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Correlation of anxiety state with blood glucose control, microinflammation and oxidative stress in patients with type 2 diabetes mellitus

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ABSTRACT

Objective: To study the correlation of anxiety state with blood glucose control, microinflammation and oxidative stress in patients with type 2 diabetes mellitus. **Methods:** A total of 138 patients with type 2 diabetes mellitus were divided into the non-anxiety group (n=43) (SAS score < 50 points), mild-to-moderate anxiety group (n=71) (SAS score 50-69 points) and severe anxiety group (n=24) (SAS score 70 points) according to the self-rating anxiety scale (SAS) score. The differences in levels of glucose metabolism indexes, microinflammation indexes and oxidative stress indexes were compared among the three groups. **Results:** Peripheral blood FPG, P2hPG, HOMA-IR, CRP, ASAA, IL-6, MDA and ROS levels of mild-to-moderate anxiety group and severe anxiety group were higher than those of non-anxiety group while CAT and GSH-Px contents were lower than those of non-anxiety group; peripheral blood FPG, P2hPG, HOMA-IR, CRP, ASAA, IL-6, MDA and ROS levels of severe anxiety group were higher than those of mid-to-moderate anxiety group while CAT and GSH-Px contents were lower than those of mid-to-moderate anxiety group. **Conclusion:** The increase of anxiety in patients with type 2 diabetes mellitus is a direct factor leading to the abnormal glucose metabolism as well as the aggravation of microinflammatory state and oxidative stress state.

1. Introduction

Anxiety is one of the important complications in patients with type 2 diabetes, statistical studies have shown that the incidence is up to 11%-60%, and severe anxiety is thought to be the direct factor leading to poor metabolic control and disease outcome[1,2]. At present, the treatment of type 2 diabetes mellitus mainly focuses on the choice of hypoglycemic drugs, diet and exercise control, etc., but pays less attention to the patients' emotional state and intervention. The direct link between anxiety and the condition of diabetic patients is not yet conclusive and is also one of the reasons why clinical psychological intervention of such patients is difficult to be implemented. In the study, the existence and severity of anxiety were used as the grouping criteria to judge the influence of anxiety on the glucose metabolism, microinflammation and oxidative stress in patients with type 2 diabetes mellitus, now reported as follows.

2. Information and methods

2.1 General information

A total of 138 patients with type 2 diabetes mellitus who were treated in the hospital between September 2015 and February 2017 were selected as research subjects, the anxiety state was evaluated by self-rating anxiety scale (SAS), and the SAS score was referred to divide the patients into the non-anxiety group (n=43) (SAS score < 50 points), mild-to-moderate anxiety group (n=71) (SAS score 50-69 points) and severe anxiety group (n=24) (SAS score ⩾70

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points). Non-anxiety group included 25 men and 18 women that were 49-71 years old; mild-to-moderate anxiety group included 38 men and 33 women that were 45-74 years old; severe anxiety group included 14 men and 10 women that were 47-75 years old. The differences in the gender and age distribution were not significant among the three groups, the follow-up data were comparable, and the hospital ethics committee approved the study.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) meeting the diagnostic criteria for clinical type 2 diabetes mellitus; (2) regularly accepting drug therapy for ⩾6 months; (3) cooperating with the whole examination and with complete clinical data. Exclusion criteria: (1) with basic anxiety or anxiety disorders prior to diagnosis of type 2 diabetes; (2) combined with inflammatory diseases of other tissue organs; (3) combined with hyperthyroidism, thyroidism, pheochromocytoma and other endocrine diseases; (4) combined with basic severe heart, liver and kidney injury.

2.3 Glucose metabolism indexes

Immediately after admission, 1.0 mL of morning (around 7:00 am) fasting cubital venous blood and 1.0 mL of 2 h venous blood were extracted from two groups of patients, and automatic biochemical analyzer (Japanese Toshiba Medical Systems Corporation, model TBA-120FR) was used to determine glucose metabolism index levels, including fasting plasma glucose (FPG), 2 h postprandial blood glucose (P2hPG) and insulin resistance index (HOMA-IR).

2.4 Microinflammation and oxidative stress indexes

Immediately after admission, peripheral blood was obtained from two groups of patients at the same time point, anti-coagulated and centrifuged at low speed to get the upper serum, which was frozen in -80 ℃ environment. Enzyme linked immunosorbent assay (ELISA) was used to determine serum levels of microinflammation indexes, including C-reactive protein (CRP), acute phase serum amyloid A (ASAA) and interleukin-6 (IL-6). ELISA was used to determine the contents of oxidative stress indexes in serum, including malonaldehyde (MDA), reactive oxygen species (ROS), catalase (CAT) and glutathione peroxidase (GSH-Px).

2.5 Statistical processing

Statistical software was SPSS 24.0. Glucose metabolism, microinflammation and oxidative stress indexes belonged to measurement data and were in terms of mean ± standard deviation, comparison among groups was by variance analysis and pair-wise comparison between two groups was by LSD. Statistic $P \leqslant 0.05$ indicated statistical significance in differences.

