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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of Serum Growth Arrest-Specific 6/ Soluble AXL Levels in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: The aim of this study was to investigate an association between serum growth arrest-specific 6 (Gas6), AXL, and soluble AXL (sAXL) levels and the glycosylated hemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR) in diabetic patients.

Materials and Methods: This study included type 2 diabetes mellitus (T2DM) patients of a department of endocrinology and healthy individuals. The HbA1c and creatinine levels of all of the participants were evaluated using autoanalyzers and the eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula. The Gas6, AXL, and sAXL serum protein concentrations were analyzed using enzyme-linked immunosorbent assays.

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). The Gas6, AXL, and sAXL concentrations were significantly lower in the patient group ($p<0.05$). There was a significant positive correlation between the Gas6, AXL, and sAXL parameters in both groups. The eGFR was negatively correlated with the Gas6 and sAXL levels in the patient group ($r=-0.285$, $p<0.047$; $r=-0.311$, $p<0.028$, respectively), while there was no correlation observed in the control group.

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

Keywords: AXL, estimated glomerular filtration rate, glycosylated hemoglobin, serum growth-arrest specific 6, soluble AXL

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia that is estimated to affect some 463 million adults worldwide (1, 2). Glycosylated hemoglobin or hemoglobin A1c (HbA1c) measurement is used as a reliable indicator of chronic glycemia in the diagnosis and management of diabetes (3). HbA1c is formed by glucose binding to one or both N-terminal valines of hemoglobin polypeptide chains, and the measurement represents an average blood glucose concentration of the previous 2 to 3 months (4, 5).

The growth arrest-specific 6 (Gas6) gene is the most recent protein added to the vitamin K- dependent protein family; its amino acid sequence shares 44% homology with 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 binds to Tyro, AXL, and c-Mer (TAM) receptors, which are submembers of the receptor tyrosine kinase family (10). AXL released from the cell membrane due to proteolysis from the N terminal region yields a soluble form (sAXL). Since it can bind to Gas6 and therefore deplete the ligand, sAXL is thought to be a critical determinant in autocrine or paracrine AXL signaling (11).

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

Studies of inflammation and cancer have yielded conflicting statements regarding the role of the Gas6/AXL signal and research related to impaired glucose metabolism remains insufficient and controversial.

The objective of this study was to investigate an association between serum Gas6, AXL, and sAXL levels and the HbA1c and estimated glomerular filtration rate (eGFR) in diabetic patients.

MATERIALS and METHODS

Ethical Considerations

This study was approved by the Erciyes University Clinical Research Ethics Committee on July 18, 2018 (no: 2018/369). All of the subjects provided written, informed consent.

Study Design

This case-control study was conducted 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 used vitamin K supplementation, warfarin, statin, or heparin sodium therapy. Other exclusion criteria for both the controls and patients were a smoking or alcohol habit, cardiovascular disease, malignant hypertension, diabetic nephropathy, or diabetic retinopathy.

Blood Sampling and Biochemical Measurements

Blood samples were collected from all of the participants in tubes containing ethylenediaminetetraacetic acid (EDTA) (3.2 mL, Vacuette; Greiner Bio-One, Kremsmünster, Austria) and serum tubes with gel separator (8 mL, Vacuette; Greiner Bio-One, Kremsmünster, Austria) between 9:00 and 11:00 AM. The tubes with gel separator were centrifuged at 2000xg for 10 minutes and the serum was separated.

The HbA1c level in the EDTA whole blood samples was measured using a Roche Cobas c501 analyzer (Roche Diagnostics, Basel, Switzerland). Serum glucose and creatinine levels were evaluated using a Roche Cobas c701 analyzer (Roche Diagnostics, Basel, Switzerland), and a complete blood count was performed using an XN-9000 automated hematology analyzer (Sysmex, Kobe, Japan). eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration 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 using the ELISA method according to the manufacturer's protocols. The Gas6 ELISA kit (YLA1896HU; Shanghai YL Biotech Co., Ltd., Shanghai, China), AXL ELISA kit (YLA3680HU; Shanghai YL Biotech Co., Ltd., Shanghai, China), and sAXL ELISA kit (YLA4070HU; Shanghai YL Biotech Co., Ltd., Shanghai, China) were used.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp., Armonk, NY, USA). 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 normal distribution was evaluated using the Shapiro-Wilks test and Q-Q plots. Summary statistics of gender distribution, a categorical variable, were expressed as numbers and percentages. The gender distribution in the 2 groups was evaluated using a chi-squared test. Summary statistics of BMI, hemoglobin, and eGFR, which displayed normal distribution, were presented as the mean±SD, and the comparison of 2 groups was performed with an independent sample t-test. The summary statistics of age, fasting glucose, HbA1c, creatinine, Gas6, AXL, and sAXL values, which did not have normal distribution, were presented as the median (25^{th}–75^{th} percentile) and the comparison of 2 groups was performed with the Mann-Whitney-U test. Spearmen's test was used for non-parametric correlation analysis. A p value of <0.05 was accepted as statistically significant.

