (SGLT-2) inhibitors [33], angiotensin-converting-enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) [26,28]. Among the 1,834 adult subjects with available adipokine data, application of these criteria led to the exclusion of 881 subjects. A final number of 953 study subjects qualified for the study.

2.2. Definitions

Participants were divided into one of three groups, representative of glucose tolerance: normal glucose tolerance (NGT), prediabetes, and diabetes mellitus. The 2010 American Diabetes Association Standards of Care were used to define diabetes mellitus was as HbA1c ≥ 6.5% or fasting blood glucose (FBG) ≥ 126 mg/dL [34]. Oral glucose tolerance tests are not conducted on the cohort participants. Participants who were on hypoglycemic medications, or were diagnosed with diabetes by a health care provider, were also defined as diabetes mellitus (i.e., as described above, subjects on some hypoglycemic medicines were ultimately excluded). Prediabetes was defined as HbA1c ranging from 5.7% to 6.4% or FBG ranging from 100 to 125 mg/dL, without either HbA1c or FBG meeting the definition of diabetes mellitus [34]. NGT was defined as both an HbA1c < 5.7% and FBG < 100 mg/dL.

2.3. Laboratory measurements

Fasting blood specimens were promptly aliquoted and stored at −80°C until analyses. Measurements were completed using methods described previously [13]. Fasting blood glucose (colorimetric assay), glycated hemoglobin (HbA1c, High Performance Liquid Chromatography), and lipid panel (colorimetric assay) were assayed in a local CLIA approved hospital laboratory. Plasma insulin levels were measured using ELISA assays (Mercodia, Uppsala, Sweden). HOMA-IR was calculated as fasting plasma insulin (FPI) × FBG (mmol/L)/22.5 and HOMA B (HOMA %Beta) was calculated as (20xFPI) / (FPG-3.5). For the purpose of these calculations, FPI was measured in mIU/L and FPG was measured in mmol/L [35].

Three key adipokines (resistin, leptin, and total adiponectin) and four relevant inflammatory markers (interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α)) were measured in house using the multiplex ELISA (Milliplex Map, Millipore, CA) bead technique, using two panels as previously described [13]. Results are read using the Luminex 200 System (Luminex Corp, Austin, TX).

2.4. Statistical analysis

We conducted univariable comparisons of demographic, anthropometric, and metabolic characteristics for the study participants grouped by glucose tolerance status (NGT vs. prediabetes vs. DM) using Chi-squared-tests for categorical variables, Analysis of Variance (ANOVA) for continuous variables, or their nonparametric equivalents (e.g. Kruskal-Wallis test) as appropriate. As the distribution of adipokines resistin, leptin, and total adiponectin were skewed, the data were transformed using the natural logarithm (ln) to produce approximately normal distributions for the main statistical analysis. We examined the relationship between those natural log-transformed adipokines and the glucose tolerance status using a univariable linear regression model (Model 1) and two multivariable linear regression models (Models 2 and 3). Model 1 examines the

unadjusted relationship of adipokines and glucose tolerance status. Model 2 adjusts for markers of inflammation (IL-1β, IL-6, TNF-α, and IL-8), while Model 3 adjusts for the same markers of inflammation as well as demographic and anthropometric characteristics (sex, blood pressure, age, BMI, triglycerides, and HDL-C). Other potential confounding and interaction effects were also explored while developing final multivariable models. Statistical significance was set at $p < 0.05$. All analyses were performed on SAS® v. 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Descriptive Demographic, Anthropometric, and metabolic characteristics by glucose tolerance status

These baseline analyses were performed on 953 Mexican-American subjects (61.49% female, average age = 41.36 ± 14.74 years, average BMI = 30.31 ± 6.34 kg/m^2). Means and standard deviations are reported for normally distributed data; medians and interquartile range are reported for non-normally distributed data in Table 1.

