YKL-40, a marker of inflammation and endothelial dysfunction, is elevated in patients with Type 1 Diabetes and increases with levels of albuminuria.

YKL-40 in Type 1 Diabetes.

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Objective. The inflammation marker YKL-40 is elevated in patients with type 1 diabetes and is associated with atherosclerosis and an increased cardiovascular mortality. In the present study, YKL-40 levels are examined in patients with type 1 diabetes with increasing levels of albuminuria, known to be associated with an increased risk of cardiovascular disease.

Research Design and Methods. One-hundred-fourty-nine patients with type 1 diabetes attending Steno Diabetes Center were examined: 58 with normoalbuminuria (N, U-albumin<30mg/24h), 46 with persistent microalbuminuria (MA, 30-300 mg/24h) and 45 with persistent macroalbuminuria/diabetic nephropathy (DN, >300 mg/24h). Control group consisted of 55 healthy individuals (C). Groups were matched according to gender and duration of diabetes (>30 years).

Results. Median levels (interquartile range) of serum YKL-40 were significantly higher in N vs. C (37 (29-52) ng/ml vs. 53 (32-105) ng/ml, p<0.01) and were increasing with increasing levels of albuminuria: MA, 74 (45-160) ng/ml; DN, 117 (68-215) ng/ml, p<0.001 for all comparisons. YKL-40 levels correlated with urinary albumin/creatinine-ratio in the total group of participants ($r^2=0.25$, p<0.001). Significant but weak intercorrelations of YKL-40 were found with age, diastolic blood pressure, hemoglobin A1c and serum creatinine. After adjustment for significant covariates, albuminuria was significantly associated with YKL-40 levels, p<0.001.

Conclusions. YKL-40 levels are elevated in patients with type 1 diabetes with an independent association between increasing YKL-40 levels and increasing levels of albuminuria. The present study is the first to suggest a role of YKL-40 in the gradually progressing vascular complications in patients with type 1 diabetes.
Persistent microalbuminuria is an established predictor of diabetic nephropathy leading to progressive renal insufficiency and end-stage renal disease and is associated with an increased risk of cardiovascular (CV) disease in both patients with type 1 and type 2 diabetes (1-3). Individuals with diabetes have in general a 2- to 4-fold increased risk of subsequent CV disease (4). A large scale study of patients with Type 1 diabetes, demonstrated up to a 9-fold increased mortality risk from ischemic heart disease, excessively higher in patients under 30 year of age (5). A substantial part of patients with type 1 diabetes will in years after onset of diabetes develop diabetic nephropathy, although studies from selected centres suggest a declining incidence (6,7).

Identification of predictors of CV disease and progression in nephropathy in patients with type 1 diabetes is important. The fact that urinary albumin excretion rate is associated with an increased risk of CV morbidity and mortality (2), even in non-diabetic individuals and also at levels below the threshold of microalbuminuria (low-grade albuminuria) (8), supports that an increasing urinary albumin excretion rate reflects vascular damage in the kidneys as part of a systemic endothelial dysfunction (9). Endothelial dysfunction is the initial step in atherogenesis, which is largely responsible for the development of ischemic heart disease and thrombotic strokes (10).

YKL-40 is marker of inflammation and endothelial dysfunction. It is a growth factor for several cell types and has an established role in extracellular matrix remodelling and angiogenesis (11). Substantial evidence indicate that YKL-40 participate in processes during early stages of atherosclerosis, and it seems to be of pathogenic importance in the low-grade inflammation that precedes the development of CV disease (11-14). We have previously found significant elevated levels of YKL-40 in patients with type 2 diabetes and an independent positive correlation with insulin resistance and parameters of the lipid profile (15,16).

Studies of YKL-40 in patients with type 1 diabetes have never been performed. The objective of the present study was to evaluate serum YKL-40 levels in patients with type 1 diabetes and with increasing levels of albuminuria. On the basis of previous studies, we expected to find 1) higher serum YKL-40 levels in patients with type 1 diabetes and 2) increasing serum YKL-40 levels with increasing levels of albuminuria explained by a progressive systemic endothelial dysfunction.

