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Title: Evaluation of serum growth arrest specific-6/sAXL levels in type 2 diabetes mellitus

Running Title: Growth arrest specific-6/sAXL in diabetes pathogenesis

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Abstract

Objective: In this study, we aimed to investigate whether the association between serum growth arrest specific-6 (Gas6), AXL, and soluble AXL (sAXL) levels with HbA1c and estimated glomerular filtration rate (eGFR) in diabetic patients.

Methods: This study included type 2 diabetes mellitus (T2DM) patients admitted to department of endocrinology and healthy individuals. In all participants, HbA1c and creatinine levels were evaluated on the available autoanalyzer and eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Gas6, AXL, and sAXL serum protein concentrations were analyzed by enzyme linked immunosorbent assay (ELISA).

Results: The study group consisted of 51 patients (34 females and 17 males) diagnosed with T2DM and 17 healthy controls (9 females and 8 males). We found that Gas6, AXL, and sAXL concentration significantly lower in the patient group \( (p<0.05) \). There was a significant positive correlation between Gas6, AXL and sAXL parameters in both groups. eGFR negatively correlated with Gas6 and sAXL in patient group \( (r=-0.285, \ p<0.047; \ r=-0.311, \ p<0.028, \text{respectively}) \), while there was not correlation in the control group.

Conclusion: Gas6, AXL and sAXL have an important role in the pathogenesis of T2DM. Besides, Gas6 and sAXL appear to have potential predictive value for diabetic nephropathy. Further clinical studies are necessary to clarify this mechanism.

Keywords: Gas6, AXL, sAXL, HbA1c, eGFR.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and four hundred sixty-three million adults worldwide suffer from diabetes mellitus (1,2). Glycosylated hemoglobin or hemoglobin A1c (HbA1c) is currently preferred in the diagnosis and management of diabetes because it is a reliable indicator of chronic glycemia (3). It is

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formed by glucose binding to one or both N-terminal valines of hemoglobin polypeptide chains and represents average blood glucose concentrations for 2-3 months (4,5).

The growth arrest–specific 6 (Gas6) gene is the last added protein to the vitamin K dependent protein family; its amino acid sequence is 44% identity to protein S, which has anticoagulant properties (6,7). Moreover, Gas6 is widely expressed in many cells, including bone marrow macrophages, platelets, leukocytes, endothelial cells, and vascular smooth muscle cells (8,9). Gas6 demonstrates these functions by binding to Tyro, AXL, and c-Mer (TAM) receptors, which are sub-members of the receptor tyrosine kinase family (10). AXL, which is bound to the membrane, is released from the cell membrane due to proteolysis from the N terminal region, and this soluble form in circulation is called sAXL. sAXL, as it can bind Gas6 and therefore deplete the ligand, is thought to be a critical determinant in affecting autocrine or paracrine AXL signaling (11).

Gas6/AXL signaling plays roles in regulating tissue homeostasis, inflammatory cytokine release, diabetic renal, vascular disease, and carcinogenesis. Recent studies have also shown that this signaling plays a role in metabolic disorders associated with glucose intolerance (8, 12).

There are conflicting statements regarding the role of the Gas6/AXL signal in both inflammation and cancer studies. Besides, impaired glucose metabolism-related studies are insufficient and controversial.

In this study, we aimed to investigate whether the association between serum Gas6, AXL, and sAXL levels with HbA1c and estimated glomerular filtration rate (eGFR) in diabetic patients.

Materials and Methods

Study design

This study is a case-control study carried out from 2018 to August 2019 at the Erciyes University Faculty of Medicine, Department of Endocrinology. A total of 51 patients diagnosed with type 2 diabetes mellitus (T2DM) based on the World Health Organization diagnostic criteria and 17 healthy controls were enrolled.
None of the study subjects were on vitamin K supplementation, warfarin, statin or heparin sodium therapy. Other exclusion criteria of patients, both control and patients, were as follows: a subject with smoking and alcohol habit, cardiovascular disease, malignant hypertension, diabetic nephropathy, and diabetic retinopathy.

