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The correlation between insulin-like growth factor with glycemic control, glomerular filtration rate, blood pressure, hematological changes or body mass index in patients with type 2 diabetes mellitus

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Abstract

Insulin-like growth factor (IGF) family is made up of two polypeptides, IGF-I and IGF-II, six specific binding proteins (IGFBPs 1–6) and specific receptors. IGF-I is involved in the regulation of growth and cellular proliferation and has a similar structure to insulin. The major IGF transport function is attributed to IGFBP-3. Some studies have highlighted the association between IGF and diabetes. The aims of this study were to analyze the correlation between IGF with glycemic control, glomerular filtration rate (GFR), blood pressure, hematological changes or body mass index (BMI) in patients with type 2 diabetes mellitus (T2DM). Thirty patients with T2DM and thirty non-diabetic control patients were included in this study. Clinical, anthropometric, biochemical parameters and morphology of blood smear were recorded. Blood pressure was determined by mercury sphygmomanometer. The anthropometric measurement included BMI. The biochemical parameters included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), GFR, serum IGF-I, IGFBP-3 levels. The IGF-I/IGFBP-3 ratio was evaluated. The plasma glucose was determined enzymatically, HbA1c was determined by high-performance liquid chromatography (HPLC) and GFR was calculated automatically. IGF-I was measured by immunoradiometric assay (ELISA – enzyme-linked immunosorbent assay) and IGFBP-3 by sensitivity immunoassay. For the analysis of the morphology of blood smear, May-Grünwald–Giemsa (MGG) was used as staining technique. The microscopic examination was performed initially with the objectives of 10×/20× and subsequently with an immersion objective of 100×. Image acquisition was done after the examination of the preparations obtained with a 40× objective, using Image Pro Plus 6.0 software. In the present study, we observed that T2DM leads to an increase in the IGF-I and IGFBP-3 levels. No relationship was obtain between IGF-I, IGFBP-3 levels and IGF-I/IGFBP-3 ratio with neither parameters studied. The difference of serum IGF-I and IGFBP-3 levels between patients with T2DM and subjects without diabetes showed that IGF-I may be a useful marker for diabetes mellitus and IGFBP-3 for possible complications of this affection.

Keywords: diabetes, insulin-like growth factor, hematological changes.

Introduction

Insulin-like growth factor (IGF) family is made up of two polypeptides, IGF-I and IGF-II, six specific binding proteins (IGFBPs 1–6) and specific receptors. IGF-I is involved in the regulation of growth and cellular proliferation and has a similar structure to insulin [1]. The major IGF transport function is attributed to IGFBP-3 [2].

Some studies have highlighted the association between IGF and diabetes [3–5]. In an article published in 2010 by Teppala & Shankar, in *Diabetes Care*, entitled "Association between serum IGF-1 and diabetes among U.S. adults", the authors mention that low levels of IGF-I were positively correlated with diabetes. The analysis by age highlighted that decreasing IGF-I levels were positively associated with diabetes in patients less than 65 years old; this feature is not present in patients over the age of 65 years [1]. Sandhu *et al.* observed, in a study in which they were included 615 subjects aged between 45–65 years, a positive association of low IGF-I levels with diabetes or glucose intolerance [6]. In a study published in 2008, Rajpathak *et al.* not find an association between IGF-I and diabetes in 922 patients with the same or greater age of 65 years old [7].

The aims of this study were to analyze the correlation between IGF with glycemic control, glomerular filtration rate (GFR), hematological changes, body mass index (BMI) in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods

Thirty patients with T2DM and thirty non-diabetic control subjects were included in this study. The diabetic patients are at the heart of the Clinical Center of Diabetes,

Craiova, Romania. The subjects of control group were recruited from non-diabetic individuals who associated other conditions, respectively: seven subjects were diagnosed with hypertension, five subjects with obesity, two subjects with liver steatosis, two subjects with hypothyroidism and one subject with dyslipidemia.

