Objective: Gremlin 1 is a novel adipokine that plays an important role in obesity and type 2 diabetes mellitus (T2DM). In the current study, we aimed to evaluate plasma levels of Gremlin 1 in diabetic and non-diabetic Saudi adult females and its correlation with body composition, glycemic control and lipid profile.

Methods: A case–control study was conducted among 41 T2DM and 31 non-diabetic adult age matched females (controls). All patients underwent body composition by bioelectrical impedance analysis, with a commercially available body analyzer. Fasting venous samples were analyzed for glycemic markers and lipids, while plasma Gremlin 1 was measured by ELISA. The results were compared between the two groups and correlated with other anthropometric and adiposity parameters.

Results: Gremlin 1 levels were elevated in T2DM patients (345 ± 26 ng/mL) when compared to control subjects (272 ± 16 ng/mL, p < 0.05). Diabetic patients having poor glycemic control had significantly higher Gremlin 1 levels (382 ± 34 ng/mL) compared to patients with good glycemic control (291 ± 37 ng/mL, p < 0.05). Pearson correlation analysis revealed a positive correlation of Gremlin 1 with fat mass (r = 0.246, p = 0.012), HbA1C (r = 0.262, p = 0.008) and HOMA-IR index (r = 0.321, p = 0.001).

Conclusion: Our study demonstrates an important role of Gremlin 1 in glycemic control and body adiposity in the pathophysiology of obesity and T2DM. Gremlin 1 may emerge as a promising biomarker and therapeutic target in obesity and T2DM.

Keywords: Gremlin 1, adiposity, diabetes mellitus, HbA1C, HOMA-IR
Thus, Gremlin 1 is a novel adipokine which is implicated in the pathogenesis of many diseases and holds the potential of novel therapeutic agent that can be used to treat obesity and T2DM, insulin resistance and related complications. The cause and effect relationship of Gremlin 1 with insulin sensitivity/resistance is not fully understood. More studies are required to understand the role of Gremlin 1 in the pathophysiology of T2DM. Therefore, in the current study, we aimed to evaluate plasma levels of Gremlin 1 in diabetic and non-diabetic Saudi adult females and its correlation with body composition, glycemic control and lipid profile.

Methods
This study was conducted in the Department of Physiology, College of Medicine, King Saud University. Seventy-two women were participated, of which 41 were diabetic and 31 were non-diabetic females of ages ranging between 30 and 65 years old, and having different BMIs. Type 2 diabetic patients who had been diagnosed with the condition at least 12 months before the study commenced, according to the American Diabetes Association Guidelines. Patients with a pregnant and/or pre-diabetic status who had impaired fasting glucose levels were excluded. Also, patients who had any disease that could affect the metabolic status of the body and/or the parameters under investigation were also excluded. For example, patients with conditions such as nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis and non-ketotic hyperosmolar coma were all excluded.

The detailed history was taken and anthropometric parameters such as BMI, waist-hip-ratio (WHR), pulse and blood pressure were recorded. Body composition was analyzed by bioelectrical impedance analysis (BIA) using a commercially available Body Composition Analyzer (Type BC-418 MA, TANITA Corporation Japan). All body compositions were performed in the early morning, with the subjects all in a state of fasting. They were asked to wear light clothing and to have an empty bladder to ensure uniformity in all subjects.

The subject was asked to first wipe the sole of the feet with a wet tissue and then stand over the electrodes of the machine and the results were recorded within 3-5 minutes. The parameters included were height, body weight, body surface area, BMI, obesity degree, protein mass, muscle mass, fat mass and body fat percentage.

Fasting blood sample (5mL) was taken after a 10–12 hours overnight fast. The plasma was separated, aliquoted, and stored at −80°C. Blood samples were analyzed for fasting blood sugar (FBS), total cholesterol, triglycerides, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels (GH Ab190811, IGF-1 Ab100545 and IGFBP-2 Ab100540) following the manufacturer’s instructions (Abcam, Cambridge, UK).

