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Plasma and vitreous selenium concentrations in patients with type 2 diabetes and diabetic retinopathy

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Abstract

Background: This work aimed to determine and compare plasma and vitreous selenium (Se) concentrations in patients with type 2 diabetes and diabetic retinopathy (DR).

Methods: A total of 60 type-2-diabetes patients including 20 without DR, 20 with non-proliferative DR (NPDR), and 20 with proliferative diabetic retinopathy (PDR), were involved in this study. Blood plasma samples were collected from above 60 patients and 20 normal controls (without diabetes). Twenty control vitreous samples were obtained from the eyes presenting a macular hole and epimacular membrane. Vitreous samples were also collected from PDR patients receiving one-week intravitreal anti-VEGF therapy or not. Plasma and vitreous Se concentrations were determined by inductively coupled plasma mass spectrometry.

Results: Plasma Se concentrations in PDR patients (163.74 ± 32.68 μg/L) were significantly higher than those in normal control patients (121.59 ± 28.33 μg/L), NPDR patients (130.34 ± 29.11 μg/L), and the patients without DR (81.23 ± 20.59 μg/L) (all $P < .001$). Similarly, Se concentrations in vitreous samples of PDR patients (56.30 ± 12.03 μg/L) were consistently higher than those in control vitreous samples (26.26 ± 6.53 μg/L). In addition, vitreous Se concentrations in PDR patients decreased to 47.76 ± 9.72 μg/L after intravitreal injection of the anti-VEGF drug ranibizumab for one week, which was significantly lower than those before injection ($P = .02$). Plasma VEGF levels of diabetic patients were lower than those of the normal controls ($P < .001$). On the contrary, the vitreous VEGF level in the PDR group (913.61 ± 193.32 pg/mL) was significantly higher than that of the normal control group (101.23 ± 21.33 pg/mL) ($P < .001$).

Conclusion: The elevation of Se concentrations may be an important risk factor in plasma and vitreous with diabetic retinopathy among type-2-diabetes patients. The elevated VEGF may be also closely related to the intraocular Se concentration in PDR patients.

Abbreviations: DR = diabetic retinopathy, NPDR = non-proliferative DR, PDR = proliferative diabetic retinopathy, Se = selenium, VEGF = vascular endothelial growth factor.

Keywords: diabetic retinopathy, ICP-MS, selenium, VEGF, vitreous

1.Introduction

Selenium (Se) is an essential trace mineral of significant importance in human health and serves as a key component of selenoproteins required for various metabolic and antioxidant functions. Enshi prefecture in the west of Hubei province of China is famous as a Se-rich region globally.[1] Mounting studies have proved that Se plays a crucial role in a range of diseases such as Keshan disease, prostate cancer, hyperthyroidism, and cardiovascular disorders.[2] Given its important role in the human body, colleagues in our lab have done some work on Se in its presence in some diseases.[3] It has been suggested that lower Se concentration may be implicated in the weak immune system and increase the risk of mortality in patients with coronary heart disease or myocardial fibrosis.[4]

Moreover, it has recently been discovered that Se could promote glucose transport and interfere with glucose metabolism, exerting an insulin-mimetic effect.[5–8] As a result, the relationship between Se and diabetes has attracted continuous attention in recent years. Intriguingly, inconsistent findings have been reported on the relationship in several studies. It is previously reported that lower Se concentration was related

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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to the onset of type 2 diabetes.[9–11] On the contrary, some studies have pointed out that the plasma or serum Se concentrations of diabetic patients are significantly higher than the normal population.[12,13] Meanwhile, some researchers have focused on the relationship between Se and ocular surface disease, cataracts, and thyroid-related eye disease.[14] To date, no previous research has investigated the role of Se in diabetic retinopathy (DR).

Here, we in this research determined and compared Se concentrations in blood plasma and vitreous body of DR patients of varying severity for a primary exploration.

2.Materials and Methods

2.1.Study participants

This study was approved by the Ethics Committee of the Minda Hospital Affiliated to Hubei University for Nationalities (Enshi, China) and was conducted according to the principles outlined in the Declaration of Helsinki. Clinical characteristics including age, gender, weight, height, and levels of fasting blood glucose and glycosylated hemoglobin were all obtained from the medical information recorded by the departments of endocrinology and ophthalmology of the Minda Hospital from June 2019 to April 2020. According to the international diagnostic criteria for type 2 diabetes and the results of fundus photography and fluorescein angiography, the diabetic patients were divided into the non-DR group (n = 20), non-proliferative DR (NPDR) group (n = 20) and proliferative DR (PDR) group (n = 20).[15,16] Written informed consent was obtained from all included participants.