**Blood sampling and biochemical measurements**

Blood samples were collected from all participants in tubes with EDTA (3.2 mL, VACUETTE) and serum tubes with gel separator (8 mL, VACUETTE) between 9-11:00 A.M. The tubes with gel separator were centrifuged at 2000xg for 10 minutes and serum were separated. HbA1c levels in EDTA whole blood samples were performed on Roche Cobas c501 (Roche Diagnostics, Germany). Serum glucose and creatinine levels on Roche Cobas c701 (Roche Diagnostics, Germany) and complete blood count on XN-9000 (Sysmex, Japan) were measured. eGFR was calculated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula using creatinine (13). After the autoanalyzer studies were completed, the remaining serum samples were aliquoted and frozen at -80°C for enzyme linked immunosorbent assay (ELISA) studies. Gas6, AXL, and sAXL serum protein concentrations were analyzed by ELISA method according to the manufacturer’s protocols Gas6 ELISA kit (YLbiont, YLA1896HU), AXL ELISA kit (YLbiont, YLA3680HU), and sAXL ELISA kit (YLbiont, YLA4070HU).

**Informed consent and ethical statement**

All the subjects gave written informed consent. This study was approved by the Erciyes University Clinical Research Ethics Committee on 18.07.2018 with Decision No 2018/369.

**Statistical Analysis**

Statistical analysis was performed with SPSS version 23.0 software. The conformity of age, gender, body mass index (BMI), fasting glucose, hemoglobin, HbA1c, creatinine, eGFR, Gas6, AXL and sAXL values of the control and patient groups to the normal distribution was evaluated with Shapiro–Wilk normality test and Q–Q graphs. Summary statistics of gender distribution, a categorical variable, were expressed as numbers and percentages. The difference between the gender distributions of the two groups was evaluated with the chi-square test. Summary statistics of BMI, hemoglobin, and eGFR, which distributed normally, were

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presented as mean ± standard deviation (SD), and the comparison of two groups was performed with the independent sample t-test. The summary statistics of age, fasting glucose, HbA1c, creatinine, Gas6, Axl, and sAXL values, which did not distribute normally, were presented as median (25.-75. percentile) and the comparison of two groups was performed with Mann Whitney-U test. Spearman's test was used for non-parametric correlation analysis. A p-value of less than 0.05 was accepted as statistically significant.

**Results**

The control group was 44.5 (41-53) years of age, and 9 (53%) were female, and 8 (47%) were male. The patient group was 51 (45-57) years of age, and 34 (67%) were female, and 17 (33%) were male. BMIs of control and patient groups were 28.3 ± 3.8 and 31.2 ± 5.3, respectively. While fasting glucose and HbA1c values in the control group were 96.5 (87.2 - 103.5) mg/dL and 5.4 (5.3 - 5.6)%, those in the patient group were 149 (117.5-203.5) mg/dL and 8.4 (6.8-10)%, respectively. Demographic characteristics and biochemical parameters other than fasting glucose and HbA1c were not statistically different. We found that the level of serum Gas6, AXL, and sAXL was significantly decreased in patients compared to controls (p<0.05) (Table 1).

There was a strong positive correlation between Gas6 and AXL and between AXL and sAXL in both groups. eGFR weakly negatively correlated with Gas6 and sAXL in the patient group. However, these correlations were not present in the control group (Table 2). Although it was not statistically significant, in the patient group, hemoglobin levels were lower than the control group (Table 1).

When all individuals were evaluated (without separating patient/control), there was a weak negative correlation between HbA1c and Gas6, AXL, and sAXL (r = -0.297, p<0.018; r = -0.261, p<0.041; r = -0.327, p<0.010, respectively). In addition, fasting glucose was weakly negatively correlated with AXL (r = -0.310, p<0.014). AXL was moderately positively correlated with Gas6 and sAXL (r = 0.463, p<0.001; r = 0.492, p<0.001, respectively). Based on the correlations with eGFR, we divided all individuals into two groups according to eGFR (eGFR <90 ml / min, n=15 and eGFR> 90 ml / min, n=53). We found no statistically significant difference in Gas6, AXL, and sAXL levels between these two groups.