RESULTS

The median age of the control group was 44.5 years (25^{th}–75^{th} percentile: 41–53 years); 9 (53%) were female, and 8 (47%) were male. The median age of the patient group was 51 years (25^{th}–75^{th} percentile: 45–57 years); 34 (67%) were female, and 17 (33%) were male. The mean BMI of the control and patient groups was 28.3±3.8 kg/m^2 and 31.2±5.3 kg/m^2, respectively. The median fasting glucose and HbA1c value in the control group was 96.5 mg/dL (25^{th}–75^{th} percentile: 87.2–103.5 mg/dL) and 5.4% (25^{th}–75^{th} percentile: 5.3–5.6%), while the results in the patient group were 149 mg/dL (25^{th}–75^{th} percentile: 117.5–203.5 mg/dL) and 8.4% (25^{th}–75^{th} percentile: 6.8–10%), respectively. There was no statistically significant difference between groups in the demographic characteristics or biochemical parameters, other than fasting glucose and HbA1c. The level of serum Gas6, AXL, and sAXL was significantly lower in the patients than in the controls (p<0.05) (Table 1).

There was a strong positive correlation between Gas6 and AXL and between AXL and sAXL in both groups. There was a weak negative correlation between eGFR and Gas6 as well as sAXL in the patient group. These correlations were not present in the control group (Table 2). Although it was not statistically significant, the hemoglobin level in the patient group was lower than that of the control group (Table 1).

When all of individuals were evaluated as a single group, 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, the participants were divided into 2 groups according to eGFR (eGFR<90 mL/min, n=15 and eGFR>90 mL/min, n=53). No statistically significant difference in Gas6, AXL, or sAXL level was observed between the groups.

When the patient group was subdivided according to eGFR (eGFR<90 mL/min, n=14 and eGFR>90 mL/min, n=37), although it was not statistically significant, the Gas6 level was lower in the group with an eGFR<90 mL/min. The median Gas6 was 11.8 ng/mL (25^{th}–75^{th} percentile: 9.8–14.2 ng/mL) in the eGFR>90 mL/min group and 11.18 ng/mL (25^{th}–75^{th} percentile: 9.0–13.7 ng/mL) in the eGFR<90 mL/min group.

When the patient group was divided into 2 groups according to hemoglobin level (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 it was not statistically significant (r=-0.573, p<0.066).

DISCUSSION

Although Gas6/AXL signaling has predominantly been investigated in cancer research, recent focus on this pathway has indicated a vital role in metabolic diseases associated with insulin resistance and glucose intolerance. Gas6 is a member of the K vita-

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

	Control group (n=17)	Patient group (n=51)	p
Age (years)	44.5 (41–53)	51 (45–57)	0.163
Gender (F/M)*	9/8	34/17	0.313
BMI	28.3±3.8	31.2±5.3	0.063
Fasting glucose (mg/dL)	96.5 (87.2–103.5)	149 (117.5–203.5)	**<0.001**
HbA1c (%)	5.4 (5.3–5.6)	8.4 (6.8–10)	**<0.001**
Hemoglobin (g/dL)	14.4±1.3	13.8±1.6	0.058
Creatinine (mg/dL)	0.77 (0.68–081)	0.71 (0.60–0.89)	0.391
eGFR (mL/min)	103±9.1	97±17.7	0.147
Gas6 (ng/mL)	12.4 (10.6–21.5)	10.8 (8.9–13)	**0.011**
AXL (ng/mL)	335.2 (270.1– 409.5)	217.6 (179.5–287.7)	**0.003**
sAXL (pg/mL)	4.3 (3.3–9.4)	3.1 (1.8–4)	**0.009**