2.2.Collection of plasma and vitreous samples

All subjects fasted for at least 8 h at night before blood collection. A total of 5 mL of peripheral venous blood was taken from each participant at 8 AM. the following day. Collection tubes with ethylenediamine tetraacetic acid were used to prevent clotting of the blood samples. After centrifugation at 3000 r/minute at 4°C for 10 minute, the supernatant was stored in a sealed EP tube in a refrigerator at −80°C for later analyses. Vitreous samples from control eyes with a macular hole and epimacular membrane (n = 20), and from PDR patients without anti-VEGF (vascular endothelial growth factor) treatment (n = 20) were obtained through vitrectomy. Vitreous samples from PDR patients receiving one-week intravitreal anti-VEGF treatment (using ranibizumab) (n = 20) were taken through vitrectomy. About 0.25 to 0.35 mL of vitreous humor was extracted before irrigation. Collected samples mixed with blood were centrifuged to obtain the supernatant for determination. All samples were stored in sealed EP tubes at −80°C for later analyses.

2.3.Determination of plasma and vitreous se concentrations

Plasma and vitreous Se concentrations were determined by the Thermo Scientific™ iCAP™ RQ ICP-MS (inductively coupled plasma mass spectrometry). This real-time trace element analyzer is characterized by fast detection speed, wide linear range, high sensitivity, and strong specificity; its quantification for samples with particularly low content of trace elements can be done even at the nanogram level.[17–19] Briefly, the samples were completely thawed at room temperature and then homogenized on a vortex mixer. Afterward, 200 µL of plasma or vitreous sample was diluted with a prepared diluent containing 65% (v/v) highly purified Triton X-100, 65% nitric acid HNO3, and purified water, to a volume of 4 mL. A prepared sample was vaporized and introduced into the nebulizer gas flow in aerosol form, and then the admitted ions were pushed to the beam axis by a radio-frequency guide field. A single collision cell technology mode with CH4 addition was used for Se determination. As proved, carbon loading could improve the sensitivity of high-ionization potential analytes, and the application of methane gas in plasma could give a sensitivity increase of seven folds for selenium.[20] The results of Se concentration were expressed as µg/L.

2.4.Determination of vitreous and plasma VEGF levels

VEGF levels in vitreous and plasma samples were determined using a commercial enzyme-linked immunoassay kit according to the manufacturer's instructions. Optical density was read at 450 nm using a microplate reader (SpectraMax Gemini UVmax; Molecular Devices). The VEGF level of each sample was calculated from the standard curve, and the result was expressed as pg/mL.

2.5.Statistical analysis

All data were analyzed using GraphPad Prism 8.0 software (GraphPad Software, San Diego). The measurement data were expressed as mean ± standard deviation (SD). Differences between the two groups were analyzed using the paired or unpaired *t* test. Comparisons between more than two groups were performed using a one-way analysis of variance with a Bonferroni post hoc test. *P* values < .05 were considered statistically significant.

3.Results

3.1.Clinical data

The baseline clinical and ocular characteristics of the participants are presented in Table 1. There were no significant differences in age, body mass index, and level of fasting blood

Table 1

Clinical features of diabetes and control patients.

	Control group	Non-DR group	NPDR group	PDR group	*p*
Age, yr	59.0 ± 10.12	59.80 ± 10.18	61.80 ± 10.25	64.05 ± 10.60	.386*
Body mass index, kg/m^2	-	24.82 ± 2.84	25.03 ± 3.04	25.43 ± 2.99	.219*
Duration of diabetes, yr	-	3.45 ± 2.37	7.55 ± 3.79	13.75 ± 4.77	-
Fasting blood glucose, mmol/L	-	7.24 ± 1.96	7.46 ± 1.71	7.94 ± 2.42	.613*
HbA1c, %	-	6.94 ± 1.42	8.51 ± 2.48	9.95 ± 3.05	-
Plasma Se concentration, µg/L	121.59 ± 28.33	81.23 ± 20.59	130.34 ± 29.11	163.74 ± 32.68	.000*
Vitreous Se concentration, µg/L	26.26 ± 6.53	-	-	56.30 ± 12.03	.000**

Non-DR group = non diabetic retinopathy group, NPDR group = non-proliferative diabetic retinopathy group, PDR group = proliferative diabetic retinopathy group, Se = selenium, HbA1c = glycosylated hemoglobin.