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When we divided the patient group into two groups according to eGFR (eGFR < 90 ml/min, n=14 and eGFR > 90 ml/min, n=37), although it was not statistically significant, we found that Gas6 were numerically lower in the group with eGFR < 90 ml/min. While Gas6 was 11.8 (9.8, 14.2) in the eGFR > 90 ml/min group, it was 11.18 (9.0-13.7) in the eGFR < 90 ml/min group.

When the patient group was divided into two groups according to hemoglobin levels (hemoglobin in the reference range n = 40, and anemia n = 11), a strong negative correlation was observed between sAXL and HbA1c (r = -0.761, p<0.006) in the anemia group. There was a moderate negative correlation between fasting glucose and sAXL but not statistically significant (r = -0.573, p<0.066).

**Discussion**

Although Gas6/AXL signaling is predominantly investigated in cancer research, recent studies have focused on this pathway, considering it plays a vital role in metabolic diseases associated with insulin resistance and glucose intolerance. Gas6 is known to be a member of the K vitamin dependent protein family. It is synthesized in alpha cells of islets of Langerhans in the pancreas (14), so the mitogenic and antiapoptotic effects of Gas6 may prevent T2DM pathogenesis (15). Many studies have reported that Gas6 concentration or gene polymorphism to be an inverse correlation with plasma glucose, HbA1c, insulin resistance, and inflammatory cytokines in T2DM patients (16,17).

In present study, we evaluated the Gas6, AXL, and sAXL serum levels of diabetic patients, the correlations between HbA1c, and whether that could be used as alternative non-invasive markers in T2DM monitoring. Consistent with other studies, Gas6, AXL, and sAXL concentrations were lower in the patients with diabetes. However, Gas6, AXL, and sAXL did not correlate with the HbA1c. The concentration of serum Gas6 and sAXL negatively correlated with eGFR in patients. Besides, a strong negative correlation was observed between sAXL and HbA1c in patients with anemia.

Similarly, Hung et al. (18) have investigated the plasma Gas6 concentration among Taiwanese adults with T2DM. They reported that Gas6 concentration significantly decreased in the diabetic group compared to the normal glucose (NG) tolerance group.
In another study with slightly more populations, Lee et al. (19) have reported that Gas6 concentration decreased in the T2DM group compared to the NG group and also reported that plasma Gas6 was negatively correlated with the oral glucose tolerance test (OGGT) group and HbA1c.

Bassiouni et al. (20) have investigated the plasma levels of Gas6/sAXL in patients with chronic hepatitis C virus (HCV) infection with and without T2DM. It has been reported that Gas6 and sAXL negatively correlated with HbA1c in the T2DM group.

Various studies have reported that inflammation and activation of the immune system are highly related to T2DM pathogenesis. However, macrophage and other immunity systems are included in adipose tissue via Gas6/AXL signaling (18, 21).

Hung et al. (18) have also reported that decreased Gas6 concentration is associated with vascular cell adhesion molecule (VCAM)-1 which is responsible for response vascular complications in the diabetic group. Accordingly, it has been suggested that Gas6 may play a role in T2DM.

Diabetic complications (neuropathy, nephropathy, and retinopathy) thought to be responsible for morbidity and mortality, are common in T2DM (22). Diabetic patients are not resistant to complications that can cause death, so it is crucial to diagnostic markers that can be used in the early stages of diabetes complications and the development of drugs targeting these markers. A few studies reported that Gas6/AXL might play a role in cardiovascular and renal complications of diabetes (23).

Lee et al. (24) have investigated the Gas6 level in patients with various kidney function. It has been shown that the levels of Gas6 increased in chronic kidney disease patients compared to the control group. Also, it has been reported that the level of Gas6 is inversely associated with eGFR.