The progression of glucose intolerance (from normal glucose tolerance to prediabetes to diabetes mellitus) associated with a significant increase in HOMA-IR ($p < 0.0001$). As expected, this was also associated with increased age ($p < 0.001$), BMI ($p < 0.001$), waist circumference ($p < 0.0001$), percent of subjects with hypertension ($p < 0.0001$), HbA1c ($p < 0.0001$), fasting blood glucose ($p < 0.0001$), and insulin ($p < 0.0001$). Corresponding median HOMA-B levels decreased ($p < 0.0001$). Median triglyceride levels increased ($p < 0.0001$) and HDL-C levels decreased ($p = 0.0049$) with worsening glucose tolerance. Decreasing median levels of resistin ($p < 0.001$) and adiponectin ($p = 0.0403$) were associated with worsening glucose tolerance. Median leptin levels varied between groups in a nonlinear trend, with the lowest level seen in the normal glucose tolerance group ($p = 0.0006$). Significant differences across groups were observed in distribution of the inflammatory markers IL-1β ($p = 0.0183$) and IL-6 ($p < 0.0001$) (Table 1).

3.2. Univariable and multivariable associations between glucose tolerance status with adipokines

Both univariable and multivariable associations (after controlling for cytokines (IL-1β, IL-6, IL-8, and TNF-α), sex, hypertension, age, BMI, triglycerides, and HDL-C) between glucose tolerance groups (NGT, prediabetes, and diabetes mellitus) and log-transformed values of the above adipokines (resistin, leptin, and adiponectin) were assessed. The unadjusted (Model 1) and adjusted (Models 2 and 3) mean differences in log-transformed resistin (Table 2), leptin (Table 3), and adiponectin (Table 4) between glucose tolerance groups are presented. Model 2 adjusted for cytokines only. Model 3 adjusted for cytokines, sex, hypertension, age, BMI, triglycerides, and HDL-C. These variables were selected to reflect similar models from Menzaghi *et al.,* who described the resistin-cytokine pathway in humans [12]. There were no statistically significant interaction effects observed, and there were no considerable confounders observed other than the variables included in the multivariable models.

Resistin (Table 2) showed significant differences in Model 1 (unadjusted) and Models 2 and 3 (adjusted) between all three group pair-wise comparisons (prediabetes vs. NGT, diabetes mellitus vs. NGT, and diabetes mellitus vs. prediabetes), highlighting a significant association between lower resistin levels and worsening glucose tolerance (overall $p < 0.0001$ for each model). Increased IL-1β and IL-8 levels were significantly associated with higher levels of resistin ($p = 0.0405$ and $p < 0.0001$ for IL-1β and IL-8 levels respectively) based on Model 2, and these relationships remain intact after further adjusting for demographic and anthropometric characteristics ($p = 0.0252$ and $p < 0.0001$ for IL-1β and IL-8 levels respectively). Interestingly in Model 3, TNF-α also appears to decrease with increased resistin levels ($p = 0.0352$), but the significance was attenuated in Model 2 ($p = 0.1109$). IL-6 levels showed no significant association with resistin levels in Model 2 ($p = 0.9339$) and Model 3 ($p = 0.8671$). Based on Model 3, resistin levels were positively associated with BMI ($p = 0.0145$) and inversely associated with HDL-C level ($p = 0.0026$).

We also found significant differences in leptin levels (Table 3) across glucose tolerance groups based on both univariable and multivariable models (overall $p = 0.0017$ for Model 1, $p = 0.0021$ for Model 2 and $p = 0.0004$ for Model 3). Models 1 and 2 showed significantly higher leptin levels in the prediabetes compared to NGT group ($p = 0.0004$ and $p = 0.0005$, respectively) and no significant differences between diabetes mellitus vs. NGT nor diabetes mellitus vs. prediabetes. Model 3, however, after further controlling for demographic and anthropometric variables showed significantly lower leptin levels in diabetes mellitus compared to NGT ($p = 0.005$) and diabetes mellitus with prediabetes ($p < 0.0001$). Cytokines were not significantly associated with leptin levels based on Models 2 and 3. Higher leptin levels were seen in females ($p < 0.0001$) and positively associated with age ($p = 0.024$) and BMI ($p < 0.0001$).

