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Research Article

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 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 progranulin 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

ABSTRACT
Objective: Progranulin (PGRN), a growth factor, modulates cell proliferation, wound repair, and inflammation. It involves glucose metabolism and is associated with insulin resistance and diabetes mellitus (DM). In the present study, we evaluate PGRN levels at admission and during follow-up in children with newly diagnosed type 1 diabetes mellitus (T1DM) in comparison with healthy controls
Material and Methods: A total of 49 children, 25 with T1DM (12F/13M) and 24 healthy controls (10F/14M) were recruited. The age, weight, height, body mass index (BMI), severity of acidosis, glucose, insulin, C-peptide, and diabetes-specific autoantibodies of children with newly diagnosed type 1 diabetes mellitus (T1DM) were examined. The PGRN was measured in children with T1DM at admission, first week of follow-up, and in healthy controls.
Results: There was no differences in age (11 ± 3.9 years vs 12.1 ± 3.1 years, p = 0.269) and BMI standard deviation score (SDS) (-0.11 ± 1.49 SD vs 0.10 ± 0.82 SD, p = 0.540) characteristics of children with T1DM and healthy controls. The basal PGRN levels of children with newly diagnosed T1DM were higher than those of controls (90.8 ± 17.3 ng/mL vs 30 ± 11.5 ng/mL, p < 0.001). In children with T1DM, basal PGRN at admission (90.8 ± 17.3 ng/mL) significantly declined (58.4 ± 16.9 ng/mL) in the first week (when glycemic regulation was achieved) (p <0.001).
Conclusion: These findings suggest that elevated PGRN levels in children with newly diagnosed T1DM may reflect both an acute inflammatory response to diabetic ketoacidosis and a persistent alteration in metabolic regulation, underscoring the potential role of PGRN as a biomarker in the early course of the disease.
Keywords: Diabetic ketoacidosis, pediatric, progranulin, PGRN, type 1 diabetes mellitus

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INTRODUCTION

Progranulin (PGRN), also called granulin-epithelin precursor, acrogranin, proepithelin, GP88, and prostate cell-derived growth factor (PCDGF), is a growth factor that is comprised of 593 amino acids with a molecular weight of 75–80 kDa [1-3]. It modulates cell proliferation, tissue regeneration, and wound repair, thus being involved in the stages of tumorigenesis, inflammation, and fibrosis [4-6]. Progranulin 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]. Progranulin 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 progranulin 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 diabetes mellitus (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, we aim to evaluate the PGRN levels measured at admission and during follow-up in children with newly diagnosed T1DM who presented with diabetic ketoacidosis (DKA) in comparison with healthy controls.

MATERIAL AND 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 Erzurum Training and Research Hospital between September 2023 and September 2024.
Anthropometric measurements (weight, height, and body mass index) were recorded. Age- and sex-specific reference ranges and standard deviation scores (SDS) were calculated.
Patients with concomitant endocrinological problems (hypothyroidism, Cushing syndrome, familial hyperlipidemia, etc.), those diagnosed with hypertension or chronic liver disease, celiac disease and those having medication such as corticosteroids were excluded. The control group consisted of healthy children who were admitted to pediatric outpatient clinics.

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 sera 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 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 these parameters, such as pH, pCO2, pO2, Na^+, K^+, Cl^-, iCa^{++}, glucose, L-lactate, total hemoglobin (tHb), hematocrit (Hct), and hemoglobin saturation (SO_2). Children with T1DM were classified as 'mild', 'moderate', 'severe' and 'without acidosis' according to the pH and HCO3 levels in blood gas at admission **[15].**