In another study on diabetic nephropathy, Li et al. (25) have investigated the association between cystatin C and Gas6 in T2DM patients with different degrees of diabetic nephropathy. It has been reported that low Gas6 levels have been observed in diabetic nephropathy. It has been thought that Gas6 may be used as a noninvasive biomarker instead of cystatin C and creatinine in the early diagnosis of diabetic nephropathy.

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Toprak et al. (26) have investigated whether plasma Gas6 concentrations are associated with albuminuria in T2DM. It has been shown that plasma Gas6 levels were higher in patients with albuminuria than normoalbuminuria.

Unexpectedly, in this study, we found that the serum Gas6 and sAXL negatively correlated with eGFR in T2DM patients. When we divided the patient group into two groups according to eGFR, although it was not statistically significant, Gas6 was lower in the group with eGFR <90 ml/min.

Although we excluded patients with diabetic nephropathy, this finding brought to mind that Gas6 and sAXL may have predictive value for diabetic nephropathy. Further studies on patients with various stages of diabetic nephropathy may reveal the variation of Gas6/sAXL between stages. In addition, a further cohort study with T2DM patients may reveal the predictive importance of these parameters in diabetic nephropathy.

Anemia is a factor that interferes with HbA1c measurement. The low proportion of young erythrocytes can result in falsely high glycosylated hemoglobin levels (27). We found a strong negative correlation between sAXL and HbA1c in patients with anemia. Based on this finding, it should be investigated whether sAXL levels can be used instead of HbA1c in the follow-up of diabetic patients with anemia.

In most diabetes studies, the mechanism of Gas6/AXL inhibition is not clear. However, we can say that the following mechanisms may play a role in this inhibition.

Firstly, the destruction of pancreatic beta cells is an important etiological factor in the development and progression of T2DM. Gas6 has been reported to have effects on the proliferation and functional activity of pancreatic beta cells. Therefore, it is thought that it may help prevent the pathogenesis of T2DM (14, 15). Conversely, as we showed in our study, low Gas6 levels will lead to diabetes.

Cell death by apoptosis is necessary for many biological processes in response to tissue development, homeostasis, and pathological conditions. Gas6-TAM interaction is significant in inflammation and tissue homeostasis (28). Phosphatidylserine, confined and normally located to the inner leaflet inside the bilayer of the plasma membrane, is externalized to the membrane during the apoptosis. Phosphatidylserine marks apoptotic cells for clearance, while TAM
receptors serve for the uptake of apoptotic cells by phagocytes (29). Thus, the physiological relevance of Gas6-mediated TAM activation was reported in clearing apoptotic cells. As a result, Gas6/AXL inhibition might be related to apoptosis as a response to inflammation.

Secondly, Vitamin K is not only responsible for the activation of coagulation factors but also activates proteins matrix GLA and Gas6 protein. Carboxylation of the GLA domain is responsible for stabilizing the protective effect of Gas6 activity. Also, Gas6 is responsive to the critical biological processes by binding to the AXL receptor as in glucose metabolism (21).

Several studies have indicated that vitamin K supplementation may be beneficial in glucose metabolism and reduced development of T2DM risk. Therefore, low vitamin K level is associated with a decrease in gamma-carboxylation of Gas6. As a result, inhibition of Gas6 may cause a decrease in its functional activity against inflammation, impaired glucose metabolism, and insulin resistance (30).

Thirdly, although the Gas6/AXL mechanism is not clear on glucose metabolism, various signal molecules are activated by binding of Gas6 to AXL. One of these signal molecules is phosphoinositide-3 kinase (PI3K) and Akt pathway. The induction of Akt by PI3K causes transcription of several genes involved in insulin secretion (15). Therefore, in our study, a decrease of serum Gas6, AXL, and sAXL may be associated with impaired insulin secretion in T2DM.