**RESEARCH DESIGN AND METHODS**

The present study was based on data used to identify biomarkers of diabetes and diabetic nephropathy by proteomic analyses. The participants were examined at Steno Diabetes Center in 2004 and consisted of 55 Caucasian healthy individuals (C) and 3 groups of Caucasian patients with type 1 diabetes attending Steno Diabetes Center. Based on 24 hour urine collections analysed as part of the routine care of the patients prior to the present study, they were divided into 58 patients with normoalbuminuria (N, U-albumin <30mg/24h), 46 patients with persistent microalbuminuria (MA, at least two out of three urines consecutive urines with albumin excretion rate 30-300 mg/24h) and 45 patients with persistent macroalbuminuria/diabetic nephropathy (DN, >300 mg/24h). Groups were matched at group level by gender, age (± 5 years) and duration of diabetes (± 3 years) (>20 years for normoalbuminuric patients). Controls (C) were randomly selected from the general healthy population by advertisement in the local news. They were enrolled in the study if
they had plasma glucose levels < 6 mmol/l after an overnight fast and had no prior history of cardiovascular disease including hypertension. Subjects referred to the hospital on the suspicion of diabetes or other endocrine diseases were not included even though a diagnosis was not confirmed. Matching of controls with individuals from all the diabetic groups at individual level was not possible.

Investigations were performed in the morning after an overnight fast. Arterial blood pressure was measured three times with an appropriate cuff size following at least 10 min. supine rest. Urinary albumin concentration was measured by an enzyme immunoassay from early morning spot urine collections. Serum and urine creatinine concentration was assessed by a kinetic Jaffé method. Plasma samples were stored at -80°C until analysis. Glomerular filtration rate (GFR) was estimated using the 4 variable MDRD GFR formula (age, gender, race, serum creatinine) (http://mdrd.com/). Diabetic retinopathy was assessed in all patients by fundus photography after pupillary dilatation and graded as nil, simplex or proliferative retinopathy. Patients were interviewed using the World Health Organization (WHO) cardiovascular questionnaire. Smoking was defined as persons smoking one or more cigarettes/cigars/pipes a day; all others were classified as non-smokers.

The study was approved by the local ethics committee and all patients gave their informed consent.

Serum YKL-40 was analyzed with a commercial assay (ELISA, Quidel, USA) on material frozen at time of inclusion. Measuring range of the assay was 20 to 300 ng/ml, and the intra-assay and inter-assay coefficients of variation were 5.8% and 6.0% respectively.

**Statistical analysis**—Comparisons between the groups were made with Kruskal-Wallis test for ordinal data. Continuous data were compared with One-Way ANOVA. If data had a non-Gaussian distribution as seen in p-plot, data was logarithmically transformed. Analyses of intercorrelations and associations were performed using multivariate linear regression analysis. P-values were two-sided, and a p-value <0.05 was considered statistically significant. All analyses were made with the statistical software package SPSS 11.5 (SPSS inc., Chicago, Il).

**RESULTS**

Clinical data of the control group and the diabetic patients differentiated according to level of albuminuria are shown in Table 1. YKL-40 levels according to level of albuminuria are illustrated in Figure 1. The groups were well matched regarding gender and duration of diabetes, but age-match was ruined due to a few patients with missing values and due to exclusion of a patient with non-diabetic nephropathy from the macroalbuminuria group.

Median YKL-40 levels were significantly different all groups in between with increasing YKL-40 levels with increasing levels of albuminuria, p<0.001. As expected we found significantly lower eGFR in the macroalbuminuria group (p<0.0001) but equivalent eGFR in the control, normo- and microalbuminuria groups. We found no significant difference in systolic blood pressure between the groups neither for all comparisons nor for comparisons of the diabetic groups, but there was a significant difference between the controls and the macroalbuminuria group (p=0.041) and controls and the microalbuminuria group (p=0.028). The significant differences in diastolic blood pressure and serum cholesterol for all comparisons were due to differences between controls and the diabetic groups in total. No significant differences in diastolic blood pressure or serum cholesterol were found the diabetic groups in between (p=0.68
and \( p=0.39 \), respectively. There were a significant difference in use of antihypertensive drugs between the groups \( (p<0.0001) \). Almost half of the normoalbuminuric group (48.3\%) and close to all subjects in the microalbuminuric (95.6\%) and macroalbuminuric (93.5\%) groups were using antihypertensive specimens.

Although we found a significant difference in hemoglobin A1c (HbA1c) for all comparisons, no significant difference was found between the micro- and macroalbuminuria group \( (p=0.94) \).

Multiple regression analyses showed correlation of YKL-40 with UACR in the total group of participants \( (r=0.50, p<0.001) \) (Table 2). This correlation was not significant in any of the different subgroups. Significant intercorrelations of YKL-40 were also found with HbA1c, serum creatinine, age and diastolic blood pressure, respectively, in the total group of participants (Table 2). No significant correlation was found between YKL-40 and systolic blood pressure, BMI or total cholesterol, and YKL-40 levels were not predicted by GFR \( (p=0.73) \).