- 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 enzyme-linked immunosorbent assay (ELISA) using the Human Progranulin 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. The 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. Progranulin concentrations were determined by comparing the optical density in the sample wells with the standard curve.
The study was approved by the Local Ethics Committee of Health Sciences University Erzurum Faculty of Medicine (Approval decision date: 05/08/2024 and number: 05/105) 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) software. The mean, standard deviation (SD), minimum and maximum values of the numeric variables were calculated. Categorical variables were determined as frequency and percentage (%). Shapiro-Wilk test was used to evaluate the normality assumption. Additionally, 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 (ANOVA) 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, inspired by a study comparing children with newly diagnosed, well-controlled, poorly controlled type 1 diabetes with a healthy control group [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 (12F/13M) and 24 healthy controls (10F/14M) were recruited. There was no statistically significant difference in age (11 ± 3.9 years vs. 12.1 ± 3.1 years, p = 0.269) and BMI SDS (-0.11 ± 1.49 SD vs. 0.10 ± 0.82 SD, p = 0.540) between children with T1DM and healthy controls. Regarding the severity of acidosis at admission, 10 patients had mild acidosis, 9 patients had moderate acidosis, and four patients had severe acidosis. Two patients 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 PGRN levels of children with T1DM at admission were significantly higher than those of healthy controls (90.8 ± 17.3 ng/mL vs. 30 ± 11.5 ng/mL, p < 0.001). There was no statistically significant difference between male and female 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), and basal PGRN levels (92.5 ± 15.8 ng/mL vs 88.8 ± 19.4 ng/mL, p = 0.609), respectively.
There was no statistically significant difference in PGRN levels among 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 concomitant infections, or dehydration (12.622 WBCs/µl vs 8.545 WBCs/µ, p = 0.015). A weak positive correlation was observed between PGRN level and white blood cell 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 revealed that PGRN levels measured at admission were significantly higher than both their 1st-week measurements and than those of healthy controls (p< 0.001, p< 0.001) (Figure 1). None of the factors that may affect the alteration in PGRN levels over time (decline between admission and 1st week PGRN value) in children with T1DM (Table 2).

DISCUSSION

In the present study evaluating PGRN levels in patients presented with newly diagnosed T1DM, we showed a statistically significantly higher PGRN level in children at first admission with DKA compared to healthy controls, which declined during an average follow-up period of one week when blood glucose stabilization was achieved.
Although a decline was observed in the PGRN levels in the first week of admission, it was still higher than healthy controls. Nevertheless, we did not detect a relationship between clinical characteristics (age and anthropometry) and laboratory parameters (glucose, insulin, c-peptide, HbA1c, 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 the acute state of 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 ($p = 0.285$), sex ($p = 0.817$), BMI SD ($p = 0.976$), or WMC counts ($p = 0.055$). However, our small sample size and the small number of subsamples may also explain why there was no statistically significant difference in the 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 CRP was not measured in most of the patients, this relationship could not be further evaluated to determine whether it is due to the high white blood cell 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 they did not detect a statistically significant relationship between PGRN levels with HOMA-IR, HOMA-B, and dynamic parameters derived from the oral glucose tolerance test (insulinogenic index, $\Delta I30/\Delta G30$ and C-peptide index, $\Delta C30/\Delta G30$) **[16].**

In another study comparing the PGRN levels of a group of healthy controls and children with T1DM (newly diagnosed, those with well 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 there was no statistically significant difference in age, sex, and BMI SDS, PGRN levels were higher in the T1DM patients compared to the healthy controls.

In a study carried out on patients with T2DM, serum PRGN level have been reported to be associated with the severity of diabetic nephropathy (DN) and diabetic retinopathy (DR) [9]. The authors suggested that serum PGRN level could be used as an early biomarker of diabetic nephropathy in patients with decreased eGFR 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 **[17].**

Schlatzer and colleagues 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 (DKD) **[18].**

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 [19].

Study Limitations

The limitations of our study include the small number of participants and the cross-sectional assessment of PGRN levels. Although we compared the 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. The literature has reported data on the relationship between progranulin and body mass index (BMI). Although we had anthropometric measurements at the 1st and 3rd months in our study, PGRN levels were not measured during these periods. The strength of our study was that we assessed PGRN levels which provide insight into the ketoacidosis period and the early period when glucose regulation is achieved.

Conclusion

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

Ethics

Ethics Committee Approval: The Ethical committee at Health Sciences University Erzurum Faculty of Medicine (Approval decision date: 05/08/2024 and number: 05/105) and carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Consent form was filled out by all participants.