There were no significant differences in adiponectin levels (Table 4) across glucose tolerance groups based on univariable or multivariable analyses (overall $p = 0.2013$ for Model 1, $p = 0.2713$ for Model 2, and $p = 0.5616$ for Model 3). Model 2 showed that increased IL-8 levels were significantly associated with higher levels of adiponectin ($p < 0.0001$) and this association remained significant with the further adjustments of Model 3 ($p < 0.0001$). In Model 3 adiponectin levels were increased in female sex ($p < 0.0001$), positively associated with age ($p = 0.0024$) and HDL-C level ($p < 0.0001$), and inversely associated with BMI ($p < 0.0001$) and triglyceride level ($p = 0.0004$).

4. Discussion

Plasma resistin levels surprisingly decreased as IR increased in this Mexican-American cohort. When adjusting for metabolic comorbidities and cytokines previously implicated in resistin signaling, three of these four cytokines (IL-1β, TNF-α, and IL-8; IL-6 excluded) associated with resistin levels. The same models showed that IR, cytokines, demographic and anthropometric variables were associated with leptin and adiponectin levels in very different ways.

The novel resistin findings in Mexican-Americans contrast prior studies showing positive correlations between resistin and IR, seen in a Mexican population (i.e., a different cohort

with a smaller sample size and excluding diabetes mellitus) [4] as well as a Japanese population [5]. Consistent with our BMI findings, some studies show that obesity is associated with higher serum resistin levels (when compared to non-obese states) in subjects from the United States and Japan [6,7]. However, other studies from Europe and the United States showed no relationship between these groups [8–10]. This inconsistent result in the literature may be explained by different population ethnicities, study sample sizes, tissues analyzed, disease status, and variations in resistin assays [11]. Compared to these studies, our study benefits from a homogenous study group, a larger sample size, and well-defined disease states. The roles of sex differences in adiposity status [10] and other hormonal factors in aging [11] may also affect findings. Notably in our study, higher BMI was associated with higher resistin levels, though sex and age showed no significant effect (Table 2). One may also reasonably speculate that genetic variance led to our findings [27,28]. Another study in a Mexican-Mestizo population demonstrated that that single nucleotide polymorphism (SNP) was associated with lower resistin levels [36]. In other (Korean and Italian) populations, polymorphisms in the *RETN* gene are implicated in significant variation in serum resistin levels [37,38]. Furthermore, four tag SNPs in the *RETN* gene were strongly associated with changing resistin levels in participants from the Framingham Offspring Study [39].

Significantly lower leptin levels in diabetes mellitus group were found compared to normal glucose tolerance group significantly when controlling for cytokines, sex, age, and BMI; there were no significant associations found between cytokines and leptin (Table 3). These results (now with a larger sample size) coincide with our prior findings in this cohort, which showed lower leptin levels in individuals with diabetes, compared to no diabetes [13]. However, they contrast those seen in Mexican-Americans from the San Antonio Heart Study, which showed no differences in leptin levels between subjects with and without diabetes mellitus [16]. The subjects from that study were slightly older than our subjects, but interestingly displayed the same associations of leptin with female sex, age, and BMI seen in our study (Table 3). Furthermore, among Mexican populations, multiple studies illustrated the association of increased obesity (a state of increased IR) with increased leptin levels [20,21]. These studies excluded diabetes mellitus and enrolled younger subjects as well as a larger percentage of female subjects. The results are consistent with our findings of positive relationships between leptin and BMI, though they contrast the inverse relationships observed between leptin and IR (Model 3). In spite of differences in ethnicity, subjects from Europe and the Middle East also displayed lower leptin levels in patients with diabetes, when compared non-diabetic control subjects [17–19]. Our cohort population contains an unusually high percentage of Amerindian genes (associated with IR), which highlights the importance of exploring the role of genetic variability [25]. Notably, some genetic studies show that SNPs of LEP and LEPR genes may affect leptin levels in Mexicans [40,41].

There were no significant differences found in adiponectin levels between IR groups, which contrasts prior findings seen in different Mexican-American populations [21,42,43]. However, adiponectin levels were higher in female sex, showed positive associations with age and HDL-C level, and inverse associations with BMI and triglyceride levels (Table 3); this is consistent with prior findings in Mexican-Americans [20]. A positive association between adiponectin and IL-8 level coincides with evidence that adiponectin increases IL-8

in some inflammatory diseases [44]. As Mexican-Americans reflect a diverse multiethnic group [25,42], it is imperative to study these individuals from a genetic perspective. Notably, SNPs in the ADIPOQ gene of Mexican-Americans are associated with IR [43].