In a multiple regression model adjusting for the significant covariates (UACR, HbA1c, serum creatinine, age and diastolic blood pressure) and cholesterol, systolic blood pressure and the presence of intermittent claudicatio and retinopathy, YKL-40 levels were significantly associated with level of albuminuria, \( p<0.001 \). Pairwise comparisons between the groups showed a significant association between YKL-40 levels and increasing levels of albuminuria to the level of microalbuminuria (Table 3). No significant difference in this association was found between the micro- and macroalbuminuria-group \( (p=0.08) \).

At baseline only a limited number of patients had symptoms of intermittent claudicatio or previous episodes of myocardial infarction or stroke (Table 1). Patients with intermittent claudicatio and stroke had significantly higher YKL-40 levels compared to individuals without these macrovascular complications \( (p=0.021 \) and \( p=0.05 \), respectively), but in accordance with the multiple regression analyses adjusting for the presence of retinopathy and intermittent claudicatio these associations became insignificant when adjusting for the significant covariates.

**DISCUSSION**

The micro- and macrovascular complications of diabetes remain a constant challenge to quality of life as well as to life expectancy. Intensive research has provided knowledge about the pathogenesis and about several potentially modifiable risk factors, including poor glycemic control, increased urinary albumin excretion, hypertension and smoking. Despite an improved and intensified treatment of diabetes and its vascular risk factors and complications, supplementary risk markers alone or in combination addressing other and earlier aspects of the pathogenesis are needed.

For the first time, YKL-40, a marker of inflammation and endothelial dysfunction, has been evaluated in patients with type 1 diabetes. We found elevated YKL-40 levels in patients with type 1 diabetes compared to control subjects and showed increasing YKL-40 levels with increasing levels of albuminuria. This finding is in accordance with previous studies showing that chronic low-grade inflammation is associated with the occurrence and progression of (micro)albuminuria (17) and that both micro- and macroalbuminuria are accompanied by increased levels of a variety of markers of endothelial dysfunction (18). Several studies have shown that biomarkers of endothelial dysfunction and inflammation are elevated in patients with type 1 diabetes without as well as with microvascular complications or diabetic nephropathy (18-20). Some studies also show an association with a decline in
GFR (20), cardiovascular morbidity (19,20) and overall mortality (20). Chronic low-grade inflammation and endothelial dysfunction appear closely linked, and it seems that chronic low-grade inflammation can be both a cause and a consequence of endothelial dysfunction (18). It therefore seems likely, that the high risk of cardiovascular disease in patients with type 1 diabetes could partly be described by an increased inflammatory activity initiated by endothelial dysfunction, and that an inflammatory state should be addressed as a risk factor in its own.

Dysfunction of the vascular endothelium is considered an important factor in the pathogenesis of diabetic micro- and macroangiopathy (18). Studies show, that YKL-40 plays a role in endothelial dysfunction in relation to cell migration, reorganization and tissue remodelling during atherogenesis (12-14). YKL-40 promotes chemotaxis, cell attachment, spreading and migration of vascular endothelial cells suggesting, that YKL-40 promotes the process of the atherosclerotic plaque formation, where vascular smooth muscle cells (VSMCs) are induced to migrate through the intima in response to exogenous signals (13). YKL-40 also modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating a role of YKL-40 in angiogenesis by stimulating the migration and reorganization of VSMCs (13). Furthermore, YKL-40 is produced and secreted by monocytes during differentiation to macrophages but is also secreted by activated macrophages (11), and YKL-40 protein expression is found in vivo in both macrophages and vascular smooth muscle cells in the atherosclerotic plaque (11). In accordance with this finding, normoalbuminuric type 1 diabetic patients have been found to have an increased monocytic activity characterized by an increased monocytic release of IL-6 and superoxide anion which accentuates in type 1 diabetic patients with microvascular complications (21). Substantial evidence therefore indicate, that YKL-40 participates in monocyte differentiation and macrophage activation as part of the endothelial dysfunction and the processes during early stages of atherosclerosis (11) and seems to be of pathogenic importance in the low-grade inflammation, that precedes the development of CV disease. We have previously found elevated YKL-40 levels in patients with type 2 diabetes (15,16) where it correlated with insulin resistance and parameters of the lipid profile, but despite a known macrophage infiltration in adipose tissue, YKL-40 has never been found to be associated with BMI (15).

