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The Course of Progranulin Levels at Admission and During Early Period of Insulin Treatment in Children with Newly Diagnosed Type 1 Diabetes Mellitus

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What is already known on this topic?

Progranulin (PGRN) is a growth factor involved in inflammation, insulin resistance, and glucose metabolism. Increased serum PGRN levels have been reported in adults with both type 2 and type 1 diabetes. However, the relationship between PGRN levels and metabolic status in children with type 1 diabetes is not clearly understood. There are very few studies in the pediatric age group evaluating the dynamic changes in PGRN levels during the early treatment period of type 1 diabetes.

What this study adds?

Our findings indicate that serum PGRN levels are markedly elevated in children with newly diagnosed type 1 diabetes during diabetic ketoacidosis and remain higher than in healthy controls even after early glycemic stabilization, suggesting a potential role for PGRN in the metabolic response to acute disease presentation.

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ABSTRACT

Objective: Progranulin (PGRN), a growth factor, modulates cell proliferation, wound repair, and inflammation. It is also involved in glucose metabolism and is associated with insulin resistance and diabetes mellitus (DM). In the present study, PGRN levels were measured at admission and during follow-up in children with newly diagnosed type 1 DM (T1DM) and compared to healthy controls.

Methods: Children with T1DM and healthy controls were included. The age, weight, height, body mass index (BMI), severity of acidosis, glucose, insulin, C-peptide, and diabetes-specific autoantibodies of children with newly diagnosed T1DM were collected. PGRN was measured in children with T1DM at admission, at first week of follow-up, and in healthy controls.

Results: A total of 49 children were included; 25 with T1DM [12 Female/13 Male (12F/13M)] and 24 healthy controls (10F/14M). There was no differences in age (11±3.9 years vs 12.1±3.1 years, p=0.269) and BMI standard deviation (SD) score (-0.11±1.49 SD vs. 0.10±0.82 SD, p=0.540) of children with T1DM and healthy controls. The mean basal PGRN level of children with newly diagnosed T1DM was higher than in controls (90.8±17.3 ng/mL vs. 30±11.5 ng/mL, p<0.001). In children with T1DM, mean basal PGRN at admission had declined significantly (58.4±16.9 ng/mL; p<0.001) in the first week after glycemic regulation was achieved but remained significantly higher than in controls (p<0.001).

Conclusion: These findings suggest that elevated PGRN levels in children with newly diagnosed T1DM may reflect either an acute inflammatory response to diabetic ketoacidosis or a persistent alteration in metabolic regulation, or both of these, highlighting the potential role of PGRN as a biomarker in the early course of T1DM.

Keywords: Diabetic ketoacidosis, pediatric, progranulin, PGRN, type 1 diabetes mellitus

Introduction

Progranulin (PGRN), also called granulin-epithelin precursor, acrogranin, proepithelin, GP88, and prostate cell-derived growth factor, is a growth factor that is comprised of 593 amino acids with a molecular weight of 75-80 kDa (1,2,3). It modulates cell proliferation, tissue regeneration, and wound repair, thus being involved in mechanisms of tumorigenesis, inflammation, and fibrosis (4,5,6). PGRN acts as an endogenous antagonist for TNF-α by competitively binding to its receptor (7). It is an adipokine involved in glucose metabolism and associated with insulin resistance, diabetes mellitus (DM), and metabolic complications (8,9). PGRN is encoded by the *GRN* gene, mapped on the chromosomal region 17q21.32, and has 12 exons (10).

Although PGRN exhibits anti-inflammatory activity, some granulin peptides derived from the proteolytic cleavage of PGRN stimulate inflammation (11,12). Besides, increased PGRN expression in adipocytes disrupts insulin signalling and induces inflammation (11). Elevation in circulating PGRN levels has been shown in patients with type 2 DM (T2DM) and reported mainly associated with impaired glucose tolerance rather than impaired fasting glucose (11).

Studies conducted in adults have shown that PGRN levels are increased in individuals with type 1 DM (T1DM) (13). In a study conducted in children, PGRN levels were shown not to differ between children with newly diagnosed T1DM, those with good and poor metabolic control, and healthy controls (14).

In the present study, the aim was to evaluate PGRN levels measured at admission and during follow-up in children with newly diagnosed T1DM who presented with diabetic ketoacidosis (DKA) and compare these with healthy controls.