Plasma Gremlin 1 levels were measured by Human Gremlin 1 ELISA kit (abx151737) kit following the manufacturer’s instructions (Abbexa, Cambridge, United Kingdom). Briefly, the plasma samples (diabetic and non-diabetic control subjects) and standard were reacted with a Gremlin 1 specific antibody coated in the 96 well microplates and incubated at 37°C for 90 minutes on a plate shaker. Next, the samples and standard were removed, and 100 μL detection reagent A was added and incubated for 1 hour as before. Following washing, 100 μL detection reagent B was added and incubated for 30 minutes. The microplate was washed and 90 μL of TMB substrate was added. The reaction was stopped by adding 50 μL of stop solution to each well, and the absorbance was read by a microplate reader (EL 800, BioTek Instruments, USA) at 450 nm.

Data were analyzed using SPSS Pc + 21.0 version statistical software. Descriptive statistics (frequencies, percentages, mean and standard deviation) were used to describe the categorical and quantitative variables. Student’s t-test was used to analyze parametric variables while Mann–Whitney test was used for the non-parametric variables. Spearman correlations were determined to see the relationship of Gremlin1 with HbA1C and fat mass. A linear regression model was computed with plasma Gremlin 1 as a dependent variable, in a univariate analysis and adjusted for age and BMI to see the association of plasma Gremlin 1 with independent predictors. Values of p < 0.05 indicate statistical significance.

Results
Anthropometric and Biochemical Analysis
Demographic and body composition analysis of 72 female participants are shown in Table 1. Anthropometric analysis showed that diabetic patients had a significantly higher fat mass (non-diabetic 31.53 ± 1.48 vs diabetic 35.90 ± 1.49 Kg)
Table 1 Comparison of Demographic and Body Composition Between Non-Diabetic and Diabetic Groups

| Parameter          | Participants | p value |
|--------------------|--------------|---------|
|                    | Non-Diabetic (n=31) | Diabetic (n=41) |
|                    | Mean±SEM     |         |
| Waist (cm)         | 91.83±1.42   | 100.59±1.71 | <0.001  |
| Hip (cm)           | 109.82±1.60  | 117.54±1.81 | 0.002   |
| WHP Ratio          | 0.84±0.01    | 0.85±0.009  | 0.372   |
| BMI (kg/m²)        | 32.16±5.77   | 34.02±5.42  | 0.097   |
| BMR (KJ)           | 5747.41±87.55| 5937.14±94.86 | 0.145   |
| BMR (kcal)         | 1372.95±20.88| 1418.81±22.62 | 0.140   |
| Fat %              | 40.82±0.95   | 43.26±0.77  | 0.049   |
| Fat Mass (Kg)      | 31.53±1.48   | 35.90±1.49  | 0.041   |
| FFM                | 43.16±0.91   | 45.11±1.00  | 0.154   |
| TBW (Kg)           | 31.88±0.57   | 33.94±0.62  | 0.017   |
| VFR                | 10.15±0.47   | 11.69±0.42  | 0.017   |
| Trunk (Fat %)      | 38.18±0.99   | 39.61±0.88  | 0.286   |
| Trunk (Fat mass)   | 16.01±0.66   | 17.31±0.73  | 0.195   |
| Trunk (FFM)        | 24.78±0.35   | 25.71±0.36  | 0.067   |
| Trunk (PMM)        | 23.71±0.33   | 24.57±0.34  | 0.076   |

Note: Values of p < 0.05 indicate statistical significance.

Abbreviations: FFM, Fat Free Mass; PMM, Predicted Muscle Mass; Fat%, Body Fat Percentage; TBW, Total Body Water; BMR, Basal Metabolic rate; BMI, Body Mass Index.