Since YKL-40 is excreted by the kidneys, we not surprisingly found a significant correlation between YKL-40 and UACR, but we did not find, that increasing YKL-40 levels were predicted by a decline in eGFR. Despite the correlation between YKL-40 and UACR, we found a significant association between YKL-40 levels and level of albuminuria after adjustment for significant covariates implicating increasing albuminuria with increasing YKL-40 levels. Patients with micro- and macroalbuminuria also had a higher prevalence of retinopathy and intermittent claudication, but adjustment for these complications did not attenuate the association between YKL-40 levels and level of albuminuria. The insignificant association when reaching macroalbuminuria level is most likely explained by a systemically accentuated inflammatory state marginalising the individual impact of YKL-40. This is in accordance with the finding of a larger proportion of individuals with proliferative retinopathy and intermittent claudication in the micro- and macroalbuminuria group and with the perception of YKL-40 as an early marker. We have previously shown an association between YKL-40 and an increased CV mortality rate in an elderly part of the general
population without known diabetes and CV disease after adjustment for known CV risk factors and markers (16). In the same study, YKL-40 and UACR were independent markers of CV mortality with only weak intercorrelation and in accordance with the studies on low-grade albuminuria and risk of CV disease, YKL-40 and low-grade albuminuria had a synergistic prediction of CV mortality. Other studies support this association between YKL-40 and CV morbidity and mortality, since YKL-40 levels are found to be associated with the presence and extent of coronary artery disease as assessed by coronary angiography (22) and just recently, YKL-40 levels have been found to be elevated in patients with myocardial infarction (23).

Several studies have investigated the role of YKL-40 in relation to cancer, but despite substantial evidence supporting a role of YKL-40 in cancer, newer results are conflicting (24,25). YKL-40 levels are particularly high in recurrent cancer states and highly differentiated cancers, which are characterized by high vascularization and a high turnover of extracellular matrix (24). One could hypothesize that YKL-40 might play a role in cancer due to its general role in extracellular tissue remodelling and its influence on proliferation and differentiation of vascular smooth muscle cells and vascular endothelial cells, but in vivo proof of this is yet to be obtained. In our previous study, where we found YKL-40 to be an independent predictor of overall and cardiovascular mortality, we did not find higher YKL-40 levels in individuals dying from cancer (16).

Limitations of the present study is the lack of investigation of other markers of endothelial dysfunction and inflammation foremost high sensitive C-reactive protein (hsCRP) due to a limited amount of biological material. However, previous studies have either not found or have found only a weak correlation between YKL-40 and hsCRP ($r=0.17$, $p=NS$ and $r=0.22$, $p<0.0001$, respectively) (15,16) and hsCRP levels have not previously been found to influence the predictive value of YKL-40 in terms of overall or cardiovascular mortality (16). Therefore, we would not expect different outcomes even though we included hsCRP in the analyses.

Perception of YKL-40 as an early marker (16) indicate, that YKL-40 could possibly correlate to other early markers of endothelial activation and/or dysfunction. We found a trend towards higher YKL-40 levels in individuals with macrovascular complications, but due to a limited number of cases the association was not statistically significant. The predictive value of YKL-40 with regard to albuminuria and the progression to nephropathy as well as the development of macrovascular complications and cardiovascular mortality is properly investigated in a prospective study, which is our next approach.

In conclusion, YKL-40 levels are elevated in patients with type 1 diabetes and increases with levels of albuminuria. YKL-40 levels are independently associated with increasing levels of albuminuria to the level of microalbuminuria after adjustment for UACR, age and other significant covariates and the presence of retinopathy and intermittent claudication.

Taken together, a role of YKL-40 in the gradually progressing vascular complications in patients with diabetes is suggested with YKL-40 being a possible early marker of microvascular complications – further studies implicating other inflammation markers and cardiovascular follow-up are needed.