3. Results

3.1 Glucose metabolism indexes

Comparison of peripheral blood glucose metabolism indexes FPG (mmol/L), P2hPG (mmol/L) and HOMA-IR levels among three groups of patients was as follows: peripheral blood FPG, P2hPG and HOMA-IR levels of mild-to-moderate anxiety group and severe anxiety group were significantly higher than those of non-anxiety group, and peripheral blood FPG, P2hPG and HOMA-IR levels of severe anxiety group were significantly higher than those of mid-to-moderate anxiety group, shown in Table 1.

Table 1.

Comparison of peripheral blood glucose metabolism index levels among groups.

Groups	*n*	FPG	P2hPG	HOMA-IR
Non-anxiety group	43	6.28±0.73	8.74±9.52	2.17±0.25
Mild-to-moderate anxiety group	71	7.19±0.84*	9.63±1.43*	2.98±0.36*
Severe anxiety group	24	9.84±1.16*#	12.61±1.58*#	3.74±0.45*#
F		14.387	11.526	8.293
P		0.000	0.000	0.000

Note: compared with indexes of non-anxiety group, *$P<0.05$; compared with indexes of mild-to-moderate anxiety group, #$P<0.05$.

3.2 Microinflammation indexes

Comparison of serum microinflammation indexes CRP (mg/L), ASAA (μg/L) and IL-6 (pg/mL) contents among three groups of patients was as follows: serum CRP, ASAA and IL-6 contents of mild-to-moderate anxiety group and severe anxiety group were significantly higher than those of non-anxiety group; serum CRP, ASAA and IL-6 contents of severe anxiety group were significantly higher than those of mid-to-moderate anxiety group, shown in Table 2.

Table 2.

Comparison of serum microinflammation index contents among groups.

Groups	*n*	CRP	ASAA	IL-6
Non-anxiety group	43	1.09±0.17	10.38±1.74	5.82±0.74
Mild-to-moderate anxiety group	71	3.42±0.48*	14.29±2.11*	7.11±0.85*
Severe anxiety group	24	5.17±0.64*#	19.63±2.46*#	10.64±1.92*#
F		9.209	13.276	11.739
P		0.000	0.000	0.000

Note: compared with indexes of non-anxiety group, *$P<0.05$; compared with indexes of mild-to-moderate anxiety group, #$P<0.05$.

3.3 Oxidative stress indexes

Comparison of serum oxidative stress indexes MDA (μmol/L), ROS (μmol/L), CAT (U/mL) and GSH-Px (pg/mL) contents among three groups of patients was as follows: serum MDA and ROS contents of mild-to-moderate anxiety group and severe anxiety group were significantly higher than those of non-anxiety group while CAT and

Table 3.

Comparison of serum oxidative stress index contents among groups.

Groups	*n*	MDA	ROS	CAT	GSH-Px
Non-anxiety group	43	5.82±0.71	8.29±0.95	11.25±1.74	29.37±4.52
Mild-to-moderate anxiety group	71	7.95±0.86*	10.17±1.84*	8.32±0.98*	20.71±2.54*
Severe anxiety group	24	12.47±1.94*#	15.46±2.31*#	5.17±0.67*#	12.04±1.63*#
F		15.398	12.436	9.861	16.483
P		0.000	0.000	0.000	0.000

Note: compared with indexes of non-anxiety group, *$P<0.05$; compared with indexes of mild-to-moderate anxiety group, #$P<0.05$.

GSH-Px contents were significantly lower than those of non-anxiety group; serum MDA and ROS contents of severe anxiety group were significantly higher than those of mid-to-moderate anxiety group while CAT and GSH-Px contents were significantly lower than those of mid-to-moderate anxiety group, shown in Table 3.

4. Discussion

Middle-aged and elderly people are the main affected population of type 2 diabetes, and some patients do not have clear understanding about the disease causes, treatment outcome and so on, which directly leads to conflict or panic, and even anxiety in severe cases, and is not conducive to the realization of the clinical treatment effect and the optimization of patients′ quality of life[3-5]. Studies have shown that the negative emotions can increase the secretion of insulin antagonism hormone and reduce the insulin sensitivity through the hypothalamus - pituitary - target gland axis, which will exacerbate the illness of diabetes, increase the difficulty of clinical treatment, and play a negative role in the treatment of type 2 diabetes mellitus[6,7]. In this study, the SAS score was referred to group the enrolled patients with type 2 diabetes, the differences in the levels of glucose metabolism indexes were compared at first, and it was found that compared with those of non-anxiety group, FPG, P2hPG and HOMA-IR levels of patients with anxiety were higher, showing that the existence of anxiety can directly lead to the increased extent of glucose metabolism disorder; further compared with those of mild-to-moderate anxiety group, FPG, P2hPG and HOMA-IR levels of severe anxiety group were higher, indicating that the glucose metabolism disorder is aggravated as the anxiety increases, and directly confirming that anxiety is positively correlated with glucose metabolism disorder.