**p* values by one-way analysis of variance for comparison among groups;

***p* values by Student's *t* test for comparison of means between cases and controls.

glucose between the control group, non-DR group, NPDR group, and PDR group. PDR patients present high HbA1c levels and long duration of type 2 diabetes as compared with other included patients, and the differences could not be excluded.

3.2.Se concentration in plasma

The included diabetic patients were randomized into three groups, non-DR group (n = 20), NPDR group (n = 20) and PDR group (n = 20). As shown in Figure 1, the plasma Se concentrations in DR patients were higher than those in non-DR patients and the normal controls. A significant difference was seen between the PDR group and the control group ($P < .001$), and between the PDR group and the non-DR group ($P = .005$) in terms of plasma Se concentration. While there was no significant difference between the NPDR group (130.34 ± 29.11 μg/L) and the control group (121.59 ± 28.33 μg/L) ($P = .19$). It could be attributed to the fact that we did not further classify NPDR patients into mild, moderate and severe groups. In addition, it suggested that the change in Se concentration was not obvious in the early stage of DR. Interestingly, there was a significant difference between non-DR patients (81.23 ± 20.59 μg/L) and the controls (121.59 ± 28.33 μg/L) ($P < .001$) (Fig. 1). There may be a U-shaped relationship between Se concentration and the presence of DR.[21] It indicates that the concentration of high or too low serum selenium may be related to the occurrence of diabetes.

3.3.Vitreous se concentration before and after anti-VEGF therapy

Since the vitreous humor of the normal controls, non-DR or NPDR patients cannot be obtained, we took the vitreous humor from the patients with a macular hole and epimacular membrane as the control for further exploration of the relationship between intravitreal Se concentration and PDR. As presented in Figure 2, vitreous Se concentration in the PDR group (56.30 ± 12.03 μg/L) was significantly higher than that in the control group (26.26 ± 6.53 μg/L) ($P < .001$). Moreover, after one-week intravitreal injection treatment with ranibizumab, vitreous Se concentrations of PDR patients (47.76 ± 9.72 μg/L) were significantly lower than before ($P = .02$). This may be attributable to our small sample volume, but there was still a significant difference between PDR patients receiving anti-VEDF treatment and the controls ($P < .001$) (Fig. 2).

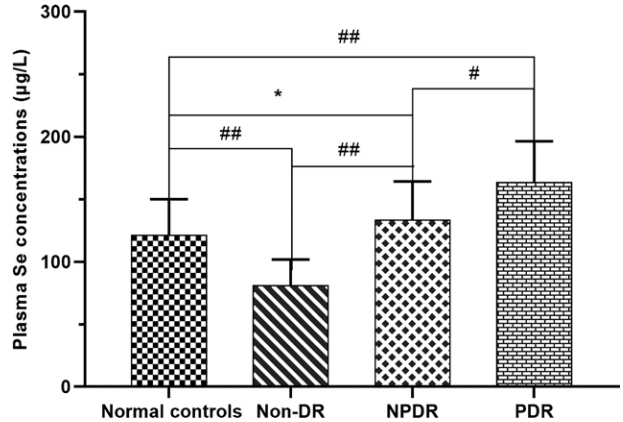

Figure 1. Comparisons between the normal control group and different groups of diabetic patients in plasma Se concentrations. PDR = proliferative diabetic retinopathy. $^{\#}P < .05$, $^{\#\#}P < .001$, $^{*}P > .05$.

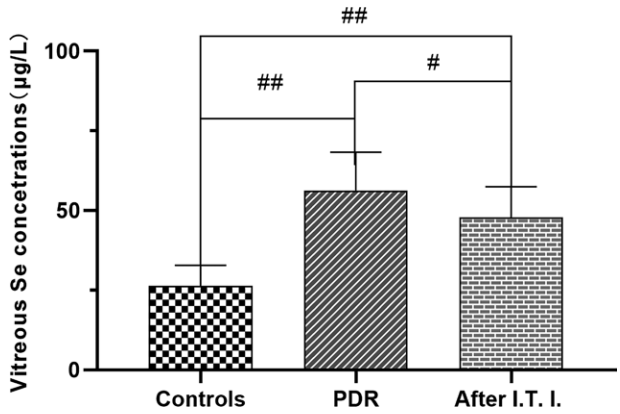

Figure 2. Comparisons in vitreous Se concentration between PDR patients without I.T.I, PDR patients after I.T.I, and healthy controls. After I.T.I. refers to the PDR patients received intravitreal injection of ranibizumab. PDR = proliferative diabetic retinopathy. $^{\#\#}P < .001$, $^{\#}P < .05$.

