University of Cincinnati

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I, Roopa Kanakatti Shankar, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Association of Glycemia with Cystatin C in Youth with Diabetes

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This work and its defense approved by:

Committee chair: Erin Nicole Haynes, DrPH
Committee member: Lawrence M. Doian, MD
Committee member: Jane Khoury, MS, PhD

UNIVERSITY OF CINCINNATI

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Association of Glycemia with Cystatin C in Youth with Diabetes

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Science in Clinical & Translational Research

In the Department of Environmental Health
Division of Epidemiology & Biostatistics
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by

Roopa Kanakatti Shankar

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Committee Chair: Erin Haynes, DrPH
Abstract

Objective: Serum cystatin C (cysC) is proposed as a biomarker of early renal dysfunction and cardiovascular disease in adults with diabetes. Potential factors affecting cysC in youth with diabetes are unknown. We sought to establish the distribution of cysC in youth with diabetes and determine the influence of measures of glycemia on cysC.

Hypothesis: CysC will correlate negatively with fasting serum glucose (FSG) and hemoglobinA1c (A1c) in youth with type 1 and type 2 diabetes.

Aim 1: Describe the distribution of cysC in youth with type 1 and type 2 diabetes

Aim 2: Determine the influence of FSG and A1c on cysC after adjusting for known determinants such as age, gender, race/ethnicity and other cardiovascular risk factors.

Methods: The study population consisted of 959 participants in the SEARCH for Diabetes in Youth study with 825 ‘type 1’, 127 ‘type 2’ and 7 ‘other’ diabetes, all of less than 5 years duration. Linear regression models were fitted for type 1 and type 2 diabetes to study the contribution of FSG and A1c to variability in cysC after adjusting for age, gender, race/ethnicity, duration of diabetes, body mass index Z-score, systolic and diastolic blood pressure Z-scores, urine albumin/creatinine ratio, total cholesterol, HDL cholesterol and triglycerides.

Results: Serum cysC showed no deviation from normality (mean 0.75mg/L, SD 0.12). In type 1 diabetes, FSG and A1c were significantly negatively associated with cysC. In type 2 diabetes, FSG but not the A1c was significantly negatively associated with cysC. FSG explained 2.7% and 5.3% of variability in the models for type 1 and type 2 diabetes.
Conclusions: Acute glycemic control is associated with cysC in both type 1 and type 2 diabetes while chronic glycemic control, measured by A1c is associated with cysC in type 1 but not type 2 diabetes. Glycemic control must be accounted for, in the interpretation of cysC measures in youth with diabetes.
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**Biostatistics Mentor:** Jane Khoury, MS, PhD

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Introduction

Cystatin C is a low molecular weight cysteine protease inhibitor, produced at a stable rate by all nucleated cells. Cystatin C is a basic protein and is freely filtered by the glomerulus and catabolized in the renal tubular cells without reabsorption (Grubb 1992). Hence serum cystatin C (cysC) concentrations are determined exclusively by elimination through glomerular filtration. CysC has gained prominence as an endogenous marker of the glomerular filtration rate (GFR) (Nilsson-Ehle and Grubb 1994). Unlike serum creatinine, CysC is not influenced by the muscle mass (Tanaka, Suemaru et al. 2007). Several studies in adults (Newman, Thakkar et al. 1994; Dharnidharka, Kwon et al. 2002) and children (Bokenkamp, Domanetzki et al. 1998; Ylinen, Ala-Houhala et al. 1999; Zaffanello, Franchini et al. 2007) have demonstrated that cysC is a better marker of GFR compared with serum creatinine.