Clinical, anthropometric, biochemical parameters and morphology of blood smear were recorded. Blood pressure was determined by mercury sphygmomanometer. The measurement protocol included three measurements; the mean of all three measurements was used as systolic and diastolic blood pressure. The anthropometric measurement included BMI. BMI was computed as a ratio of weight to the square of height (kg/m^2). The biochemical parameters included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), GFR, serum IGF-I, IGFBP-3 levels. The IGF-I/IGFBP-3 ratio was evaluated. The plasma glucose was determined enzymatically, HbA1c was determined by high-performance liquid chromatography (HPLC) and GFR was calculated (using link http://www.qxmd.com/calculate-online/nephrology/ckd-epi-efrg). IGF-I was measured by immunoradiometric assay (ELISA – enzyme-linked immunosorbent assay) and IGFBP-3 by sensitivity immunoassay. For the analysis of the morphology of blood smear, May-Grünwald–Giemsa (MGG) was used as staining technique. The microscopic examination was performed initially with the objectives of 10×/20× and subsequently with an immersion objective of 100×. Image acquisition was done after the examination of the preparations obtained with a 40× objective, using Image Pro Plus 6.0 software. Red changes included cells that differ in color, size or shape from normal erythrocytes (hypochromia, anisocytosis, poikilocytosis). According to hematological changes, diabetic patients may present no hematological changes, one, two or three hematological changes. The initial results of the study conducted in the Project No. POSDRU/159/1.5/S/136893 were previously published [8].

In the first phase of the project, we have followed the prevalence of hematological changes in diabetic patients and the correlation of the red cell changes with markers of glycemic control.

It should be mentioned that the determinations of age, anthropometric, biochemical parameters (FPG, HbA1c, GFR) and morphology of blood smear were made at the initiation of the project. The determination of serum levels of IGF-I and IGFBFP-3 was subsequently made within the same Project.

For data analysis, diabetic patients group was divided into four hematological changes, subgroups noted with 0 for no hematological changes, 1 for one hematological change, 2 for two hematological changes and 3 for three hematological changes.

Statistical analysis

Results are expressed as mean±SEM (standard error of the mean). Differences between groups were assessed by the Student's *t*-test. The differences between subgroups were analyzed with One-Way ANOVA (Analysis of Variance). The correlation among different parameters was analyzed using the Pearson's correlation coefficient (*r*) as well as the linear and multiple regression methods. Data were analyzed using SPSS (Statistical Package for the Social Sciences) software.

Results

In the study group, mean age was 60.93±8.5 years and in control group, 60.33±9.48 years (p=NS – not significant). Mean serum IGF-I levels in diabetic patients (n=30) were higher than in non-diabetic control patients (n=30) – 64.62±4.48 *vs.* 36.34±3.99 ng/mL, respectively (p<0.001) (Figures 1 and 2). Serum IGFBP-3 levels tended to show higher values in diabetic patients compared to the control group (4061.75±275.67 *vs.* 3595.53±190.57 ng/mL, respectively) but not significantly different (p=0.17>0.05) (Figures 3 and 4). The IGF-I/IGFBP-3 ratio in diabetic patients was higher than in control patients (0.021±0.006 *vs.* 0.012±0.003, respectively; p=0.012<0.05). In our study, we observed that T2DM leads to an increase in the IGF-I and IGFBP-3 levels.

In what regards the hematological changes, subgroup 1 was made up of 10 (33.33%) patients, subgroup 1 – 5 (16.66%) patients, subgroup 2 – 11 (36.66%) patients and subgroup 3 – 4 (13.33.%) patients. Blood smear from patients with diabetes with one, two or three hematological changes are present in Figures 5–7.

In this study, no relations were found between IGF-I, IGFBP-3 and IGF-I/IGFBP-3 ratio with the above-mentioned parameters. No significant differences were found between the hematological changes subgroups for IGF-I (p=0.86>0.05) or for IGFBP-3 (p=0.77>0.05). Also, no significant differences were found between the blood pressure and IGF-I (p=0.95>0.05) or for IGFBP-3 (p=0.55 >0.05). The statistical sampling of the obtained data is show in Table 1.