3.4.VEGF concentrations in vitreous and plasma

At present, many studies have pointed out that appropriate Se concentration could inhibit tumor neovascularization by reducing VEGF levels in tumor vessels and suppressing the growth of new vessels.[22] Therefore this study measured plasma and vitreous VEGF levels in each group. As shown in Figure 3A, plasma VEGF levels of diabetic patients (non-DR group: 42.00 ± 10.47 pg/mL, NPDR group: 59.95 ± 11.59 pg/ml, PDR group: 60.56 ± 13.35 pg/mL) were lower than those of the normal controls (216.88 ± 21.33 pg/mL) ($P < .001$). On the contrary, the vitreous VEGF level in the PDR group (913.61 ± 193.32 pg/mL) was significantly higher than that of the normal control group (101.23 ± 21.33 pg/mL) ($P < .001$) (Fig. 3B).

4.Discussion

Diabetes is on the rise throughout the world and accounts for an estimated 4.2 million deaths in 2019. DR is the fifth most common cause of severe vision loss and blindness worldwide; about 3.7 million cases of visual impairment and 0.83 million cases of blindness were reported to directly relate to its presence by 2010 across the globe.[23] The presence of, or the complex interactions between glucose-induced oxidative stress, inflammation, formation of advanced glycation end products, and other factors that could bring damage to the retina and blood vessels, could cause DR or determine its development. Retinal neovascularization is the main cause of blindness in DR patients, and VEGF might play a key role in the retinal microvascular complications of diabetes and represent an exciting target for therapeutic intervention in DR.[24]

Se is of fundamental importance to human health, as an essential trace mineral. A range of diseases associated with an inadequate intake of Se has been reported around the world, which has attracted abundant attention from health departments and agencies as well as relevant researchers. Increasing studies on the relationship between Se and diabetes indicate that Se plays an important role in the occurrence and progression of diabetes.[4,6,7] Se could not only exert positive effects on glucose homeostasis and decrease oxidative stress in diabetic patients owing to its antioxidant and insulin-mimetic properties, but also influence the inflammatory response in a variety of ways. It was first discovered that Se can inhibit the inflammatory response in diabetic rats.[25] Se may induce the production of interleukin and tumor necrosis factor-α by inhibiting the activation of nuclear factor-kB which controls the transcription of various genes that have roles in inflammation. One study found

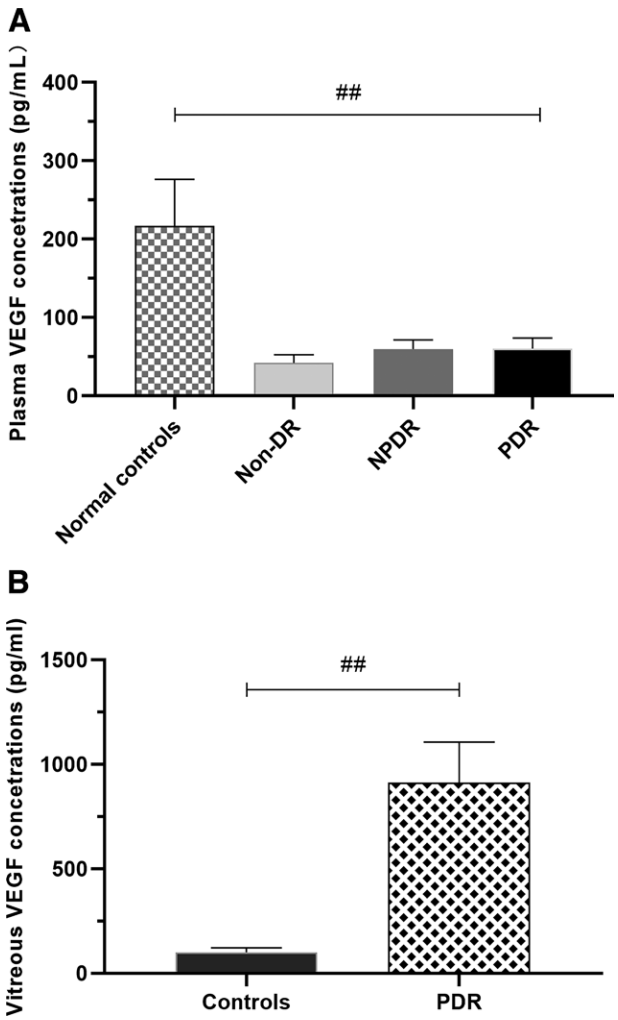

Figure 3. Comparisons between the normal control group and different groups of diabetic patients in plasma VEGF concentration (A), and comparisons between PDR patients and the controls in vitreous VEGF concentration (B). VEGF = vascular endothelial growth factor, PDR = proliferative diabetic retinopathy. $^{\#\#}P < .001$.

that Se could significantly inhibit the sprouting of aortic rings and neovessel formation on the chick embryo chorioallantoic membrane, namely, suppression of angiogenesis.[26] These effects may also be closely related to the occurrence of DR, but the relationship between Se and DR has not been reported to date.