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; F: Female; Gas6: Growth arrest-specific protein 6; HbA1c: Glycosylated hemoglobin; M: Male; sAXL: Soluble AXL

Table 2. Correlations in control and patient groups

	Fasting glucose	HbA1c	Creatinine	eGFR	Gas6	AXL	sAXL
Control group							
Gas6	0.242	-0.131	0.064	0.370	1	**0.818***	0.573
AXL	0.469	-0.299	0.109	0.273	**0.818***	1	**0.657***
sAXL	0.560	0.137	-0.049	0.420	0.573	**0.657***	1
Patient group							
Gas6	0.101	-0.088	0.115	**-0.285***	1	**0.329***	0.057
AXL	-0.119	0.039	0.061	-0.113	**0.329***	1	**0.354***
sAXL	-0.046	-0.157	0.087	**-0.311***	0.057	**0.354***	1

*: p<0.05; eGFR: Estimated glomerular filtration rate; Gas6: Growth arrest-specific protein 6; HbA1c: Glycosylated hemoglobin; sAXL: Soluble AXL

min-dependent protein family and is synthesized in the alpha cells of the islets of Langerhans in the pancreas (14). The mitogenic and antiapoptotic effects of Gas6 may prevent T2DM pathogenesis (15). Several studies have reported that Gas6 concentration or gene polymorphism demonstrated 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 correlation with HbA1c, and whether these could be used as alternative noninvasive markers in T2DM monitoring. Consistent with the results of other studies, the Gas6, AXL, and sAXL concentrations were lower in the patients with diabetes. However, Gas6, AXL, and sAXL did not correlate with HbA1c. The concentration of serum Gas6 and sAXL was negatively correlated with eGFR in our patients. A strong negative correlation was observed between sAXL and HbA1c in patients with anemia.

Similarly, Hung et al. (18) investigated the plasma Gas6 concentration among Taiwanese adults with T2DM. They reported that the Gas6 level was significantly lower in the diabetic group compared with a normal glucose (NG) tolerance group.

In another study with a slightly larger population, Lee et al. (19) reported that the Gas6 concentration was lower in the T2DM group than the NG group and that plasma Gas6 was negatively correlated with glucose level in an oral glucose tolerance test (OGGT) group and the HbA1c level.

Bassyouni et al. (20) investigated the plasma level of Gas6/sAXL in patients with chronic hepatitis C virus infection with and without T2DM. They found that Gas6 and sAXL were 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. Macrophage and other immune system elements are present in adipose tissue via Gas6/AXL signaling (18, 21).

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

Diabetic complications (neuropathy, nephropathy, and retinopathy) leading to morbidity and mortality are common in T2DM (22).

This vulnerability means that it is crucial to have diagnostic markers that can be used in the early stages of diabetes complications and the development of drugs targeting these markers. It has been reported that Gas6/AXL might play a role in cardiovascular and renal complications of diabetes (23).

Lee et al. (24) investigated the Gas6 level in patients with chronic kidney disease and found that dysregulation of circulating Gas6 was associated with renal disease and inversely proportional to renal function. The level of Gas6 was also reported to be inversely associated with eGFR.

In another study of diabetic nephropathy, Li et al. (25) investigated the association between cystatin C and Gas6 in T2DM patients with different degrees of diabetic nephropathy. A low Gas6 level was observed in diabetic nephropathy. Gas6 may be a better noninvasive biomarker than cystatin C and creatinine in the early diagnosis of diabetic nephropathy.

Toprak et al. (26) investigated whether plasma Gas6 concentration was associated with albuminuria in T2DM. They found that the plasma Gas6 level was higher in patients with albuminuria than normoalbuminuria.

Unexpectedly, we found that the serum Gas6 and sAXL levels were negatively correlated with eGFR in T2DM patients. When we divided the patient group into 2 groups according to eGFR, although it was not statistically significant, the Gas6 was lower in the group with an eGFR<90 mL/min.

Although we excluded patients with diabetic nephropathy, this finding suggested that Gas6 and sAXL may have a predictive value for diabetic nephropathy. Further studies on patients with various stages of diabetic nephropathy may reveal a variation in Gas6/sAXL between stages. In addition, a cohort study with T2DM patients may demonstrate 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 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 the sAXL level can be used instead of HbA1c in the follow-up of diabetic patients with anemia.