There are some limitations to our study: (1) The number of patients group was small, (2) the low number of healthy individuals compatible with our study may have affected some of our results in terms of significance, and (3) We could not evaluate the PI3K/Akt pathway, apoptosis-related signaling molecules and finally vitamin K (4) Urine albumin and serum cystatin C levels could not be evaluated for diabetic nephropathy.

Conclusion
Gas6, AXL and sAXL have an important role in the pathogenesis of T2DM. Further studies may clarify their role in the pathogenesis of diabetes. The development of therapies targeting this pathway could be a new therapeutic approach for T2DM. Besides, Gas6 and sAXL appear to have potential predictive value for diabetic nephropathy. Therefore, we think that more clinical studies are necessary to clarify this mechanism.

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Table 1. Demographic characteristics and biochemical parameters in the control and patient groups.

Table 2. Correlations in control and patient groups.

Table 1. Demographic characteristics and biochemical parameters in the control and patient groups.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=17)</th>
<th>Patient group (n=51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.5 (41-53)</td>
<td>51.0 (45-57)</td>
<td>0.163</td>
</tr>
<tr>
<td>Gender (F/M)*</td>
<td>9/8</td>
<td>34/17</td>
<td>0.313</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3 ± 3.8</td>
<td>31.2 ± 5.3</td>
<td>0.063</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>96.5 (87.2-103.5)</td>
<td>149 (117.5-203.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.4 (5.3-5.6)</td>
<td>8.4 (6.8-10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.4 ± 1.3</td>
<td>13.8 ± 1.6</td>
<td>0.058</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.77 (0.68-0.81)</td>
<td>0.71 (0.60-0.89)</td>
<td>0.391</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>103 ± 9.1</td>
<td>97 ± 17.7</td>
<td>0.147</td>
</tr>
<tr>
<td>Gas6 (ng/mL)</td>
<td>12.4 (10.6-21.5)</td>
<td>10.8 (8.9-13)</td>
<td>0.011</td>
</tr>
<tr>
<td>AXL (ng/mL)</td>
<td>335.2 (270.1-409.5)</td>
<td>217.6 (179.5-287.7)</td>
<td>0.003</td>
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<tr>
<td>sAXL (pg/mL)</td>
<td>4.3 (3.3-9.4)</td>
<td>3.1 (1.8-4)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; Gas6, growth arrest specific protein6

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Table 2. Correlations in control and patient groups.

<table>
<thead>
<tr>
<th></th>
<th>Fasting Glucose</th>
<th>HbA1c</th>
<th>Creatinine</th>
<th>eGFR</th>
<th>Gas6</th>
<th>AXL</th>
<th>sAXL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas6</td>
<td>0.242</td>
<td>-0.131</td>
<td>0.064</td>
<td>0.370</td>
<td>1</td>
<td></td>
<td>0.818*</td>
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<tr>
<td>AXL</td>
<td>0.469</td>
<td>-0.299</td>
<td>0.109</td>
<td>0.273</td>
<td>0.818*</td>
<td>1</td>
<td>0.657*</td>
</tr>
<tr>
<td>sAXL</td>
<td>0.560</td>
<td>0.137</td>
<td>-0.049</td>
<td>0.420</td>
<td>0.573</td>
<td>0.657*</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patient group</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas6</td>
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<td>-0.088</td>
<td>0.115</td>
<td>-0.285*</td>
<td>1</td>
<td>0.329*</td>
<td>0.057</td>
</tr>
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<td>AXL</td>
<td>-0.119</td>
<td>0.039</td>
<td>0.061</td>
<td>-0.113</td>
<td>0.329*</td>
<td>1</td>
<td>0.354*</td>
</tr>
<tr>
<td>sAXL</td>
<td>-0.046</td>
<td>-0.157</td>
<td>0.087</td>
<td>-0.311*</td>
<td>0.057</td>
<td>0.354*</td>
<td>1</td>
</tr>
</tbody>
</table>

*p < 0.05