There are several limitations to this study. Due to its cross-sectional nature, we cannot infer causal relationships, or specific temporal mechanisms for our findings. The study population is homogenously Mexican-American, so it is difficult to generalize the findings to all Hispanics. Furthermore, findings cannot be generalized to other ethnicities. Differences in genetic variability may play a role in our findings, given the high prevalence of Amerindian genes in this cohort [25].

5. Conclusions

Resistin levels decreased with increasing IR while supporting evidence of a previously-described cytokine pathway in this Mexican-American cohort. Leptin levels fell with elevated IR and were associated with sex, age, and BMI. Adiponectin levels showed no significant association with IR status and appeared to be associated with sex, BMI, and lipid levels. These findings are unique when compared to other ethnicities, including other Hispanics. Further studies should examine the effects of polymorphisms in RETN, LEP, LEPR, and ADIPOQ genes on adipokine levels and IR. As obesity largely influences adipokine levels [6,7,20], this should also be studied separately from the overall metabolic syndrome. One may also explore the mechanisms of these markers in IR by examining the effects of therapeutic agents known to reduce IR-thiazolidinediones and incretin mimetics - in this population.

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Table 1

Demographic, anthropometric and metabolic characteristics by glucose tolerance status.

Variable	ALL n = 953	Normal glucose tolerance n = 419 (43.97%)	Prediabetes n = 338 (35.47%)	Diabetes Mellitus n = 196 (20.57%)	*p*-value*
Demographic Characteristics					
Sex, Female N (%)	586 (61.5)	253 (60.4)	204 (60.4)	129 (65.8)	0.3771
Age (years), mean (SD)	41.4 (14.7)	36.7 (13.2)	43.3 (14.5)	47.9 (15.1)	<0.001
BMI (kg/m^2), mean (SD)	30.4 (6.3)	29.1 (6.4)	31.2 (6.2)	32.0 (6.0)	<0.001
Waist circumference (cm), mean (SD)	101.1 (14.9)	97.5 (14.3)	102.8 (14.3)	105.8 (15.2)	<0.0001
Hypertension, N (%)	119 (12.5)	25 (6.0)	50 (14.8)	44 (22.5)	<0.0001
Anthropometric and Metabolic Characteristics					
HbA1c (%), median (IQR)	5.4 (4.7,6.0)	4.8 (4.0, 5.3)	5.7 (5.1, 6.0)	7.2 (6.5, 9.1)	<0.0001
HbA1c (mmol/mol), median (IQR)	36 (28, 52)	29 (20, 34)	39 (32, 42)	55 (48, 76)	<0.0001
Fasting blood glucose (mg/dL), median (IQR)	96.0 (90.0, 105.0)	91.0 (87.0, 95.0)	102.0 (95.0, 106.0)	118.5 (99.0, 170.5)	<0.0001
Insulin (pmol/L), median (IQR)	12.1 (7.8, 19.0)	10.7 (7.0, 15.4)	13.7 (9.6, 21.4)	13.8 (8.2, 20.4)	<0.0001
HOMA-IR, median (IQR)	3.0 (1.8, 4.8)	2.4 (1.5, 3.5)	3.3 (2.3, 5.3)	4.5 (2.4, 7.5)	<0.0001
HOMA B, median (IQR)	130.2 (81.5, 206.7)	143.7 (94.0, 218.0)	138.0 (92.5, 213.4)	81.4 (46.7, 150.4)	<0.0001
Resistin (ng/mL), median (IQR)	19.2 (8.4, 30.4)	20.7 (14.0, 31.0)	19.6 (5.0, 34.0)	13.1 (1.3, 24.0)	<0.001
Leptin (ng/mL), median (IQR)	17.1 (7.6, 28.7)	14.3 (6.7, 25.2)	20.0 (8.9, 33.1)	18.7 (7.7, 28.6)	0.0006
Adiponectin (μg/mL), median (IQR)	15.0 (10.0, 22.0)	15.6 (11.1, 22.2)	14.5 (9.7, 22.8)	13.7 (9.5, 20.7)	0.0403
Triglycerides (mg/dL), median (IQR)	121.0 (82.0, 171.0)	104.5 (72.0, 142.0)	132.0 (95.0, 179.0)	149.0 (100.0, 205.0)	<0.0001
Total Cholesterol (mg/dL), mean (SD)	180.7 (40.1)	177.6 (38.9)	184.7 (42.4)	180.5 (38.1)	0.0501
HDL-C (mg/dL), mean (SD)	46.7 (12.0)	47.6 (11.2)	46.6 (13.1)	44.6 (11.2)	0.0049
LDL-C (mg/dL), mean (SD)	107.8 (34.6)	106.8 (31.7)	109.9 (35.9)	106.1 (38.2)	0.2592
IL-1β (pg/mL), median (IQR)	0.6 (0.5, 1.1)	0.6 (0.4, 1.2)	0.6 (0.6, 1.2)	0.6 (0.6, 0.9)	0.0183
IL-6 (pg/mL), median (IQR)	1.9 (0.9, 4.0)	1.5 (0.7, 3.1)	2.4 (1.0, 4.4)	2.3 (1.0, 4.8)	<0.0001
TNF-α (pg/mL), median (IQR)	1.9 (0.9, 4.0)	1.5 (0.7, 3.1)	2.4 (1.0, 4.4)	2.3 (1.0, 4.8)	0.0782
IL-8 (pg/mL), median (IQR)	4.4 (3.2, 6.4)	4.4 (3.1, 6.0)	4.7 (3.3, 7.0)	4.1 (3.1, 6.0)	0.1095