Methods

Subjects

This cross-sectional case-control study was conducted on patients admitted to Pediatric Endocrinology Outpatient Clinics, Inpatient Clinics, and Pediatric Emergency Services of University of Health Sciences Türkiye, Erzurum City Hospital between September 2023 and September 2024.

Anthropometric measurements [weight, height, and body mass index (BMI)] were recorded. Age- and sex-specific reference ranges and standard deviation scores (SDS) were calculated (15). Patients with concomitant endocrinological problems, such as hypothyroidism, Cushing syndrome, or familial hyperlipidemia, those diagnosed with hypertension or chronic liver disease, celiac disease and those taking medication, such as corticosteroids, were excluded. The control group consisted of healthy children who were attended pediatric outpatient clinics for routine health evaluations and found to have no significant illness.

Laboratory Measurements

Blood samples collected from the patient and control groups were left in tubes in a vertical position for 30 min for coagulation. They were then centrifuged at +4 °C for 7 min at 4500 rpm. The serum specimens obtained were aliquoted and placed into a deep freeze at -80 °C until the day of analysis.

Biochemical measurements were performed using the Beckman Coulter AU 5800 (Beckman Coulter, CA, USA) analyzer. Insulin levels were measured with the Beckman Coulter DXI 800 (Beckman Coulter, CA, USA) device. The glycated haemoglobin (HbA1c) levels were measured by a high-performance liquid chromatography method (Lifotronic H9, Lifotrophic Technology,

Shenzhen, China). The ABL 800 Flex (Radiometer, Copenhagen, Denmark) device, which is available as a blood gas analyzer in our laboratory, provides quantitative measurement of parameters, such as pH, pCO_2, pO_2, Na^+, K^+, Cl^-, iCa^{++}, glucose, L-lactate, total hemoglobin, hematocrit, and hemoglobin saturation. Children with T1DM were classified as "mild", "moderate", "severe" and "without acidosis" according to the pH and HCO_3 levels in blood gas at admission (16). The specific crieria are shown below:

- Mild acidosis: venous pH <7.3 or serum bicarbonate <18 mmol/L,

- Moderate acidosis: pH <7.2 or serum bicarbonate <10 mmol/L,

- Severe acidosis: pH <7.1 or serum bicarbonate <5 mmol/L.

Blood samples for biochemical examinations of PGRN measurement were collected after 6-8 hours of overnight fasting where applicable. Serum, obtained from whole blood samples collected, was analyzed by sandwich enzyme-linked immunosorbent assay (ELISA) using the Human PGRN ELISA Kit (BT LAB, Cat. No. E1755Hu, China) according to the manufacturer's instructions. The kit measurement range for PGRN was 10-700 ng/mL, and the sensitivity of this assay was 5.12 ng/mL. Intra- and interassay coefficients of variation for PGRN were <5% and <10%, respectively. Briefly, the samples and standards were added to wells pre-coated with human PGRN antibodies. PGRN present in the samples was bound by the antibodies coating the wells. A biotinylated human PGRN antibody was then added to bind to the bound PGRN, followed by streptavidin-horseradish peroxidase (HRP) to bind to the biotinylated PGRN antibody. After incubation, the unbound streptavidin-HRP was washed away. Substrate solution was added and color developed proportionately to the amount of human PGRN in the well. The reaction was terminated by adding an acidic stop solution and absorbance was measured at 450 nm. PGRN concentrations were determined by comparing the optical density in the sample wells with a standard curve constructed with included kit reagents.

The study was approved by the Scientific Research Ethics Committee of Health Sciences University Erzurum Faculty of Medicine (approval no.: 05/105, date: 05/08/2024) and carried out in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the participants or their legal guardians.

Statistical Analysis

Data were analyzed by using SPSS, version 24.0 (IBM Corporation, Armonk, NY, USA). The mean, SD, minimum and maximum values of the numeric variables were calculated. Categorical variables are presented as frequency and percentage (%). Shapiro-Wilk test was used to evaluate the normality assumption. However, variables with kurtosis and skewness values within the range of -2 to +2 were considered to have a normal distribution. Histogram and Q-Q plot graphs were examined. The chi-square test was used to compare categorical variables, and the Student's t-test was used to compare independent variables. One-way analysis of variance was used to compare numerical variables in more than two independent groups. An examination of repeated measurements was performed using the paired t-test. The relationship between normally distributed variables was evaluated with Pearson correlation analysis, and those without normal distribution were evaluated with Spearman's rank test. A p value less than 0.05 was considered statistically significant.

