Original Article

Plasma Prolactin Level in Type 2 Diabetic Patients with and without Retinopathy

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Abstract

Background: Prolactin (PRL) is expressed in anterior pituitary gland and throughout retina. The peptide vasoconstrictive antiangiogenic vasoinhibins are PRL-derived and inversely correlates the development of retinopathy. **Objective:** The aim of this study was to assess the relationship between PRL level and development/progression of retinopathy in type 2 diabetic (T2DM) patients, and their relationship with changes in lipogram and glycemic control indices. **Patients and Methods:** This study included 62 male patients with T2DM on metformin and 45 male healthy subjects as a control group. Diabetic patients were divided into two main groups: diabetic group with retinopathy included 38 patients and diabetic group without retinopathy included 24 patients. Diabetic retinopathy patients were subdivided into non-proliferative diabetic retinopathy subgroup (NPDR) included 25 patients and proliferative diabetic retinopathy subgroup (PDR) included 13 patients. NPDR was further classified into mild (9 patients), moderate (8 patients) and severe (8 patients). Fasting blood samples were collected from all participants to recover plasma. Plasma PRL, total cholesterol, HDL-cholesterol, LDL-cholesterol and blood HbA_{1c} were measured. **Results:** There were non-significant differences in plasma PRL levels between diabetic patients with and without retinopathy and also between the two diabetic groups vs. healthy controls. There were non-significant differences in plasma PRL levels comparing mild, moderate and severe non-proliferative retinopathy patients vs. each other or vs. diabetic patients without retinopathy. There was a significant increase in HbA1c level in diabetic patients with retinopathy compared to those without retinopathy ($p<0.05$). **Conclusion:** Our results highlight the important role in the development and progression of diabetic retinopathy that the uncontrolled blood glucose level may play. However, variation in PRL blood levels may not have a role to play in this concern. **AbdelMoneim M, Abd-Eltawab A, Mostafa-Hedeab G, Zaki KA, Mohamed AA, Ibrahim MA. Plasma Prolactin Level in Type 2 Diabetic Patients with and without Retinopathy. AUMJ, 2015 December 1; 2(4): 1 - 6.**

Key Words: Prolactin, Retinopathy, Vasoinhibins, Type 2 diabetes, Angiogenesis.

Introduction

Type 2 diabetes mellitus (T2DM) is the most common chronic disease worldwide. Its long-term sequealae include retinopathy, neuropathy, nephropathy and macrovascular diseases[1]. Retinopathy is one of the common causes of visual loss worldwide. It is a blinding complication of DM that damages the retina and occurs within 20 years from diagnosis of diabetic patients. There are many factors that play a role in the pathogenesis of retinopathy, viz.: hyperglycemia, duration of diabetes, hypertension and age[2]. Diabetic retinopathy is characterized by capillary cell reduction and increased vasopermeability that induce hypoxia and ischemia leading to increased angiogenesis. Disturbance in anti-angiogenic protection mechanisms can accelerate neovascularization and retinopathy[3].

Prolactin (PRL) hormone is secreted from anterior pituitary gland and is expressed throughout retina. Vasoinhibins are peptides derived from PRL, growth hormone and placenta lactogen. These peptides decrease vasodilatation and angiogenesis[4]. Intra-cardiac injection of radioactive PRL would incorporate into ocular tissue[5]. PRL level was reported to be elevated in diabetic patients. It decreases in patients with retinopathy compared to those without retinopathy. This indicates that induction of hyperprolactinemia could have a therapeutic potential against diabetic retinopathy[6].

In this study, we aimed at evaluating the relationship between blood prolactin level and presence and absence of retinopathy in diabetic patients, and, their relationship with changes in lipogram and glycemic control indices.

Patients and Methods

Participants and sampling: The local Research and Ethics Committee of Faculty of Medicine, Suez Canal University, Ismailia, Egypt, approved the study which adhered to the creed of the Declaration of Helsinki. An informed consent was secured from each participant. The current study included all of the voluntarily participating 62 adult male patients with type T2DM reviewed at Cortba Ophthalmic Center, Erashyat-Masr, Ismailia, Egypt from April - September, 2015 and 45 normal healthy adult male controls. *Inclusion criteria*: Male patients with T2DM on metformin. *Exclusion criteria:* The diabetic patients with history of hyperprolactinemia, thyroid disease, renal failure, liver disease, treatment with drugs that increase prolactin level, recent psychological stress and adrenal diseases. Overnight fasting blood samples were collected from all participants for whole blood (for HbA1c**)** and recovering plasma (for other parameters) in heparin tubes.