Table 2 Comparison of Biochemical Profiles Clinical Parameters Between Non-Diabetic and Diabetic Groups

| Parameter          | Participants | p value |
|--------------------|--------------|---------|
|                    | Non-Diabetic (n=31) | Diabetic (n=41) |
|                    | Mean±SEM     |         |
| FBS (mmol/L)       | 5.2±0.08     | 9.19±0.58 | <0.001  |
| HbA1C (%)          | 5.26±0.057   | 8.35±0.30 | <0.001  |
| Cholesterol (mmol/L)| 5.03±0.07   | 4.73±0.14 | 0.051   |
| Triglyceride (mmol/L)| 1.20±0.10  | 1.45±0.10 | 0.096   |
| LDL (mmol/L)       | 3.04±0.09    | 2.73±0.14 | 0.058   |
| HDL (mmol/L)       | 1.37±0.06    | 1.26±0.09 | 0.337   |
| Insulin (mIU/L)    | 12.82±0.69   | 18.40±1.97| 0.003   |
| HOMA-IR            | 2.77±0.16    | 7.48±1.05 | <0.001  |

Note: Values of p < 0.05 indicate statistical significance.

Abbreviations: FBS, Fasting Blood Sugar; HbA1C, Hemoglobin A1C; HDL, High-density Lipoprotein; LDL, Low-density Lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

and visceral fat ratio (control 10.15 ± 0.47 vs diabetic 11.69 ± 0.42, p < 0.05). Table 2 shows the biochemical profiles clinical parameters between non-diabetic and diabetic groups. There was a significant increase in FBS (from 5.2 ± 0.08 to 9.19 ± 0.58 mmol/L unit [mean±SEM]), hemoglobin A1C (HbA1C) (from 5.26 ± 0.057 to 8.35 ± 0.30 mmol/L unit), insulin (from 12.82 ± 0.69 to 18.40 ± 1.97, mIU/L) and HOMA-IR index (from 2.77 ± 0.16 to 7.48 ± 1.05), p < 0.001 in diabetic patients compared to non-diabetic control subjects. Total cholesterol was significantly lowered, from 5.03 ± 0.07 to 4.73 ± 0.14 in diabetic patients (p = 0.051), however there were no significant differences in triglycerides and LDL and HDL levels in diabetic and non-diabetic participants (p > 0.05).
Analysis of Plasma Gremlin 1 Levels in Diabetic and Non-Diabetic Subjects

Plasma Gremlin 1 levels were increased in diabetic patients (345 ± 26 ng/mL) as compared to non-diabetic subjects (272 ± 16 ng/mL), [mean±SEM] (p < 0.05) Figure 1. Segregation of diabetic patients into having good and poor glycemic control, according to American Diabetes Association criteria (7.5% and above), revealed that patients with poor glycemic control exhibited significantly higher Gremlin 1 levels (382 ± 34 ng/mL) as compared to patients with good glycemic control (291 ± 37 ng/mL, p < 0.05), Figure 1. Pearson correlation analysis revealed a positive correlation of Gremlin 1 with fat mass ($r = 0.246, p = 0.012$, Figure 2), HbA1C ($r = 0.262, p = 0.008$, Figure 3). Anthropometric and biochemical parameters of patients with good and poor glycemic control are described in Tables 3 and 4.

![Figure 1](https://doi.org/10.2147/DMSO.S372146)

Figure 1 Analysis of Gremlin 1 levels in diabetic and non-diabetic females. Gremlin 1 levels in diabetic and non-diabetic females were analysed by ELISA. The error bars represent standard error of the mean. *Indicates statistical significant differences between non-diabetic (n=31) vs diabetic females (n=41) and between patients with good glycemic control (n=17) and poor glycemic control (n=24). Values of p < 0.05 indicate statistical significance.

**Abbreviations:** DM2, Type 2 diabetes mellitus; GGC, Good glycemic control; PGC, Poor glycemic control.

![Figure 2](https://doi.org/10.2147/DMSO.S372146)

Figure 2 Pearson’s correlation of Gremlin 1 with fat mass in all subjects.
A linear regression model was computed with plasma Gremlin 1 as a dependent variable, in a univariate analysis and adjusted for age and BMI to see the association of plasma Gremlin 1 with independent predictors. Significant predictors were HbA1C and HOMA-IR (Table 5).