A post-hoc G-power analysis was conducted, using a study comparing children with newly diagnosed, well-controlled, or poorly controlled type 1 diabetes with a healthy control group as reference (14). The effect size was 0.85, the critical t-value was 2.01, the degrees of freedom were 44, and the power was 81% if the study was conducted with a total of 46 children, 23 in each group.

Results

A total of 49 children, 25 with T1DM [12 Female/13 Male (12F/13M)] and 24 healthy controls (10F/14M) were recruited. There was no difference in age (11±3.9 years vs. 12.1±3.1 years, p=0.269) or BMI SDS (-0.11±1.49 SD vs. 0.10±0.82 SD, p=0.540) between children with T1DM and healthy controls. In terms of severity of acidosis at admission, 10 (40%) patients had mild acidosis, nine (36%) patients had moderate acidosis, and four (16%) patients had severe acidosis. Two patients (8%) did not have acidosis at the time of admission. Laboratory characteristics of patients with T1DM are displayed in Table 1. The number of patients with at least one serologically positive diabetes autoantibody was 17 (68%). The mean basal PGRN level of children with newly diagnosed T1DM at admission was higher than in controls (90.8±17.3 ng/mL vs. 30±11.5 ng/mL, p<0.001). There was no significant difference between male and female newly diagnosed diabetics according to age (11.3±3 years vs. 10.7±4.8 years, p=0.737), BMI SDS (-0.18±1.2 SD vs -0.04±1.8 SD, p=0.819), or basal PGRN levels (92.5±15.8 ng/mL vs. 88.8±19.4 ng/mL, p=0.609), respectively.

Furthermore, no significant difference was found in PGRN levels when comparing the patients with mild, moderate, and severe acidosis at admission (p=0.940).

The white blood cell (WBC) counts of children with T1DM were higher than healthy controls at admission, presumably due to dehydration, stress response, and systemic inflammatory activation associated with DKA (12.622 WBCs/µL vs. 8.545 WBCs/µ, p=0.015). A weak positive correlation was observed between PGRN level and WBC count (r=0.292, p=0.042).

Comparison of the PGRN levels measured at admission and after stabilization of blood glucose levels under insulin therapy showed that PGRN levels measured at admission were significantly higher than both their 1st-week measurements and than those of healthy controls (both p<0.001) (Figure 1). Of note, despite a significant decrease in PGRN levels over the first week of treatment, these one-week levels in the children with newly diagnosed T1DM remained signifiacntly higher than in the control group (p<0.001). None of the variables that may have affected the change in PGRN levels over the first week of insulin treatment in children with T1DM was found to be significant (Table 2).

Discussion

In the present study evaluating PGRN levels in patients presenting with newly diagnosed T1DM, a significantly higher PGRN level in children at first admission with DKA compared to healthy controls was found. The level of PGRN declined during an average follow-up period of one week when blood glucose stabilization was achieved using insulin therapy.

Although a decline was observed in the PGRN levels in the first week of admission, it remained significantly higher than in healthy controls. Nevertheless, we did not detect a relationship between clinical characteristics (age and anthropometry) and laboratory parameters (glucose, insulin, c-peptide, HbA1c,

Table 1. Laboratory characteristics of patients with type 1 diabetes mellitus

	Mean±SD	Median (Q1-Q3)	Min.	Max.
VBG pH	7.17±0.11	7.19 (7.14-7.24)	6.93	7.37
VBG HCO3 (mmol/L)	11.08±3.54	10.4 (8.65-12.75)	6.6	21.9
Base deficit (mmol/L)	-18.1±5.64	-19.4 (-22.9– -14.1)	-26.4	-1.9
Glucose (mg/dL)	487.6±196.2	412 (342-593.5)	219	930
Urine pH	6.06±0.30	6 (6-6)	5	6.5
Urine density	1031±7.9	1031 (1026-1036)	1022	1053
HbA1c (%)	13.1±2.1	13.1 (11.2-14.4)	10	18
Insulin (mU/L)	2.41±1.93	1.9 (1.2-3.3)	0.6	9
C-peptide (µg/L)	0.37±0.26	0.39 (0.14-0.50)	0.06	0.93
PGRN (1st day) ng/mL	90.8±17.3	97.1 (75.4-105)	50.9	108.7
PGRN (1st week) ng/mL	58.4±16.9	60.2 (48.8-69.9)	14.9	88.6