*p-values from Kruskal-Wallis test for non-normal data (summary statistics reported as median and IQR), ANOVA for normal data (summary statistics reported as mean and SD).

Table 2

Associations Between Glucose Tolerance Status and Log-Transformed Resistin based on Univariable (Unadjusted) and Multivariable (Adjusted) linear regression models.

Resistin	**Model 1**		**Model 2**		**Model 3**	
	Unadjusted β (SE)	***p*-value**	**Adjusted* β (SE)**	***p*-value**	**Adjusted** β (SE)**	***p*-value**
Glucose Tolerance Group		<0.0001		<0.0001		<0.0001
Prediabetes vs. NGT	−0.234 (0.097)	0.0157	−0.266 (0.093)	0.0042	−0.313 (0.096)	0.0011
Diabetes Mellitus vs. NGT	−0.829 (0.115)	<0.0001	−0.795 (0.110)	<0.0001	−0.881 (0.117)	<0.0001
Diabetes Mellitus vs. Prediabetes	−0.594 (0.119)	<0.0001	−0.529 (0.114)	<0.0001	−0.569 (0.115)	<0.0001
IL-1β (pg/mL)			0.015 (0.007)	0.0405	0.016 (0.007)	0.0252
IL-6 (pg/mL)			0.0001 (0.0004)	0.9339	0.0001 (0.0004)	0.8671
TNF-α (pg/mL)			−0.008 (0.005)	0.1109	−0.010 (0.005)	0.0352
IL-8 (pg/mL)			0.060 (0.006)	<0.0001	0.059 (0.006)	<0.0001
Sex: Female vs. Male					−0.169 (0.088)	0.0553
Hypertension: yes vs. no					−0.200 (0.131)	0.1255
Age (year)					0.005 (0.003)	0.0991
BMI					0.016 (0.007)	0.0145
Triglycerides (mg/dL)					−0.0001 (0.0003)	0.6402
HDL-C (mg/dL)					−0.011 (0.004)	0.0026

*adjustment for IL-1β, IL-6, TNF-α, and IL-8.

**additional adjustment for sex, hypertension, age, BMI, triglycerides, and HDL-C.

Note: all models were constructed using linear regressions based on each log-transformed marker (i.e. ln(resistin)).

NGT = normal glucose tolerance.

SE = Standard Error.

r^2: 0.051839, 0.131629, 0.156741, for Model 1, 2 and 3, respectively.

Table 3

Associations Between Glucose Tolerance Status and Log-Transformed Leptin based on Univariable (Unadjusted) and Multivariable (Adjusted) linear regression models.