![Figure 3](image-url)

**Figure 3** Pearson’s correlation of Gremlin 1 with HbA1C in all subjects.

**Abbreviation:** HbA1C, hemoglobin A1C.

| Parameter        | Participants | p value |
|------------------|--------------|---------|
|                  | GGC (n=17)   | PGC (n=24) |
|                  | Mean±SEM     |          |
| Waist            | 98.94±12.25  | 101.72±10.37 | 0.433 |
| Hip              | 117.76±13.13 | 117.40±11.01 | 0.923 |
| WHR Ratio        | 0.84±0.05    | 0.86±0.05   | 0.160 |
| BMI              | 34.07±5.25   | 33.99±5.63  | 0.965 |
| BMR (Kj)         | 5852.88±552.93 | 5994.44±658.34 | 0.456 |
| BMR (kcal)       | 1398.88±132.17 | 1432.36±156.91 | 0.460 |
| Fat %            | 43.48±5.08   | 43.12±5.08  | 0.824 |
| Fat Mass (Kg)    | 35.59±9.33   | 36.11±10.05 | 0.865 |
| FFM              | 45.22±3.89   | 45.04±7.88  | 0.921 |
| TBW (Kg)         | 33.07±2.78   | 34.53±4.69  | 0.215 |
| VFR              | 11.88±2.73   | 11.56±2.83  | 0.160 |
| Trunk (Fat %)    | 39.64±6.04   | 39.58±5.62  | 0.974 |
| Trunk (Fat mass) | 17.17±4.78   | 17.41±4.89  | 0.878 |
| Trunk (FFM)      | 25.49±2.20   | 25.86±2.46  | 0.610 |
| Trunk (PMM)      | 24.34±2.06   | 24.73±2.33  | 0.572 |

**Note:** Values of p < 0.05 indicate statistical significance.

**Abbreviations:** GGC, Good Glycemic Control; PGC, Poor Glycemic Control.
The present study demonstrates plasma Gremlin 1 levels in Saudi adult females with T2DM and its associations with clinical and anthropometric parameters. Gremlin 1 is a highly conserved soluble extracellular secreted glycoprotein and is involved in limb morphogenesis, organogenesis and bone development. Gremlin 1 is also implicated in pathological conditions such as cancer, renal fibrosis, diabetes and obesity.

In our study, the levels of plasma Gremlin 1 were higher in T2DM patients compared to the non-diabetic control subjects. Our findings are in consistent with a previous study that reported elevated serum levels of Gremlin 1 in obese male and female subjects with T2DM.

Our study population consisted of only females and we are not sure of any gender-based effect of Gremlin 1 secretion in pathological conditions. However, an earlier study reported higher Gremlin 1 levels in males compared to females in patients with pulmonary arterial hypertension.

Thus, further studies are required to understand the gender-based effect of Gremlin 1 in different disease conditions. It should be noted that we used commercially available ELISA kit to analyse Gremlin 1 levels while Hedjazifar et al used in-house modified ELISA with noncommercially available antibody in their study.

An additional finding of note in our study was the elevated plasma levels of Gremlin 1 in patients with poor glycemic control compared to patients who had good glycemic control. However, there was no significant difference between T2DM patients with good glycemic control and healthy subjects. Gremlin 1 secreted by adipose tissue has an antagonistic effect to insulin signaling and contributes to insulin resistance. Therefore, it is possible that Gremlin 1 levels are elevated with dysglycemia in our study cohort having poor glycemic control. This also suggests that achieving good glycemic control in diabetes would lead to a positive

### Table 4 Clinical Parameters of Participants with Good and Poor Glycemic Control

| Parameter          | Participants | p value |
|--------------------|--------------|---------|
|                    | GGC (n=17)   | PGC (n=24) |       |
| Mean±SEM           |              |         |       |
| FBS (mmol/L)       | 6.80±1.06    | 10.80±4.19 | <0.001 |
| HbA1C (%)          | 6.68±0.55    | 9.56±1.64   | <0.001 |
| Cholesterol (mmol/L) | 4.57±0.87   | 4.83±0.95   | 0.372  |
| Triglyceride (mmol/L) | 1.35±0.65   | 1.54±0.49   | 0.286  |
| LDL (mmol/L)       | 2.57±0.90    | 2.83±0.80   | 0.328  |
| HDL (mmol/L)       | 1.38±0.61    | 1.27±0.33   | 0.434  |
| Insulin (mIU/L)    | 14±6.50      | 21.40±15.07 | 0.036  |
| HOMA-IR            | 4.36±2.33    | 7.41±3.01   | 0.001  |

Note: Values of p < 0.05 indicate statistical significance.