The mechanism of Gas6/AXL inhibition in diabetes is not clear. However, we can say that the following may play a role: Firstly, the destruction of pancreatic beta cells is an important etiological factor in the development and progression of T2DM. Gas6 has been reported to affect the proliferation and functional activity of pancreatic beta cells. Therefore, it may help prevent the pathogenesis of T2DM (14, 15). Conversely, our results indicated that a low Gas6 level may contribute to diabetes.

Cell death by apoptosis occurs as part of many biological processes in response to tissue development, homeostasis, and pathological conditions. A Gas6-TAM interaction is significant in inflammation and tissue homeostasis (28). Phosphatidylserine, normally located in the inner leaflet of the bilayer of the plasma membrane, is externalized to the membrane during apoptosis. Phosphatidylserine is a marker of apoptotic cell clearance, while TAM receptors contribute to the uptake of apoptotic cells by phagocytes (29). Gas6-mediated TAM activation has physiological relevance in clearing apoptotic cells. Consequently, 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 matrix GLA protein and Gas6. Carboxylation of the GLA domain is responsible for stabilizing the protective effect of Gas6 activity. Also, as a ligand for AXL, Gas6 is significant to critical biological processes, such as glucose metabolism (21).

Several studies have indicated that vitamin K supplementation may be beneficial to glucose metabolism and reduced development of T2DM risk. A 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 yet clear with respect to glucose metabolism, various signal molecules are activated by the binding of Gas6 to AXL. One of these signal molecules is phosphoinositide-3 kinase (PI3K) and the Akt pathway. The induction of Akt by PI3K causes transcription of several genes involved in insulin secretion (15). Therefore, our findings of 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 small number of healthy individuals enrolled may have affected some of our results in terms of significance, (3) we could not evaluate the PI3K/Akt pathway, apoptosis-related signaling molecules, or vitamin K, and (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 further. The development of therapies targeting this pathway could provide a new therapeutic approach for T2DM. Gas6 and sAXL appear to have potential predictive value for diabetic nephropathy. Additional research could be very beneficial.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 18.07.2018, number: 2018/369).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – GB, FB; Design – GB, FB; Supervision – GB, FB; Materials – FB, AHA; Data Collection and/or Processing – GB, MÖ, AHA, YA; Analysis and/or Interpretation – GB, FB, MÖ, HS,NS; Literature Search – GB, MÖ, HS, NS; Writing – GB, FB, MÖ, HS; Critical Reviews – GB, FB.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Vinik A, Flammer M. Diabetes and macrovascular disease. J Diabetes Complications 2002; 16: 235–45. [CrossRef]
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019; 157: 107843. [CrossRef]
3. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights 2016; 11: 95–104. [CrossRef]
4. Vicki F. Glucose and Hemoglobin A1c. Lab Medicine 2014; 45(1): e21–4. [CrossRef]
5. Benett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of Type 2 diabetes: a systematic review. Diabet Med 2007; 24(3): 333–43. [CrossRef]
6. Martín LB, García de Frutos P. Vitamin K-dependent actions of Gas6. Vitam Horm 2008; 78: 185–209. [CrossRef]
7. Laurance S, Lemarié CA, Blostein MD. Growth arrest-specific gene 6 (gas6) and vascular hemostasis. Adv Nutr 2012; 3(2): 196–203. [CrossRef]
8. van der Meer JH, van der Poll T, van 't Veer C. TAM receptors, Gas6, and protein S: roles in inflammation and hemostasis. Blood 2014; 123(16): 2460–9. [CrossRef]
9. Tjwa M, Bellido-Martin L, Lin Y, Lutgens E, Plaisance S, Bono F, et al. Gas6 promotes inflammation by enhancing interactions between endothelial cells, platelets, and leukocytes. Blood 2008; 111(8): 4096–105. [CrossRef]