Ophthalmological examination: Patients underwent thorough ophthalmic examination comprising corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), Goldman Applanation Tonometry, and dilated fundus examination. Fundus examination was done by direct and indirect ophthalmoscope and by slit lamb biomicroscopic examination with +90 non-contact lens. Fundus was photographed to document any abnormal findings appropriate. *Grouping:* The diabetic patients were classified

according to fundus examination (Table 1). Diabetes group with retinopathy included 38 patients with the mean age of 58.6 ± 7 years and disease duration of 13 ± 2.6, and, diabetes group without retinopathy included 24 patients with the mean age of 54.1 ± 10 years and disease duration of 12 ± 2.6. Diabetic retinopathy group was subdivided into non-proliferative (25 patients) and proliferative (13 patients). Non-proliferative diabetic retinopathy group (NPDR) was further classified into mild (9 patients), moderate (8 patients) and severe (8 patients) according to Wilkinson et al[7].

Table 1: Classification of Diabetic Retinopathy (DR)[7].

Stages of DR	Clinical Criteria
Mild non-proliferative DR	At least one microaneurysm. Criteria not met for other level of retinopathy
Moderate non-proliferative DR	Hemorrhages or microaneurysm, venous beading, cotton-wool spots, and intraretinal microvascular abnormality (IRMA).
Severe non-proliferative DR	Hemorrhages or microaneurysm in all four quadrants, or venous beading in at least 2 quadrants, or IRMA in at least 2 quadrants.
Proliferative DR	Neovascularization in optic disc or retina, preretinal hemorrhages, vitreous hemorrhages, traction retinal detachments, and, neovascular glaucoma.

Biochemical investigations were done using Semi-Autoanalyser utilizing kits supplied by Human Glesellschaft Fur Biochemica und Diagnostics mbH, Wiesbaden, Germany. Colorimetrically, fasting blood glucose (FBG) was measured using glucose oxidase method[8], total cholesterol was measured by cholesterol oxidase method[10], HDL-Cholesterol (HDL-C)[11], LDL-Cholesterol (LDL-C) was calculated using Friedwald formula[12] and creatinine[13] were measured. HbA1c was measured using G8 Tosoh Automated HPLC Glycohemoglobin Analyser HLC-723G8 (cat#021560 and cat#021848 for the ion-exchange column, Tosoh Bioscience Inc., King of Prussia, PA 19406, USA[9]. Plasma prolactin was measured by specific ELISA kit (cat#DS-EIA-Prolactin, DSI S.r.l., Saronno, Volonterio, Italy - with a lower detection limit of 10 mIU/L)[14]. *Statistical analysis:* Data were collected, tabulated, subjected to analysis using SPSS (Version 17, Chicago, USA) using the student's "t" test or ANOVA. Data were presented as mean ± standard deviation (SD). P value is considered statistically significant if <0.05.

Results

The current study included 45 normal healthy adult male controls with a mean age of 52 ± 12.4 and 62 adult male patients with type T2DM and a mean age of 56 ± 10.7. Their mean disease duration was 14 ± 3.5 years.

Plasma levels of prolactin, total cholesterol, HDL-C, and creatinine were of non-significant difference comparing diabetic and healthy control groups but plasma LDL-C and creatinine levels were significantly higher in the two diabetic

groups vs. controls (Table 2). Mean fasting plasma glucose and HbA1c were significantly higher in diabetic groups with retinopathy and without retinopathy than that in control group. Mean fasting plasma glucose and HbA_{1c} were significantly increased in diabetic group with retinopathy when compared to diabetic group without retinopathy (Table 2).

Table 2: Mean plasma prolactin, total cholesterol, HDL-Cholesterol (HDL-C), LDL-Cholesterol (LDL-C), creatinine, fasting blood glucose (FBG) and HbA1c in type II diabetic patients with retinopathy (DM-WRP) and without retinopathy (DM-W_{out}RP) vs. healthy control participants. Data presented are mean ± standard deviation, n and p value. a = significance of difference comparing healthy controls vs. each of the two diabetic subgroups, and, b = significance of difference comparing the two diabetic groups against each other.