Abbreviations: GGC, Good Glycemic Control; PGC, Poor Glycemic Control.

### Table 5 Linear Regression Model of Plasma Gremlin 1 with Age and BMI as a Dependent Variable

| Unstandardized Coefficients Beta | Standardized Coefficients Beta | t | Sig. | 95% Confidence Limits |
|----------------------------------|--------------------------------|---|------|----------------------|
|                                  |                                |   |      |                      |
| HbA1C                            | 19.624                         | 0.255 | 2.616 | 0.010 | 4.741 | 34.507 |
| HOMA-IR                          | 13.955                         | 0.256 | 2.626 | 0.010 | 3.411 | 24.499 |
| Total cholesterol                | 7.469                          | 0.037 | 0.376 | 0.708 | −31.991 | 46.928 |
| Triglycerides                    | 18.943                         | 0.082 | 0.824 | 0.412 | −26.689 | 64.576 |
| LDL                              | 4.848                          | 0.023 | 0.236 | 0.814 | −35.901 | 45.596 |
| HDL                              | −38.876                        | −0.101 | −1.010 | 0.315 | −115.266 | 37.513 |

Discussion

The present study demonstrates plasma Gremlin 1 levels in Saudi adult females with T2DM and its associations with clinical and anthropometric parameters. Gremlin 1 is a highly conserved soluble extracellular secreted glycoprotein and is involved in limb morphogenesis, organogenesis and bone development. Gremlin 1 is also implicated in pathological conditions such as cancer, renal fibrosis, diabetes and obesity.

In our study, the levels of plasma Gremlin 1 were higher in T2DM patients compared to the non-diabetic control subjects. Our findings are in consistent with a previous study by that reported elevated serum levels of Gremlin 1 in obese male and female subjects with T2DM. Our study population consisted of only females and we are not sure of any gender-based effect of Gremlin 1 secretion in pathological conditions. However, an earlier study reported higher Gremlin 1 levels in males compared to females in patients with pulmonary arterial hypertension. Thus, further studies are required to understand the gender-based effect of Gremlin 1 in different disease conditions. It should be noted that we used commercially available ELISA kit to analyse Gremlin 1 levels while Hedjazifar et al used in-house modified ELISA with noncommercially available antibody in their study.

An additional finding of note in our study was the elevated plasma levels of Gremlin 1 in patients with poor glycemic control compared to patients who had good glycemic control. However, there was no significant difference between T2DM patients with good glycemic control and healthy subjects. Gremlin 1 secreted by adipose tissue has an antagonistic effect to insulin signaling and contributes to insulin resistance. Therefore, it is possible that Gremlin 1 levels are elevated with dysglycemia in our study cohort having poor glycemic control. This also suggests that achieving good glycemic control in diabetes would lead to a positive
adipokine profile. Adiponectin is a cardioprotective adipokine which is significantly lower in obesity and T2DM and so having good glycemic control in T2DM is associated with a better adiponectin profile.16,17

We also aimed to find correlations between plasma Gremlin 1 and various anthropometric and clinical parameters. Cumulative analysis of Gremlin 1 from diabetic and control subjects showed positive correlations with fat mass, HbA1C and HOMA-IR index. This was an important observation since adiposity and hyperglycemia both lead to increased insulin resistance. Our study shows that an additive effect of Gremlin 1 on glycemic control and insulin resistance exists in both control and diabetic subjects. Similar findings of a positive correlation between Gremlin 1 and other body indices such as HOMA-IR, body fat and HbA1C have been reported in previous studies.9,18,19 Gremlin 1 is an antagonist of insulin signaling in skeletal muscle, adipocytes and liver cells, thus making it an important therapeutic target in insulin resistance and T2DM as well as other related complications. Diabetic patients with acute coronary syndrome showed increased levels of Gremlin 1 and Macrophage migration inhibitory factor.20 An earlier study reported increased urinary excretion of Gremlin 1 in type 1 and T2DM patients with diabetic kidney disease.21 In an animal model, knockout mice lacking Gremlin 1 gene were protected against the experimentally induced model of type 1 diabetes, whereas over-expression of Gremlin 1 in renal tubules in transgenic mice resulted in glomerular and interstitial injury.22,23 These studies suggest the potential of Gremlin 1 as a promising biomarker to predict the illnesses.