CysC production is known to be increased with age and with high-dose glucocorticoid therapy (Filler, Bokenkamp et al. 2005). Mild thyroid dysfunction also affects cysC, with lower concentrations seen in the hypothyroid state (Fricker, Wiesli et al. 2003). Diabetes is associated with 8.5% higher cysC concentrations in adults (Stevens, Schmid et al. 2009). CysC is also correlated with several inflammatory markers and monocytes (Lee, Park et al. 2010; Evangelopoulos, Vallianou et al. 2012). Obesity is associated with higher cysC in children and adults (Naour, Fellahi et al. 2009; Codoner-Franch, Ballester-Asensio et al. 2011) and a positive association of BMI with cysC (Muntner, Winston et al. 2008) has been described. In the NHANES III population, age, gender and race appear to influence cysC levels in youth (Groesbeck, Kottgen et al. 2008).
In patients with diabetes, serum creatinine-based Modification of Diet in Renal Disease (MDRD) equation poorly estimates the GFR in the normal to high GFR range and is not useful to measure early GFR decline (Beauvieux, Le Moigne et al. 2007; Rigalleau, Beauvieux et al. 2011). However, cysC based equations were noted to be better than the creatinine-based equations in the normal to high GFR range (>90 ml/min/1.73m2), and cysC was proposed as a biomarker of early renal dysfunction in patients with diabetes (Pucci, Triscornia et al. 2007; Willems, Wolff et al. 2009). Longitudinal studies in patients with type 1 and type 2 diabetes showed that serial cysC measures may be used to track changes in GFR and screen for early renal dysfunction (Perkins, Nelson et al. 2005; Perkins, Ficociello et al. 2007).

In addition to being a marker of GFR, cysC is also a marker for cardiovascular outcomes and mortality in adults, independent of the GFR (Shlipak, Sarnak et al. 2005). CysC is associated with metabolic syndrome in dyslipidemic adult patients (Servais, Giral et al. 2008). In adult patients with type 2 diabetes, cysC is correlated with inflammatory markers and is a predictive marker of cardiovascular disease, independent of nephropathy (Ogawa, Goto et al. 2008; Lee, Park et al. 2010). Maahs et al. showed that cysC predicts the progression of subclinical coronary atherosclerosis in adults with type 1 diabetes (Maahs, Ogden et al. 2007). There are no studies on the association of cysC and cardiovascular risk in youth with diabetes.

Previously, the clinical utility of cysC was limited due to non-standard assay techniques and systematic drift in the assay (Inker and Okparavero 2011; Maahs, Jalal et al. 2011). The issues have been recently resolved with the establishment of international reference standards (Grubb, Blirup-Jensen et al. 2010).
The factors that influence cysC in youth with diabetes are largely unknown. Prior to assessing the association of cysC with cardiovascular disease or renal dysfunction in youth with diabetes, it is important to define the factors that affect cysC measures in youth with type 1 and type 2 diabetes. CysC was shown to be related to age, gender, glycated hemoglobin (A1c), body mass index and C-reactive protein in youth with type 1 diabetes (Maahs, Prentice et al. 2011). No data are available on the distribution of cysC in youth with type 2 diabetes.

Glycemic control is also associated with the GFR in early type 1 diabetes in adults as well as in type 2 diabetes (Soper, Barron et al. 1998; Rigalleau, Lasseur et al. 2006). The relationship has not been studied in youth with early type 1 and type 2 diabetes, but we hypothesized that glycemic control is associated with cysC in youth with diabetes.

The objective of this study was to establish the distribution of cysC in youth, soon after the diagnosis of diabetes and to examine the association of glycemia with cysC.

**Hypothesis:** CysC will correlate negatively with fasting serum glucose (FSG) and hemoglobin A1c (A1c) in youth with type 1 and type 2 diabetes

**Aim 1:** Describe the distribution of cysC in youth with Type 1 and type 2 diabetes

**Aim 2:** Determine the influence of FSG and A1c on cysC after adjusting for known determinants such as age, gender, race/ethnicity and other cardiovascular risk factors.