Our study found that plasma Se concentration in DR patients was significantly higher than that in the normal controls, while lower plasma Se concentration was found in diabetic patients without retinopathy as compared with normal controls. Some scholars believe that plasma Se concentration may be related to the level of fasting blood glucose.[4] However, in our study, there was no significant difference in fasting blood glucose level between the diabetic groups, and the effect of fasting blood glucose on plasma Se concentration was ruled out. We also found that the more severe the retinopathy of diabetic patients, the higher the plasma Se concentration. A number of studies have found that the activity of glutathione peroxidases is directly related to plasma Se concentration.[27] This may be due to the stimulation of the activity of glutathione peroxidases by various factors in the aggravation of DR. Some studies reported that higher plasma Se concentration was positively correlated with the prevalence of diabetes, which was similar to these findings.[12,13] We speculate that a larger proportion of DR patients in the selected diabetic subjects could explain the correlation. Diabetes generally comes without DR in the early stage, but with the concomitant presence of lower plasma Se concentration, which may be associated with the involvement of selenoproteins in the depletion of complex oxidative stress and the antioxidant enzymes.[28] Studies found that serum Se concentration was low in patients with gestational diabetes and this population usually rarely has obvious DR, which is consistent with our results about diabetic patients without DR.[29] In our study, the plasma Se concentration of normal people reached 121.59 ± 28.33 μg/L, which was much higher than the average level of normal people in other regions. For instance, serum Se concentration of healthy adults in Europe ranged from 50.22 to 145.29 μg/L, and that of most subjects was lower than the average concentration (78.96 μg/L).[5,30] Studies from the United States have suggested that people with a serum or plasma Se concentration below 122 μg/L may require Se supplements, and Se concentration in the range of 130 to 150 μg/L would be of great benefit.[4,30,31]

Interestingly, the study detected the vitreous Se concentration of PDR patients. Results showed that vitreous Se concentration was much lower than plasma, which was consistent with the findings from other studies that Se concentration in aqueous fluid and semen was much lower than that in plasma.[4,14] It may be due to the loss or absence of selenoproteins or special protein carriers which serves for passing through the blood-ocular barrier to the vitreous body. The elevation of Se concentration in the vitreous body may be associated with the increased activity of glutathione peroxidases (GPX) stimulated by VEGF. In this study, vitreous Se concentration decreased after intravitreal injection of the anti-VEGF drug, which indicates that vitreous selenoproteins activity or Se content may be related to the stimulation of VEGF. We also found that plasma VEGF level in diabetic patients, especially in PDR subjects, was lower than that in the controls, which may be related to the lesions of and the adhesion to endothelial cells. A Higher VEGF level in the vitreous body indicates a higher VEGF level in the retina. Similarly, lower VEGF level in plasma appears with higher VEGF content in endothelial cells owing to its increased adhesion to injured endothelial cells in diabetes.[24] Recently, the formation in intraocular neovascularization might be closely related to regulatory T cells.[32] Another study pointed out that selenium GPX4 might play an important role in maintaining T cell homeostasis via inhibiting lipid peroxidation.[3] These studies indicated that Se or selenoproteins might have a close connection with VEGF in the relevant potential mechanisms in our research.

To summarize, this study found that DR patients have higher Se concentration in plasma and vitreous humor than normal people. The downtrend in vitreous Se concentration after intravitreal anti-VEGF treatment in the patients may be associated with the stimulation of the activity of selenoproteins by VEGF, which indicates that higher Se concentration may be a risk factor for the development or progression of DR. There may be a U-shaped relationship between Se concentration and the presence of DR. It would be helpful to know how exactly Se concentration interacts with the development or progression of DR among diabetic patients. It suggested that DR might have a potential new mechanism mediated by Se or selenoproteins. The related mechanism of Se underlying the effects on DR requires further research.

Author contributions

Conceptualization: Chunmiao Wang, Ruijin Ran.
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Formal analysis: Xiaohong Zhu.
Funding acquisition: Ruijin Ran.
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Validation: Chunmiao Wang.
Visualization: Chunmiao Wang.
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Writing – review & editing: Ruijin Ran.

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