The additive list of adipokines is increasing day by day with diversity in their functions and effects ranging from protective to pathogenic roles for instance proinflammatory to dysmetabolic activity.24,25 In this regard some of the friendly adipokines are adiponectin and leptin, while others like visfatin and resistin have inverse effects.26 The novel adipokine Gremlin 1 can be added to this list as well.

To the best of our knowledge, there is scarce clinical data on the role of Gremlin 1 in adipogenesis and insulin resistance syndromes. We report that fat mass and glycaemia correlates positively with Gremlin 1 levels both in T2DM and healthy subjects. Although this is a cross-sectional study with a small sample size, it unravels the need for further work in this area.

**Conclusions**

Diabetic patients with poor glycemic control exhibited higher plasma levels of Gremlin 1 than patients with good glycemic control and Gremlin 1 was positively correlated with fat mass and glycemic parameters. Our data highlight the potential of Gremlin 1 as a biomarker and therapeutic target in obesity and T2DM.

**Ethical Approval**

The study protocol followed the Helsinki Declaration and was approved by the Institutional Review Board, College of Medicine, King Saud University (Ref. No. 20/0977/IRB). Informed consent was obtained from the study participants prior to study commencement.

**Acknowledgments**

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number IFKSURG-2-015. The funding body played no role in the design of the study and data collection, analysis, interpretation or writing of the manuscript.

**Disclosure**

Khalid A Al-Regaiey, Syed Shahid Habib and Muhammad Iqbal are senior authors. The authors declare no potential conflicts of interest.

**References**

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* 2019;15:288–298. doi:10.1038/s41574-019-0176-8
2. Bragg F, Holmes MV, Iona A, et al. Association between diabetes and cause-specific mortality in rural and urban areas of China. *JAMA.* 2017;317 (3):280–289. doi:10.1001/jama.2016.19720
3. Owolabi LF, Adama B, Imam AI, et al. Systematic review and meta-analysis estimating the prevalence, burden, and trend of diabetes mellitus in Saudi Arabia. *J Diabetes Endocr Pract.* 2020;3:1–8.
4. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes.* 2012;19(2):81–87. doi:10.1097/MED.0b013e328351e13

5. Gustafson B, Hammarstedt A, Hedjazifar S, et al. BMP4 and BMP antagonists regulate human white and beige adipogenesis. *Diabetes.* 2015;64:1670–1681. doi:10.2337/db14-1127

6. Modica S, Straub LG, Balaz M, et al. Bmp4 promotes a brown to white-like adipocyte shift. *Cell Rep.* 2016;16:2243–2258. doi:10.1016/j.celrep.2016.07.048

7. Yanagita M. BMP antagonists: their roles in development and involvement in pathophysiology. *Cytokine Growth Factor Rev.* 2005;16(3):309–317. doi:10.1016/j.cytogfr.2005.02.007

8. Denton NF, Eghbali M, Al-Sharifi S, et al. Bone morphogenetic protein 2 is a depot-specific regulator of human adipogenesis. *Int J Obes.* 2019;43(12):2458–2468. doi:10.1038/s41366-019-0421-1

9. Hedjazifar S, Shahidi RK, Hammarstedt A, et al. The novel adipokine gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH. *Diabetes.* 2020;69(3):331–341. doi:10.2337/db19-0701

10. American Diabetes Association. 2. classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care.* 2019;42(Suppl1):S13–S28. doi:10.2337/db19-S002

11. Michos O, Panman L, Vintersten K, et al. Gremlin-mediated BMP antagonism induces the epithelial-mesenchymal feedback signaling controlling metanephric kidney and limb organogenesis. *Development.* 2004;131(14):3401–3410. doi:10.1242/dev01251