**Research Design and Methods**

**Study design**

The SEARCH for Diabetes in Youth study (SEARCH) is a multi-center study with population-based ascertainment of diabetes in youth 0-19 years of age. A detailed description of SEARCH
methodology is published elsewhere (SEARCH Study Group (2004)). Healthcare provider-diagnosed diabetes cases were identified in geographically defined populations in Ohio, Washington, South Carolina and Colorado and among health plan enrollees in Hawaii (Hawaii Medical Service Association, Med-Quest, Kaiser Permanente Hawaii) and in southern California (Kaiser Permanente). The study was reviewed and approved by the local institutional review boards (IRBs). Using a protocol that conformed to the Health Insurance Portability and Accountability Act of 1996 (HIPAA), youth with diabetes (or parents, when participants <18 years) were asked to complete a brief survey that asked for their age at diagnosis of diabetes, race/ethnicity, and a limited health history. They were invited to participate in a study visit at which written informed assent and/or consent were obtained according to the guidelines established by the local institutional review board (IRB) from participants ≥18 years of age and participants and their parents/guardians for participants < 18 years of age. At the study visit undertaken when the participant was not in diabetic ketoacidosis, additional clinical information was collected including symptoms at presentation, family history of diabetes, and medication use. The diabetes “type” was assigned based on the healthcare provider’s diagnosis. A physical examination was performed to measure height, weight, blood pressure (BP) and body mass index (BMI). Participants had blood drawn for laboratory testing that included FSG, fasting lipid profile, A1c and a random urine albumin/creatinine ratio (ACR). CysC was specifically measured in the incidence cohort of SEARCH participants from 2002-2005 at the one-year, two-year and five year follow up study visit. All SEARCH study participants with type 1 or type 2 diabetes who had a cysC measure < 5 years after diagnosis of diabetes, at one of the study visits, were included in this analysis. The first available measure of cysC was included for participants with multiple measures.
Laboratory methods

Blood samples were obtained fasting, under conditions of metabolic stability, in the absence of fever and acute infections. Samples were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories), where they were analyzed. Measurements of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were performed enzymatically using Roche reagent on a Hitachi Modular P autoanalyzer (Roche Diagnostics, Indianapolis, IN). HbA1c was measured by ion-exchange high-performance liquid chromatography (TOSOH G7, TOSOH Biosciences Inc., South San Francisco, CA). A spot urine sample was collected in the morning after an overnight rest. Urine was not collected in girls who were menstruating. Urinary creatinine was measured by the Jaffe method using Roche Diagnostics reagent on the Hitachi 917 autoanalyzer. Two quality control samples were analyzed in each run, and the inter-assay coefficient of variation was consistently <2%. Urine albumin was measured immunochemically using Dade-Behring reagent on the BNII nephelometer. The sensitivity of that assay was 0.2 mg/dL. The inter-assay coefficient of variation was <5% for the high-level quality control sample and <6.5% for the low-level.

CysC was measured by using a precise immune-nephelometric assay (Siemens N Latex Cystatin C assay, FDA approved) with a sensitivity of 0.002 mg/L. Good assay precision was noted with intra and inter assay coefficient of variation 2.9% and 3.2 % respectively. Since there have been previously reported concerns of a systematic shift in the commercially available Dade-Behring/Siemens assay for cysC (Maahs, Jalal et al. 2011), we compared our assay performance to the peer group “CAP survey” and noticed a 10% difference in the results obtained after September 2008. Hence we restricted this study analysis to only the participants who had cysC
measures between March 2006 and May 2008 when the assay performance was verified to be consistent. All physical and laboratory measures compared with cysC were obtained at the same study visit as the cysC measurement. One value of cysC (0.06 mg/L) in a subject with type 2 diabetes was deemed to be an outlier due to an error in measurement and was omitted from the analyses leaving 959 measures.