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REFERENCE


Table 1. Clinical data of control group and the diabetic patients differentiated according to level of albuminuria.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, total</td>
<td>55</td>
<td>58</td>
<td>45</td>
<td>46</td>
<td>0.46</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65.4</td>
<td>51.7</td>
<td>53.3</td>
<td>58.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.5 (10.9)</td>
<td>55.6 (10.8)</td>
<td>54 (11.1)</td>
<td>49 (9.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>DM duration (years)</td>
<td>36.8 (10.5)</td>
<td>35.5 (11.3)</td>
<td>33.9 (10.5)</td>
<td>35.4 (11.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (3.6)</td>
<td>24.7 (2.9)</td>
<td>25.1 (3.7)</td>
<td>25.1 (4.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (18.2%)</td>
<td>12 (20.7%)</td>
<td>13 (28.9%)</td>
<td>19 (41.3%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Use of antihypertensiva</td>
<td>0</td>
<td>28 (48.3%)</td>
<td>43 (95.6%)</td>
<td>43 (93.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Use of statins</td>
<td>2 (3.6%)</td>
<td>16 (27.6%)</td>
<td>18 (40%)</td>
<td>23 (50%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Use of aspirin</td>
<td>2 (3.6%)</td>
<td>21 (36.2%)</td>
<td>27 (60%)</td>
<td>29 (63%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>YKL-40 (ng/ml) *</td>
<td>37 (27-52)</td>
<td>53 (32-105)</td>
<td>74 (45-160)</td>
<td>117 (68-215)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HbA1c (%) **            | 5.5 (0.3)     | 8.2 (1.1)        | 8.8 (1.3)        | 8.8 (1.1)        | 0.0001  |
Creatinine (µmol/l) **  | 95 (87-104)   | 92 (83-97)       | 89 (81-101)      | 125 (100-174)    | 0.0001  |
UACR (mg/g) **          | 5 (3-8)       | 5 (4-8)          | 26 (11-63)       | 500 (208-1155)   | 0.0001  |
Systolic BP (mmHg) **   | 132 (16)      | 138 (21)         | 141 (23)         | 140 (24)         | 0.94    |
Diastolic BP (mmHg) **  | 81 (10)       | 74 (11)          | 74 (12)          | 76 (12)          | 0.003   |

History of:
Myocardial infarction  | 0             | 3 (5%)           | 5 (11.1%)        | 3 (6.5%)         | 0.11    |
Stroke                 | 0             | 4 (6.9%)         | 4 (8.9%)         | 4 (8.7%)         | 0.17    |
Intermittent claudicatio | 0             | 4 (6.9%)        | 8 (17.8%)        | 8 (17.4%)        | 0.005   |
Retinopathy:
- none                 | -             | 6 (10.3%)        | 1 (2.2%)         | 2 (4.4%)         | 0.0001  |
- simplex              | -             | 19 (32.8%)       | 11 (24.4%)       | 10 (21.7%)       | 0.0001  |
- proliferative        | -             | 33 (56.9%)       | 33 (73.3%)       | 34 (73.9%)       | 0.0001  |

Presented as numbers (%) where not specified. * Median (IQR). ** Mean (SD). † Some patients had UACR levels reduced by antihypertensive medication which was not stopped when spot urine samples were collected for the study.
N, numbers; DM, diabetes mellitus; HbA1c, hemoglobin A1c; UACR, urinary albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; BP, blood pressure.

Table 2. Intercorrelations of YKL-40.

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACR</td>
<td>0.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.16</td>
<td>0.025</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.14</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Log-transformed data. Multiple regression analyses adjusted for gender, body mass index, creatinine, cholesterol and systolic blood pressure.
UACR, urinary albumin/creatinine ratio; HbA1c, hemoglobin A1c; BP, blood pressure.
Table 3. Associations between YKL-40 and levels of albuminuria.

<table>
<thead>
<tr>
<th>Pairwise comparisons of levels of albuminuria</th>
<th>Mean difference of YKL-40</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroalbuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>1.38 (0.96-1.98)</td>
<td>0.08</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>2.02 (1.41-2.90)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Control subjects</td>
<td>4.31 (2.48-7.46)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>1.46 (1.09-1.96)</td>
<td>0.012</td>
</tr>
<tr>
<td>Control subjects</td>
<td>3.13 (1.85-5.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>2.13 (1.35-3.38)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Multiple regression analysis after adjustment for urinary albumin/creatinine ratio, age, hemoglobin A1c, creatinine, cholesterol, systolic and diastolic blood pressure and the presence of retinopathy and intermittent claudicatio.

Figure 1. Median levels (IQR) of YKL-40 in the 3 diabetic groups compared to the control group: 37 (29-52) ng/ml in the control group, 53 (32-105) ng/ml in the patients with normoalbuminuria, 74 (45-160) ng/ml in patients with microalbuminuria and 117 (68-215) ng/ml in patients with macroalbuminuria/diabetic nephropathy, p<0.0001.