SD: standard deviation, VBG: venous blood gas, PGRN: progranulin, HbA1c: glycated haemoglobin

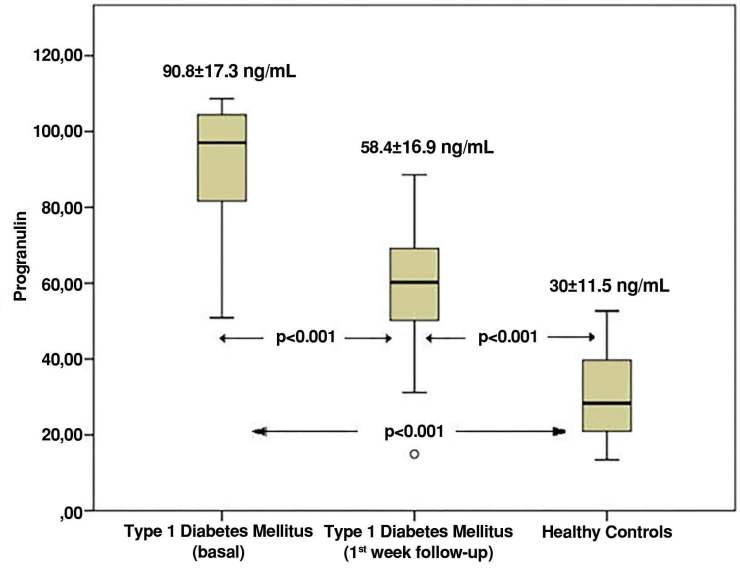

Figure 1. The comparison of progranulin levels in type 1 diabetes mellitus and healthy controls according to measurements at admission and at the first week

Table 2. Factors that may affect the alteration of PGRN levels over time (decline between admission and first week PGRN value) in children with type 1 diabetes mellitus

	Correlation coefficient	p
Age	-0.169	0.418$^{\phi}$
Height SDS	0.211	0.311$^{\phi}$
Weight SDS	0.032	0.881$^{\phi}$
BMI SDS	-0.101	0.633$^{\phi}$
VBG pH	0.087	0.680$^{\phi}$
VBG HCO3	0.075	0.723$^{\Psi}$
Glucose	-0.248	0.232$^{\phi}$
Insulin	0.381	0.060$^{\Psi}$
HbA1c	-0.137	0.515$^{\phi}$
C-peptide	-0.226	0.278$^{\phi}$
ICA	-0.165	0.429$^{\Psi}$
Anti-GAD	0.193	0.355$^{\phi}$
Anti-insulin	0.323	0.115$^{\Psi}$

$^{\phi}$Pearson correlation analysis, $^{\Psi}$Spearman correlation analysis.

PGRN: progranulin, SDS: standard deviation score, VBG: venous blood gas, ICA: islet cell antibody, GAD: glutamic acid decarboxylase antibody

degree of acidosis, and diabetes autoantibodies) and the decline in PGRN level over time. Although the elevation in PGRN levels can be attributed to the inflammatory or immune response-related increase in PGRN in children with T1DM due to acute DKA, since PGRN levels remained higher than those of healthy controls, we could not exclude the role of diabetes in elevated PGRN levels. When we divided the subgroups according to the degree of acidosis, we observed no difference in terms of age, sex, BMI SDS, or WBC count. However, our small sample size and the even smaller numbers in subgroups may also explain why there was no significant difference in between DKA severity subgroups in terms of PGRN levels. Further studies with larger case series and longer-term follow up are required to elucidate the role of the overlapping factors.

There was a positive correlation between the PGRN level and the WBC count at admission. Since sensitive C-reactive protein was not measured in most of the patients, this relationship could not be further evaluated to determine whether it is due to the high WBC count, dehydration or inflammation.

In a study conducted in China comparing PGRN levels in obese and healthy controls, PGRN levels were found to be higher in obese children, but these authors did not find a significant relationship between PGRN levels and HOMA-IR, HOMA-B, and dynamic parameters derived from the oral glucose tolerance test (insulinogenic index, ΔI30/ΔG30 and C-peptide index, ΔC30/ΔG30) (17).