Statistical Methods

The distribution of cysC was analyzed to assess for deviation from the assumption of normality. In case of significant deviation, we planned to use an appropriate transformation in order to use parametric approaches for analyses. Baseline characteristics were compared between type 1 and type 2 diabetes using t-tests for continuous variables and chi-squared tests for categorical variables. Univariate Pearson correlations of cysC were assessed for all the continuous variables. Multiple linear regression models were fitted to explore the influence of the independent variables: fasting serum glucose and A1c, after adjusting for known determinants such as age, gender, and race/ethnicity, as well as other possible covariates such as duration of diabetes, BMI-Z score, systolic and diastolic blood pressure Z-scores (SBP-Z and DBP-Z), TC, HDL-c and TG on the dependent variable cysC. Given the differences in comorbidities by diabetes type, regression analyses were run separately for type 1 and type 2 diabetes. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Nine hundred and fifty nine participants had at least one measure of cysC within 5 years of diagnosis of diabetes. Eight hundred and twenty five of these participants had a provider
diagnosis of type 1 diabetes and 127 had a provider diagnosis of type 2 diabetes and the remaining 7 were grouped as having “other” diabetes referring to non-gestational forms of diabetes that have not been classified as type 1 or type 2 (e.g. monogenic diabetes). These 7 participants with “other” diabetes were excluded from the multivariate analyses by type of diabetes. CysC was normally distributed with a mean of 0.75 mg/L (SD: 0.12 mg/L; range: 0.37-1.22 mg/L). Mean cysC in participants with type 1 diabetes was 0.75 mg/L (SD: 0.12 mg/L, range: 0.37-1.15). Mean cysC in participants with type 2 diabetes was 0.72 mg/L (SD: 0.14 mg/L, range: 0.43-1.22). CysC distribution was significantly different by type of diabetes (p<0.05).

Participants with type 2 diabetes were older with a greater proportion of female gender, non-Hispanic black and Hispanic ancestry compared to those with type 1 diabetes. Participants with type 2 diabetes had a higher BMI Z-score, SBP Z-score, DBP Z-score, TC and TG and a lower HDL-c (all p<0.05). The baseline characteristics of SEARCH participants with cysC measures and their distribution by type of diabetes are shown in Table 1.

Univariate analyses in participants with type 1 diabetes demonstrated that cysC was negatively correlated with duration of diabetes, BMI Z-score, SBP Z-score, FSG, A1c, TC and TG (Table 2). In type 2 diabetes, univariate analysis showed that cysC was positively associated with BMI and negatively associated with duration of diabetes, FSG, A1c and TC, but not significantly associated with SBP Z-score or TG (Table 2).

The findings of the separate multivariate regression analyses by diabetes type are shown in Table 3. In type 1 diabetes, FSG and A1c levels were negatively and independently associated with adjusted cysC. Older age was positively and significantly associated with adjusted cysC, while non-Hispanic black ancestry and female gender were also negatively associated. This model explained 25% of the variability in cysC.
In type 2 diabetes, FSG was independently and negatively associated with the adjusted cysC but A1c was not independently associated. ACR was positively associated and total cholesterol was negatively associated. The model explained 50% of the variability in cysC.

FSG explains 2.7% and 5.3% of adjusted cysC variability in the type 1 and type 2 diabetes models, respectively. A1c explains 0.2% of the variability in the type 1 diabetes model.

**Discussion**

CysC is normally distributed in youth with a short duration of diabetes. The distribution of cysC in type 1 and type 2 diabetes appears to be different (Table 1, p<0.05). However, after adjusting for the differences in age, race, gender, BMI, SBP and DBP, glycemic control (acute and chronic), urine albumin/creatinine ratio and lipid profile in the multiple regression model, the type of diabetes was no longer significant.

In univariate analysis, cysC was negatively correlated with both A1c and FSG in type 1 and type 2 diabetes. In type 1 diabetes, the BMI Z-score was negatively correlated with cysC, but was positively correlated in type 2 diabetes. The negative association of cysC with BMI was also described by Maahs et al. in youth with type 1 diabetes (Maahs, Prentice et al. 2011). A positive association of BMI with cysC has been previously reported in adults without kidney disease with and without diabetes (Galteau, Guyon et al. 2001; Shankar and Teppala 2011). The association of BMI Z-score with cysC needs further study in youth with diabetes.

In multivariate regression analyses in type 1 diabetes, female gender and non-Hispanic black ancestry were associated with lower cysC levels similar to non-diabetic youth described in the NHANES study (Groesbeck, Kottgen et al. 2008). We found that older age was associated with increased cysC in youth with type 1 diabetes, unlike the previous studies (Groesbeck, Kottgen et
Our findings may be due to the wider age range (2.3-23 years at the study visit) in our type 1 diabetes population. Groesbeck et al. showed that peak cysC was seen around 12 years of age in females and 14 years of age in males in the NHANES population (range: 12-19 years) and the values declined thereafter until age 19 years (Groesbeck, Kottgen et al. 2008). Similar negative association of cysC with age was described by Maahs et al. in a population of youth with type 1 diabetes (range: 12-19 years) (Maahs, Prentice et al. 2011).