12. Merino R, Rodriguez-Leon J, Macias D, et al. The BMP antagonist Gremlin regulates outgrowth, chondrogenesis and programmed cell death in the developing limb. *Development.* 1999;126(23):5515–5522. doi:10.1242/dev.126.23.5515

13. Canalis E, Parker K, Zanotti S. Gremlin1 is required for skeletal development and postnatal skeletal homeostasis. *J Cell Physiol.* 2012;227(1):269–277. doi:10.1002/jcp.22730

14. Mezzano S, Droguett A, Lavoz C, Krall P, Egido J, Ruiz-Ortega M. Gremlin and renal diseases: ready to jump the fence to clinical utility? *Nephrol Dial Transplant.* 2018;33(5):735–741. doi:10.1093/ndt/gfx194

15. Al-Najeem HT, Al-Dujaili ANG. Assessment of Gremlin-1 level in pulmonary arterial hypertension disease. *Research J Pharm Tech.* 2017;10(11):3803–3806.

16. Habib SS, Al Regaiey AK, Al Dokhi L. Assessment of adipokines relationships with cardiovascular risk markers in relation to body indices in normoglycemic males. *Pak J Med Sci.* 2013;29(1):21–26. doi:10.12669/pjms.291.29113

17. Herder C, Kannenberg JM, Niersmann C, et al. Independent and opposite associations of serum levels of omentin-1 and adiponectin with increases of glycaemia and incident type 2 diabetes in an older population: KORA F4/FF4 study. *Eur J Endocrinol.* 2017;177(4):277–286. doi:10.1530/EJE-17-0100

18. Habib SS, Eshki A, AlTassan B, Fatani D, Helmi H, AlSaif S. Relationship of serum novel adipokine chemerin levels with body composition, insulin resistance, dyslipidemia and diabesity in Saudi women. *Eur Rev Med Pharmacol Sci.* 2017;21(6):1296–1302. PMID: 28387898.

19. Habib SS, Sultan M, Khan A, Al-Khlaiwi T, Bashir S. Circulating adiponectin and resistin levels are associated with adiposity indices and physical fitness in healthy adult males. *Med Sci Monit Basic Res.* 2021;27:e930322. PMID:34158467.

20. Müller KA, Rath D, Schmid M, et al. High plasma levels of Gremlin-1 and macrophage migration inhibitory factor, but not their ratio, indicate an increased risk for acute coronary syndrome in patients with type 2 diabetes mellitus. *Clin Cardiol.* 2016;39(4):201–206. doi:10.1002/clc.22509

21. Afkarian M, Hirsch IB, Tuttle KR, Greenbaum C, Himmelfarb J, de Boer IH. Urinary excretion of RAS, BMP, and WNT pathway components in diabetic kidney disease. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2012;5(5):471–479. doi:10.2147/dmso.s18102

22. Roxburgh SA, Kattla JJ, Curran SP, et al. Allelic depletion of grem1 attenuates diabetic kidney disease. *Diabetes.* 2012;61(9):3246–3253. doi:10.2337/db11-0418

23. Fasshauer M, Blüher M. Adipokines in health and disease. *Nat Rev Endocrinol.* 2012;8(10):531–542. doi:10.1038/nrendo.2012.141

24. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Cytokine Growth Factor Rev.* 2016;27:e930322. PMID:34158467.

25. Marchant V, Droguett A, Valderrama G, et al. Tubular overexpression of Gremlin in transgenic mice aggravates renal damage in diabetic nephropathy. *Am J Physiol Renal Physiol.* 2015;309(6):F559–F568. doi:10.1152/ajprenal.00223.2015

26. Ouchi N, Parker JL, Lagus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol.* 2011;11(2):85–97. doi:10.1038/nri2921

27. Fasshauer M, Blüher M. Adipokines in health and disease. *Trends Pharmacol Sci.* 2015;36(7):461–470. doi:10.1016/j.tips.2015.04.014

28. Habib SS, Bashir S, Habib SH. Serum visfatin relationship with glycemic control and adiposity indices in patients with type 2 diabetes mellitus. *Khyber Med Univ J.* 2020;12(4):263–267. doi:10.35845/kmuj.2020.20254