10. Ekman C, Stenhoff J, Dahlbäck B. Gas6 is complexed to the soluble tyrosine kinase receptor Axl in human blood. J Thromb Haemost 2010; 8(4): 838–44. [CrossRef]
11. Holstein E, Binder M, Mikulits W. Dynamics of AXL receptor shedding in hepatocellular carcinoma and its implication for theranostics. Int J Mol Sci 2018; 19(12): 4111. [CrossRef]
12. Lee CH, Changchien CY, Hung YJ. Targeting inflammation in type 2 diabetes by antibody-mediated Tyro-3, Axl, Mer receptor activation. J Diabetes Investig 2015; 6(5): 491–4. [CrossRef]
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9): 604–12. [CrossRef]
14. Stenberg LM, Nilsson E, Ljungberg O, Stenflo J, Brown MA. Synthesis of gamma-carboxylated polypeptides by alpha-cells of the pancreatic islets. Biochem Biophys Res Commun. 2001; 283(2): 454–9. [CrossRef]
15. Dihingia A, Kalita J, Manna P. Implication of a novel Gla-containing protein, Gas6 in the pathogenesis of insulin resistance, impaired glucose homeostasis, and inflammation: A review. Diabetes Res Clin Pract 2017; 128: 74–82. [CrossRef]
16. Lee CH, Chu NF, Shieh YS, Hung YJ. The growth arrest-specific 6 (Gas6) gene polymorphism c.834+7G>A is associated with type 2 diabetes. Diabetes Res Clin Pract 2012; 95(2): 201–6. [CrossRef]
17. Fouad NA, Eltaher SM, Abdullah OA, Metwally RA. Serum level of growth arrest-specific 6 (Gas6) protein and genetic variations in the Gas6 gene in patients with Type 2 diabetes mellitus. Egypt J Immunol 2015; 22(1): 41–7.
18. Hung YJ, Lee CH, Chu NF, Shieh YS. Plasma protein growth arrest-specific 6 levels are associated with altered glucose tolerance, inflammation, and endothelial dysfunction. Diabetes Care 2010; 33(8): 1840–4. [CrossRef]
19. Lee CH, Shieh YS, Hsiao FC, Kuo FC, Lin CY, Hsieh CH, et al. High glucose induces human endothelial dysfunction through an Axl-dependent mechanism. Cardiovasc Diabetol 2014; 13: 53. [CrossRef]
20. Bassyouni RH, Gomaa AA, Hassan EA, Ali ESG, Khalil MAF, Mashahit MA, et al. Possible association of elevated plasma levels of growth arrest-specific protein 6 and the soluble form of tyrosine kinase receptor axl with low hepatitis C viral load in patients with Type 2 diabetes mellitus. Viral Immunol 2020; 33(2): 105–11. [CrossRef]
21. Korshunov VA. Axl-dependent signalling: a clinical update. Clin Sci (Lond) 2012; 122(8): 361–8. [CrossRef]
22. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008; 88(11): 1254–64. [CrossRef]
23. Cavet ME, Smolock EM, Ozturk OH, World C, Pang J, Konishi A, et al. Gas6-axl receptor signaling is regulated by glucose in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2008; 28(5): 886–91. [CrossRef]
24. Lee IJ, Hilliard B, Swami A, Madara JC, Rao S, Patel T, et al. Growth arrest-specific gene 6 (Gas6) levels are elevated in patients with chronic renal failure. Nephrol Dial Transplant 2012; 27(11): 4166–72. [CrossRef]
25. Li W, Wang J, Ge L, Shan J, Zhang C, Liu J. Growth arrest-specific protein 6 (Gas6) as a noninvasive biomarker for early detection of diabetic nephropathy. Clin Exp Hypertens 2017; 39(4): 382–7. [CrossRef]
26. Erek-Toprak A, Bingol-Ozakpinar O, Karaca Z, Cikrikcioglu MA, Hursitoglu M, Uras AR, et al. Association of plasma growth arrest-specific protein 6 (Gas6) concentrations with albuminuria in patients with type 2 diabetes. Ren Fail 2014; 36(5): 737–42. [CrossRef]
27. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2011; 57(6): e1–e47. [CrossRef]
28. Wium M, Paccez JD, Zerbini LF. The dual role of TAM receptors in autoimmune diseases and cancer: an overview. Cells 2018; 7(10): 166.
29. Lemke G. Phosphatidylserine is the signal for TAM receptors and their ligands. Trends Biochem Sci 2017; 42(9): 738–48. [CrossRef]
30. Manna P, Kalita J. Beneficial role of vitamin K supplementation on insulin sensitivity, glucose metabolism, and the reduced risk of type 2 diabetes: A review. Nutrition 2016; 32(7-8): 732–9. [CrossRef]