Table 1 – ***The statistical sampling of the obtained data***

		Glycemic level	HbA1c	GFR	Blood pressure	Hematological changes	BMI
IGF-I	*r*	0.111	0.244	0.073	-0.084	-0.072	0.001
	p-value	0.560	0.193	0.702	0.661	0.704	0.5
IGFBP-3	*r*	-0.129	-0.088	0.042	0.098	0.009	-0.001
	p-value	0.498	0.643	0.827	0.608	0.961	0.498
IGF-I/IGFBP-3 ratio	*r*	0.139	0.167	-0.053	-0.125	-0.070	0.007
	p-value	0.464	0.379	0.780	0.511	0.714	0.486

HbA1c: Glycated hemoglobin; GFR: Glomerular filtration rate; BMI: Body mass index; IGF-I: Insulin-like growth factor I; IGFBP-3: Insulin-like growth factor-binding protein 3; *r*: Pearson's correlation coefficient. Statistical correlation is significant at p<0.05 level.

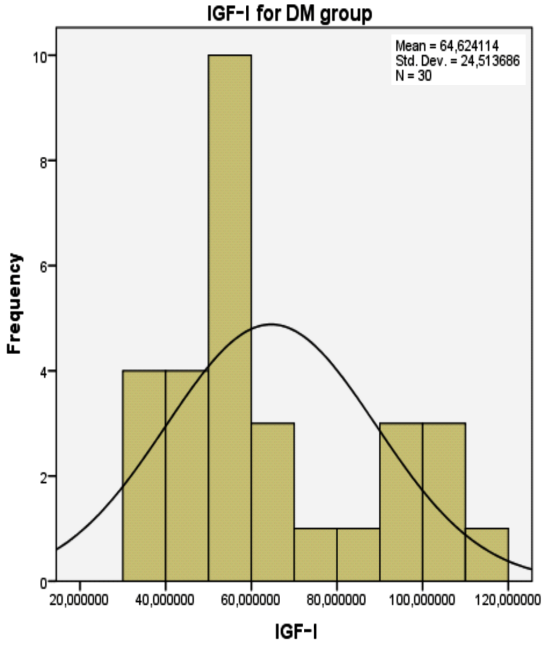

Figure 1 – *IGF-I levels in the study group. DM: Diabetes mellitus.*

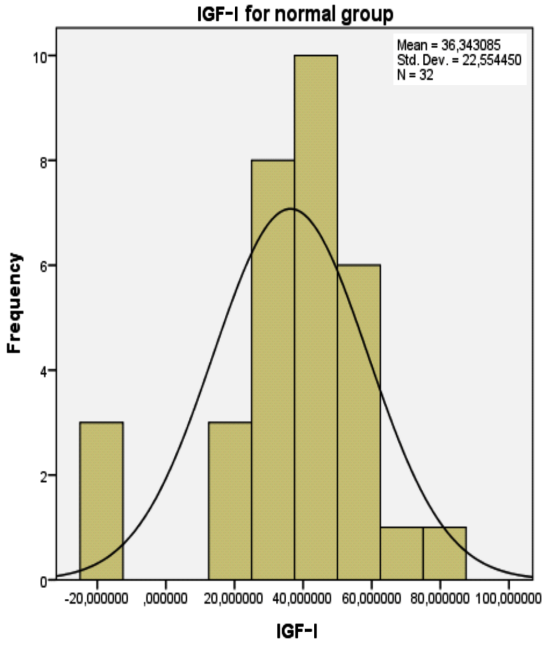

Figure 2 – *IGF-I levels in the control (normal) group.*