In the multivariate analyses in type 2 diabetes, age, race/ethnicity and gender were no longer independently associated with cysC. This may be the result of a smaller sample size.

Serum glucose at the time of measurement was independently and negatively associated with cysC. The relationship between cysC and acute glycemic control raises the issue that glycemia should be accounted for, in the interpretation of cysC in youth with both type 1 and type 2 diabetes. Serum creatinine is not known to be similarly affected by the changes in serum glucose.

A1c was independently and significantly associated with cysC in type 1 but not type 2 diabetes suggesting that the effect of chronic hyperglycemia (as measured by the A1c) on cysC may differ by type of diabetes. Negative association with A1c has previously been reported in type 1 diabetes (Maahs, Prentice et al. 2011) and type 2 diabetes (Oh, Lee et al. 2012) of longer duration.

ACR was positively associated in early type 2 diabetes but not in type 1 diabetes, suggesting that the type 2 diabetes may be of longer duration but detected late or, that, the pathophysiology of kidney dysfunction may differ by type of diabetes.
Our study is limited by the cross-sectional design, and the early time point in the course of diabetes. We also do not have markers of inflammation that are known to affect cysC. We do not have a gold standard measure of the GFR (e.g. iohexol clearance) and our study was not designed to look at the ability of cysC based equations to accurately measure the true GFR in this range of hyperfiltration. However, the data suggest that cysC is sensitive to acute glycemic changes in early diabetes. We speculate that this may be mediated in part or completely through changes in GFR. In support of our hypothesis, Cherney et al. recently demonstrated that in clamped hyperglycemia, the change in e-GFR by cysC correlated with gold standard GFR measures using inulin (Cherney, Sochett et al. 2010).

Previous studies using cysC in adult and pediatric populations with diabetes have not accounted for dysglycemia as pointed out in a recent review (Maahs 2012). If serial measures of cysC are to be used as a biomarker of early renal dysfunction, ensuring minimal glycemic variability among multiple measures becomes especially important. Further studies are needed to study the relationship of glucose with cysC in relation to true GFR changes by gold standard measures as well as longitudinal studies to capture this relationship with progressive renal dysfunction.

Conclusions

This is the first study of the factors associated with cysC in early diabetes in youth. Acute glycemia is significantly correlated with cysC in youth with both type 1 and type 2 diabetes suggesting that glycemia should be accounted for, in the interpretation of cysC in youth with diabetes. Further studies to elucidate the relationship of cysC with glycemia, both acute and chronic, will shed light on the pathophysiology of early renal dysfunction and cardiovascular disease in patients with diabetes.
Bibliography


15. Lee SH, Park SA, Ko SH, Yim HW, Ahn YB, Yoon KH, Cha BY, Son HY and Kwon HS: Insulin resistance and inflammation may have an additional role in the link between cystatin C and cardiovascular disease in type 2 diabetes mellitus patients. *Metabolism* 59:241-6, 2010