Leptin	**Model 1**		**Model 2**		**Model 3**	
	Unadjusted β (SE)	***p*-value**	**Adjusted* β (SE)**	***p*-value**	**Adjusted** β (SE)**	***p*-value**
Glucose Tolerance Group		0.0017		0.0021		0.0004
Prediabetes vs. NGT	0.274 (0.078)	0.0004	0.269 (0.077)	0.0005	0.068 (0.053)	0.1957
Diabetes Mellitus vs. NGT	0.169 (0.092)	0.0649	0.172 (0.092)	0.06	−0.181 (0.064)	0.005
Diabetes Mellitus vs. Prediabetes	−0.105 (0.095)	0.2718	−0.097 (0.095)	0.3105	−0.249 (0.063)	<0.0001
IL-1β (pg/mL)			−0.003 (0.006)	0.5886	−0.005 (0.004)	0.2447
IL-6 (pg/mL)			0.0001 (0.0003)	0.8817	−0.0001 (0.0002)	0.6312
TNF-α (pg/mL)			0.002 (0.004)	0.5404	0.005 (0.003)	0.086
IL-8 (pg/mL)			0.009 (0.005)	0.1058	0.007 (0.004)	0.0603
Sex: Female vs. Male					1.239 (0.048)	<0.0001
Hypertension: yes vs. no					0.029 (0.072)	0.6874
Age (year)					0.004 (0.002)	0.024
BMI					0.082 (0.004)	<0.0001
Triglycerides (mg/dL)					0.0002 (0.0002)	0.3567
HDL-C (mg/dL)					0.002 (0.002)	0.3021

*adjustment for IL-1β, IL-6, TNF-α, and IL-8

**additional adjustment for sex, hypertension, age, BMI, triglycerides, and HDL-C

Note: all models were constructed using linear regressions based on each log-transformed marker (i.e. ln(leptin)).

NGT = normal glucose tolerance

SE = Standard Error

r^2: 0.013253, 0.017487, 0.584275, for Model 1, 2 and 3, respectively

Table 4

Associations Between Glucose Tolerance Status and Log-Transformed Adiponectin based on Univariable (Unadjusted) and Multivariable (Adjusted) linear regression models.

Adiponectin	**Model 1**		**Model 2**		**Model 3**	
	Unadjusted β (SE)	***p*-value**	**Adjusted* β (SE)**	***p*-value**	**Adjusted** β (SE)**	***p*-value**
Glucose Tolerance Group		0.2013		0.2713		0.5616
Prediabetes vs. NGT	−0.010 (0.065)	0.883	−0.023 (0.064)	0.7228	0.008 (0.063)	0.9008
Diabetes Mellitus vs. NGT	−0.131 (0.077)	0.0873	−0.121 (0.076)	0.1108	−0.070 (0.077)	0.3634
Diabetes Mellitus vs. Prediabetes	−0.122 (0.080)	0.1265	−0.098 (0.079)	0.2127	−0.078 (0.075)	0.3031
IL-1β (pg/mL)			0.007 (0.005)	0.1394	0.005 (0.005)	0.2784
IL-6 (pg/mL)			0.0001 (0.0003)	0.6396	0.0001 (0.0003)	0.7261
TNF-α (pg/mL)			0.0001 (0.003)	0.9903	0.002 (0.003)	0.5897
IL-8 (pg/mL)			0.023 (0.004)	<0.0001	0.024 (0.004)	<0.0001
Sex: Female vs. Male					0.235 (0.058)	<0.0001
Hypertension: yes vs. no					0.038 (0.086)	0.6613
Age (year)					0.006 (0.002)	0.0024
BMI					−0.018 (0.004)	<0.0001
Triglycerides (mg/dL)					−0.001 (0.000)	0.0004
HDL-C (mg/dL)					0.013 (0.002)	<0.0001

*adjustment for IL-1β, IL-6, TNF-α, and IL-8.

**additional adjustment for sex, hypertension, age, BMI, triglycerides, and HDL-C.

Note: all models were constructed using linear regressions based on each log-transformed marker (i.e. ln(adiponectin)).

NGT = normal glucose tolerance.

SE = Standard Error.

r^2: 0.003359, 0.032558, 0.152272, for Model 1, 2 and 3, respectively.