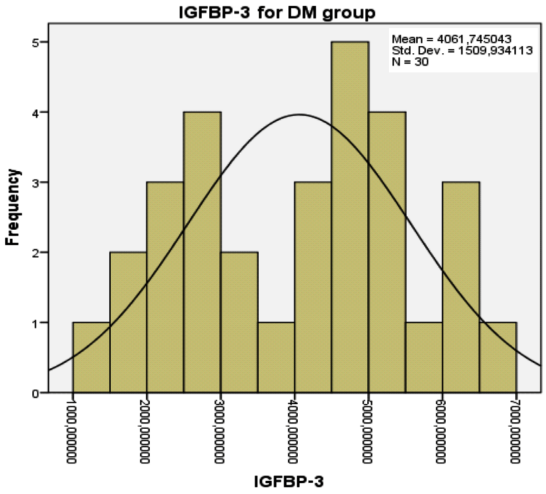

Figure 3 – *IGFBP-3 levels in the study group. DM: Diabetes mellitus.*

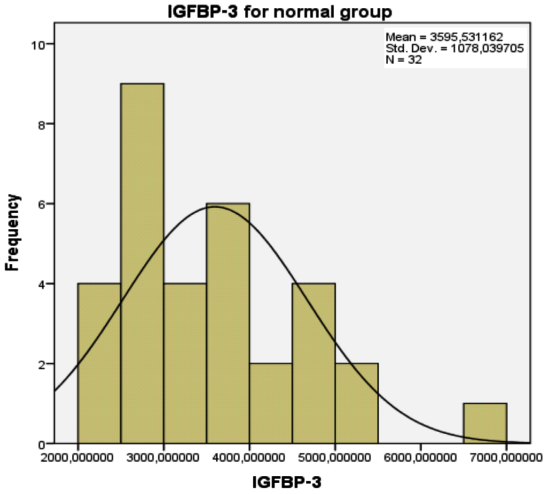

Figure 4 – *IGFBP-3 levels in the control (normal) group.*

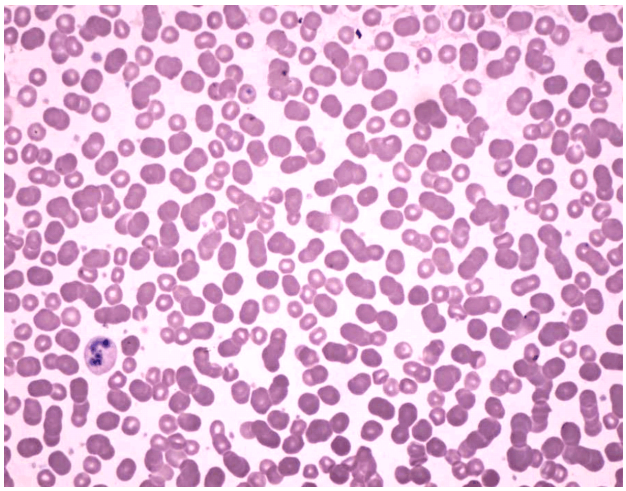

Figure 5 – *Blood smear from a patient with diabetes (one hematological change): anisocytosis (1+). MGG staining, ×400.*

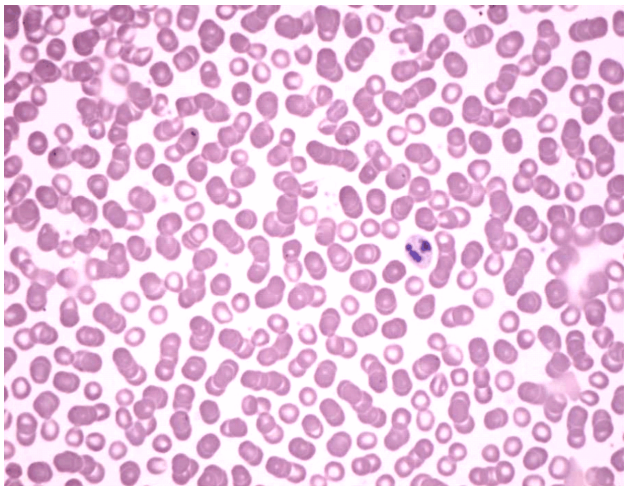

Figure 6 – *Blood smear from a patient with diabetes (two hematological changes): hypochromia (2+), anisocytosis (1+ very rare macrocytes). MGG staining, ×400.*

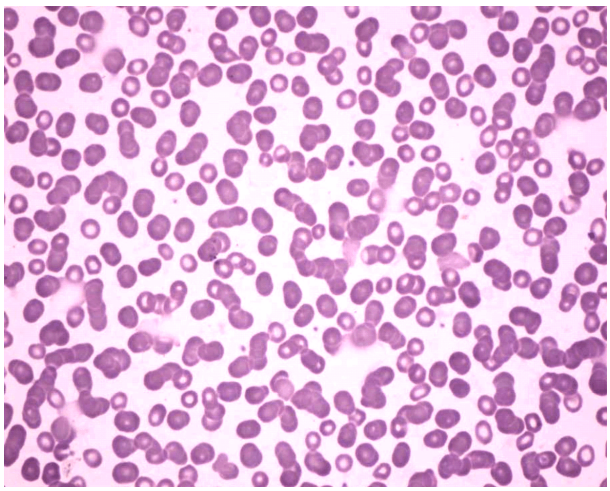

Figure 7 – ***Blood smear from a patient with diabetes (three hematological changes): hypochromia (2+ rare anulocytes), anisocytosis (1± with microcytes), poikilocytosis (1± rare oval-shaped red blood cells). MGG staining, ×400.***