Parameter	Controls (n = 45)	DM-WRP (n = 24)	DM-W_{out}RP (n = 38)
Prolactin, ng/mL	6.95 ± 0.62	7.03 ± 0.91	6.92 ± 0 .65
Total cholesterol, mg/dL	195.82 ± 17.77	200.25 ± 14.86	210.38 ± 13.40
HDL-C, mg/dL	44.59 ± 5.49	45.75 ± 6.11	45.65 ± 6.78
LDL-C, mg/dL	90.84 ± 9.24	121.67 ± 11.41 (p = 0.017)[a]	128.65 ± 12.12 (p = 0.02)[a] (p = 0.015)[b]
Creatinine, mg/dL	0.91 ± 0.17	1.09 ± 0.19 (p = 0.014)[a]	1.09 ± 0.20 (p = 0.034)[a]
FBG, mg/dL	82.60 ± 9.30	212.0 ± 27.69 (p = 0.015)[a]	228.59 ± 24.34 (p = 0.011)[a] (p = 0.002)[b]
HbA1c, %	4.55 ± 0.29	7.32 ± 0.62 (p = 0.022)[a]	9.07 ± 0.22 (p = 0.011)[a] (p = 0.01)[b]

Plasma prolactin levels showed non-significant difference comparing diabetic patients with non-proliferative retinopathy (6.98 ± 0.79) vs. those with proliferative retinopathy (6.87 ± 0.71). Also, the mean prolactin plasma levels were non-significantly different among the three sub-grades of non-proliferative retinopathy; mild = 7.17 ± 0.75, moderate = 6.98 ± 0.45, and, severe = 6.79 ± 0.43. Mean prolactin plasma levels were non-significant different comparing each of these sub-grades of diabetic non-proliferative retinopathy vs. diabetic patients without retinopathy (7.03 ± 0.91).

Discussion

The aim of this study was to assess the relationship between plasma prolactin and the extent, type and severity of retinopathy in diabetic patients. The rationale was based on the fact that prolactin is the main source of specific vasoconstrictive and antiangiogenic vasoinhibins[4]. Our results showed a non-significant difference in plasma prolactin levels between diabetic patients with vs. without retinopathy and comparing each of them vs. healthy controls. Also, there were non-significance changes in plasma prolactin comparing diabetic patients with non-proliferative retinopathy vs. those with proliferative retinopathy.

Moreover, the three sub-grades of non-proliferative diabetic retinopathy, viz.: mild, moderate and severe, showed non-significant decreases in plasma prolactin in severe retinopathy. These non-significant changes may suggest that prolactin does not play a significant protective role against the development of diabetic retinopathy. This is in agreement with study of Bonakdaran et al[15]. However, Triebel et al[3] showed that diabetic patients with retinopathy had lower level of serum prolactin-V (vasoinhibin) that could contribute to the development of diabetic retinopathy. Our results are in contradiction with those of Arnold et al[6] who reported a significant increase in serum prolactin in diabetic patients compared with the controls and in those without retinopathy than patients with proliferative retinopathy. They elaborated that prolactin is converted intraocularly into vasoinhibins, which block angiogenesis, permeability and vasodilatation by its direct action on endothelial cells and by stimulation of vascular regression mediated by apoptosis.

In our study, duration of diabetes was more than 10 years in patients with retinopathy. We suggested that abnormally high blood sugar in these diabetic patients is an important risk factor for this complication. Diabetes duration independent of blood glucose level was the main factor responsible for retinopathy[16]. In our study we found that HbA_{1C} was significantly higher in retinopathy group compared to non-retinopathy group. Such results run in parallel with those reported by Bonakdaran et al[15]. Our results also showed that high cholesterol level is not a predictor of retinopathy because there were non-significant changes between diabetic patients and healthy controls. In the light of the previously published strong evidences connecting prolactin-derived vasoinhibins against the development and progression of diabetic retinopathy[15-20], our results may point to discordance between levels of prolactin as a hormone and its vasoinhibins - if reproducible on larger scale multi-centric studies.

Conclusion

Plasma prolactin does not correlate with the extent, type and severity of diabetic retinopathy and may not have a role in its development, whereas, glycemic control indices and disease duration may have the salient role in its development and/or progression.

Limitations of the Study

- Although we included all the voluntarily participating diabetic patients in our medical center, the sample size was small particularly upon subgrouping within the short study time.
- We wished if we could have afforded measuring the prolactin-derived vasoinhibins along with the hormone.

Conflict of Interest: The authors declared no conflict of interests.

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