Table 1: Baseline characteristics of SEARCH population by type of diabetes (Data presented as mean [SD]); P-values depict comparisons between type 1 and type 2 (significant values in bold).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants (n=959)</th>
<th>Type 1 (n=825)</th>
<th>Type 2 (n=127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at visit (years)</td>
<td>12.8 [4.4]</td>
<td>12.2 [4.3]</td>
<td>17 [2.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>9.8 [4.3]</td>
<td>9.2 [4.3]</td>
<td>13.8 [2.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>2.6 [0.8]</td>
<td>2.6 [0.9]</td>
<td>2.9 [0.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Male</td>
<td>48.7%</td>
<td>50.7%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Race/ Ethnicity (%)**</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NHW</td>
<td>65.1%</td>
<td>72.9%</td>
<td>16.5%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16.3%</td>
<td>11.3%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13%</td>
<td>11.6%</td>
<td>20.5%</td>
<td></td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>0.8 [1.0]</td>
<td>0.59 [0.9]</td>
<td>2.1 [0.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP Z-score</td>
<td>-0.29 [0.95]</td>
<td>-0.38 [0.89]</td>
<td>0.35 [1.08]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP Z-score</td>
<td>0.13 [0.89]</td>
<td>0.08 [0.87]</td>
<td>0.42 [0.97]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSG (mg/dL)</td>
<td>189 [82]</td>
<td>192 [82]</td>
<td>175 [82]</td>
<td>0.032</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>8.4 [1.9]</td>
<td>8.4 [1.7]</td>
<td>8.2 [2.8]</td>
<td>0.362</td>
</tr>
<tr>
<td>ACR (mcg/mg)&quot;</td>
<td>7 (5-13)</td>
<td>7 (5-13)</td>
<td>2 (4-20)</td>
<td>0.107</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>168 [36]</td>
<td>166 [35]</td>
<td>177 [43]</td>
<td>0.013</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>56 [14]</td>
<td>58 [14]</td>
<td>42 [10]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>85 [83]</td>
<td>75 [60]</td>
<td>151 [154]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>0.75 [0.12]</td>
<td>0.75 [0.12]</td>
<td>0.72 [0.14]</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Other diabetes (N=7); **Other race ethnicity remaining %; " ACR is non-normally distributed. Median (interquartile range) is depicted in the table.
Table 2: Univariate analyses: Correlates of cysC by diabetes type (significant estimates in bold)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Type 1 diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson ‘r’</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.03</td>
<td>0.324</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>-0.07</td>
<td>0.048</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>-0.09</td>
<td>0.012</td>
</tr>
<tr>
<td>SBP Z-score</td>
<td>-0.11</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP Z-score</td>
<td>-0.05</td>
<td>0.191</td>
</tr>
<tr>
<td>FSG (mg/dL)</td>
<td>-0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>-0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR (mg/mg)</td>
<td>-0.03</td>
<td>0.456</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>-0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>-0.08</td>
<td>0.021</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-0.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3: Multivariate Regression Analyses: Correlates of cysC by diabetes type (significant estimates in bold)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Type 1 diabetes (N=825)</th>
<th>Type 2 diabetes (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(R^2 = 0.25)</td>
<td>(R^2 = 0.50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.0041 (&lt;0.001)</td>
<td>-0.0036 (0.654)</td>
</tr>
<tr>
<td>Race – Black vs. NHW</td>
<td>-0.0536 (&lt;0.001)</td>
<td>-0.0682 (0.121)</td>
</tr>
<tr>
<td>Race- Hispanic vs. NHW</td>
<td>-0.0276 (0.099)</td>
<td>-0.0852 (0.155)</td>
</tr>
<tr>
<td>Race- other vs. NHW</td>
<td>-0.0013 (0.958)</td>
<td>-0.0285 (0.700)</td>
</tr>
<tr>
<td>Gender- F vs. M</td>
<td>-0.0471 (&lt;0.001)</td>
<td>-0.044 (0.166)</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>0.0002 (0.692)</td>
<td>-0.0006 (0.740)</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>-0.0025 (0.603)</td>
<td>0.0393 (0.151)</td>
</tr>
<tr>
<td>SBP Z-score</td>
<td>-0.0087 (0.152)</td>
<td>0.0022 (0.885)</td>
</tr>
<tr>
<td>DBP Z-score</td>
<td>0.0032 (0.585)</td>
<td>-0.0196 (0.273)</td>
</tr>
<tr>
<td>FSG (mg/dL)</td>
<td>-0.0003 (&lt;0.001)</td>
<td>-0.0008 (0.012)</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>-0.0071 (0.028)</td>
<td>0.0013 (0.892)</td>
</tr>
<tr>
<td>ACR (mg/mg)</td>
<td>-0.0027 (0.932)</td>
<td>0.1289 (0.005)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>-0.0003 (0.143)</td>
<td>(0.0011) (0.023)</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>-0.0002 (0.562)</td>
<td>0.0001 (0.946)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-0.0002 (0.054)</td>
<td>-0.00005 (0.594)</td>
</tr>
</tbody>
</table>