Discussion

The study highlighted that diabetic patients had elevated IGF-I and IGFBP-3 levels compared to the control group. The results of studies in the literature on the correlation between IGF-I values and diabetes are not unitary. Some studies have highlighted low values of IGF-I at patients with T2DM [1, 6]. Other studies suggesting normal or elevated levels of IGF-I in patients with obesity or T2DM [7, 9–11].

In a review article published in 2008, in *Diabetes, Obesity and Metabolism*, entitled "The role of IGF-I and its binding proteins in the development of type 2 diabetes and cardiovascular disease", Ezzat *et al.* state that the progression from the first β-cell lesion, through impaired glucose tolerance (IGT) status and to diabetes is individualized; authors consider that the dynamics of hepatic and peripheral insulin sensitivity (which have a decreasing tendency), together with IGF-I (with increasing tendency) might influence the evolution from pre-diabetes to diabetes [12]. To mention that at the time of inclusion the patients had an evolution of the intercourse between four months and 30 years.

In terms of association between IGFBP-3 and diabetes, literature offers little data. Wu *et al.* reported, in 2012, that IGFBP-3 was significantly increased in patients with T2DM [13]. In 2011, Yoo *et al.* published in *Endocrinology* a study suggesting that the redox imbalance associated with high glucose enhances IGFBP-3 expression, thus inducing apoptosis; on the other hand, increased expression of IGFBP-3 additionally contributes to the redox imbalance, constituting an amplifying factor of the vicious circle [14].

Studies on animal models and in cell culture have shown that elevated values of IGFBP-3 can generate insulin resistance in adipocytes [15, 16] and represent a physiological response to injury, and according to the author's statements may represent a therapeutic strategy for the therapy of diabetic retinopathy [17].

The correlation between glycemic control, GFR, BMI and blood pressure and IGF level has been analyzed in numerous studies. Fasting serum IGF-I concentrations were negatively correlated with FPG in a study published in 2008, in *International Journal of Diabetes in Developing Countries*. In the study were included 12 subjects with normal glucose tolerance, nine subjects with impaired glucose tolerance and 18 patients with T2DM [18]. In 2012, Kim *et al.*, in a study in which they were included 66 adolescents – 32 with normal glucose tolerance, 11 with impaired glucose tolerance group and 23 with diabetes –, mention increased values of IGF-I and IGFBP-3 in adolescents with T2DM and determinations were positively correlated with HbA1c and FPG. In this study, IGFBP-3 level was associated with lipid profile. The results obtained suggest that IGFBP-3 it can be marker for glycemic control and/or development of dyslipidemia in adolescents with T2DM [19]. Lam *et al.*, in a study in which they were included 3977 subjects, have taught that IGF-I was inversely correlated with BMI, the presence of diabetes, and GFR [20]. Kim & Lee report that serum IGF-I and IGFBP-3 levels were significantly correlated with BMI in patients wit type 1 diabetes [21].

Previous studies have highlighted the presence of hematological changes in patients with T2DM [22–24]. *In vitro* and in animal studies, IGF-I stimulate erythropoiesis [25, 26]. In the analyzed studies, we not obtain information on the correlation between IGF-I values and hematological changes in T2DM.

Conclusions

The patients with diabetes mellitus had high serum levels of IGF-I and IGFBP-3 when compared with normal controls. No relationships were obtained between IGF-I, IGFBP-3 levels and IGF-I/IGFBP-3 ratio with neither studied parameters. The differences of serum IGF-I and IGFBP-3 levels between T2DM patients and subjects without diabetes showed the possibility that IGF-I may be a useful marker for diabetes mellitus and IGFBP-3 for possible complications of this affection.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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