In another study comparing the PGRN levels of a group of healthy controls and children with T1DM (newly diagnosed, those with good metabolic control, and those with poor metabolic control), no difference was observed in PGRN levels (14). Nevertheless, in that study, there was a difference in age and BMI of the patient groups. The authors also reported a negative correlation between PGRN levels and age, as well as between PGRN levels and BMI, in newly diagnosed T1DM patients (14). In our study, although age, sex, and BMI SDS were similar between patients and controls, PGRN levels were higher in the T1DM patients compared to the healthy controls.

In a study in patients with T2DM, serum PRGN level were reported to be associated with the severity of diabetic nephropathy (DN) and diabetic retinopathy (9). The authors suggested that serum PGRN level could be used as an early biomarker of DN in patients with decreased estimated glomerular filtration rate but without albuminuria (9). Another explanation for the increased serum PGRN level in patients with DN, similar to what we observed in patients with DKA, could be a compensatory mechanism that reduces renal impairment, as PGRN can alleviate inflammation in an acute situation (18). Schlatzer et al. (19) investigated PGRN in the urine of 74 patients with T1DM and concluded that it can be used in a panel together with three protein levels (urinary Tamm-Horsfall glycoprotein, clusterin, and human α-1 acid glycoprotein) to predict early signs of diabetic kidney disease. In another study conducted on young adults between the ages of 20 and 30, PGRN levels in type 1 diabetics were significantly higher than in healthy controls, while no relationship was found between diabetic microvascular complications (retinopathy, nephropathy, neuropathy) and PGRN levels (13).

The half-life of PGRN is approximately 40 hours. In our study, early elevation of PGRN levels in newly diagnosed T1DM patients, followed by a decline in the first week of glycemic control, may suggest that the PGRN molecule acts as an acute-phase reactant. However, higher PGRN levels in T1DM patients compared to healthy controls during follow-up, suggests that the relationship of PGRN levels and T1DM remains unknown and merits further investigation (20).

Study Limitations

The limitations of our study include the small number of participants and the cross-sectional assessment of PGRN levels. Although we compared initial and short-term follow-up PGRN levels, longitudinal studies with larger number of cases and long-term courses of PGRN levels are needed to explore how PGRN levels alter over time with disease duration and various treatment regimens. Data on the relationship between PGRN and BMI has been published. Although we had anthropometric measurements at the first and third months in our study, PGRN levels were not measured at these time points. The strength of

our study was that PGRN levels were assessed during DKA and the early period when glucose regulation was achieved.

Conclusion

In this cross-sectional small-scale study, we showed an elevated PGRN level in children with T1DM who presented with DKA, and which declined shortly after achieving normoglycemia and stabilization of the acute phase of presentation with T1DM. None of the clinical or laboratory parameters investigated was associated with the change between PGRN measured at the time of admission and at follow-up. However, the one-week PGRN level remained higher than in healthy controls, suggesting a need to clarify whether elevated PGRN was due to diabetes-specific metabolic changes or an increased inflammatory response to the acute phase of DKA. Larger-scale longitudinal studies performed in T1DM children are required to elucidate this relationship.

Ethics

Ethics Committee Approvel: The study was approved by the Scientific Research Ethics Committee of Health Sciences University Erzurum Faculty of Medicine (approval no.: 05/105, date: 05/08/2024) and carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from the participants or their legal guardians.

Footnotes

Authorship Contributions

Concept: Ayşe Sena Dönmez, Atilla Çayır, Esra Laloğlu, Esra Dişci, Serap Kılıç Kaya, Serkan Bilge Koca, Hüseyin Demirbilek, Design: Alev Lazoğlu Özkaya, Esra Dişci, Serap Kılıç Kaya, Kamber Kaşali, Serkan Bilge Koca, Hüseyin Demirbilek, Data Collection or Processing: Ayşe Sena Dönmez, Esra Laloğlu, Alev Lazoğlu Özkaya, Kamber Kaşali, Serkan Bilge Koca, Analysis or Interpretation: Atilla Çayır, Esra Dişci, Serap Kılıç Kaya, Kamber Kaşali, Writing: Ayşe Sena Dönmez, Atilla Çayır, Esra Laloğlu, Alev Lazoğlu Özkaya, Hüseyin Demirbilek.

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