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Footnotes

Authorship Contributions

Concept: Atilla Cayir, Hüseyin Demirbilek, Serkan Bilge Koca, Ayse Sena Donmez, Esra Disci, Serap Kilic Kaya, Esra Laloglu, Data Collection or Processing: Ayse Sena Donmez, Esra Laloglu, Alev Lazoglu Ozkaya, Kamber Kasali, Serkan Bilge Koca, Analysis or Interpretation: Kamber Kasali, Atilla Cayir, Serap Kilic Kaya, Esra Disci, Design: Serkan Bilge Koca, Esra Disci, Alev Lazoglu Ozkaya, Serap Kilic Kaya, Huseyin Demirbilek, Kamber Kasali, Writing: Atilla Cayir, Ayse Sena Donmez, Huseyin Demirbilek, Esra Laloglu, Alev Lazoglu Ozkaya

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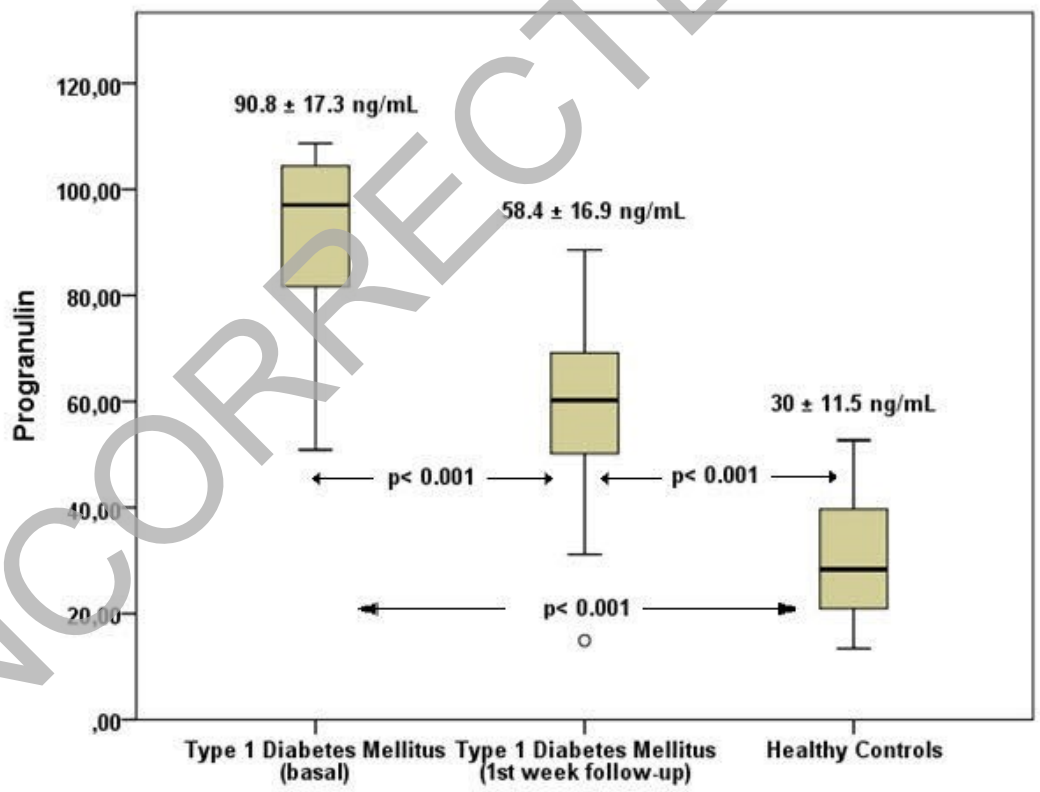

Figure 1. The comparison of progranulin levels in type 1 diabetes mellitus and healthy controls according to measurements at admission and at the first week

Table 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

SDS: standard deviation score, VBG: venous blood gas, PGRN: progranulin

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

	Correlation coefficient	*P*-Value
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$^{\Psi}$
PGRN: progranulin, SDS: standard deviation score, VBG: venous blood gas, ICA: islet cell antibody, GAD: glutamic acid decarboxylase		
$^{\Phi}$Pearson correlation analysis, $^{\Psi}$Spearman correlation analysis.		