There is a general hidden increase in the levels of inflammatory markers in patients with type 2 diabetes, which is clinically called "microinflammation" state, and is caused by blood glucose fluctuations and insulin resistance, etc[8,9]. The long-term microinflammation state in the body can improve the endoplasmic reticulum stress system responsiveness and induce mitochondrial dysfunction, and fatty infiltration of macrophages is the characteristic of microinflammation state, and can produce proinflammatory factors such as IL-6, induce neutrophil local and secrete more inflammatory markers[10-12]. In this study, the differences in serum levels of typical inflammatory cytokines were compared between two groups of patients, and it was found that compared with those of non-anxiety group, serum CRP, ASAA and IL-6 contents of patients with anxiety were higher, showing that anxiety can induce the increase of microinflammation in patients with type 2 diabetes; further compared with those of mild-to-moderate anxiety group, serum CRP, ASAA and IL-6 contents of severe anxiety group were higher, showing that with the microinflammation state is aggravating with the increase of anxiety, and confirming that the anxiety is positively correlated with the microinflammation status in patients with type 2 diabetes.

Many studies have shown that the blood glucose fluctuation in patients with diabetes is closely related to the oxidative stress state and vascular endothelial injury, whereas the oxidative stress state in patients with diabetes can objectively reflect the status of blood glucose control and the overall severity of the illness[13,14]. MDA and ROS are typical oxidation products, which have a strong oxidative effect and are the main substances that cause the vascular endothelial injury in diabetic patients[15-17]; CAT and GSH-Px are factors that have antioxidant effects, which can neutralize oxidant factors and inhibit the aggravation of oxidative stress response[18-20]. In this study, the differences in serum levels of these oxidative stress factors were compared between two groups of patients, and it was found that compared with those of non-anxiety group, serum MDA and ROS contents of patients with anxiety were higher while CAT and GSH-Px contents were lower, indicating that anxiety is the direct cause of increased oxidation products and decreased antioxidant capacity; further compared with those of mild-to-moderate anxiety group, serum MDA and ROS contents of severe anxiety group were higher while CAT and GSH-Px contents were lower, indicating that the oxidative stress degree in patients with type 2 diabetes is aggravating with the increase of anxiety, and confirming that anxiety is positively associated with the degree of oxidative stress in patients with type 2 diabetes.

The severity of anxiety in patients with type 2 diabetes is directly related to blood glucose control, microinflammation state and oxidative stress state, intervention of the patient's anxiety is expected to become the important auxiliary means to optimize the illness and treatment outcome of type 2 diabetes, and it is worthy of popularization and application in clinical practice in the future.

References

[1] Pinna F, Diana E, Sanna L, Deiana V, Manchia M, Nicotra E, et al. Assessment of eating disorders with the diabetes eating problems survey - revised (DEPS-R) in a representative sample of insulin-treated diabetic patients: a validation study in Italy. *BMC Psychiatry* 2017; **17**(1): 262.

[2] Aragão EIS, Portugal FB, Campos MR, Lopes CS, Fortes SLCL. Different patterns of social support perceived and their association with physical (hypertension, diabetes) or mental diseases in the context of primary health care. *Cien Saude Colet* 2017; **22**(7): 2367-2374.

[3] Corathers SD, Mara CA, Chundi PK, Kichler JC. Psychosocial patient-reported outcomes in pediatric and adolescent diabetes: a review and case example. *Curr Diab Rep* 2017; **17**(7): 45.

[4] Newby J, Robins L, Wilhelm K, Smith J, Fletcher T, Gillis I, et al. Web-based cognitive behavior therapy for depression in people with diabetes mellitus: a randomized controlled trial. *J Med Internet Res* 2017; **19**(5): e157.

[5] Hilliard ME, Hagger V, Hendrieckx C, Anderson BJ, Trawley S, Jack MM, et al Strengths, risk factors, and resilient outcomes in adolescents with type 1 diabetes: results from diabetes miles youth-Australia. *Diabetes Care* 2017; **40**(7): 849-855.

[6] Levy M, Burns RJ, Deschenes SS, Schmitz N. Does social support moderate the association among major depression, generalized anxietydisorder, and functional disability in adults with diabetes. *Psychosomatics* 2017; **58**(4): 364-374.

[7] Safar ME, Gnakamene JB, Bahous SA, Yannoutsos A, Thomas F. Longitudinal study of hypertensive subjects with type 2 diabetes mellitus: overall and cardiovascular risk. *Hypertension* 2017; **69**(6): 1029-1035.

[8] Li LM, Liu X, Wang L, Wang Y, Liu X, Tian X, et al. A novel dual eigen-analysis of mouse multi-tissues' expression profiles unveils new perspectives into type 2 diabetes. *Sci Rep* 2017; **7**(1): 5044.

[9] Roberts FR, Hupple C, Norowski E, Walsh NC, Przewozniak N, Aryee KE, et al. Possible type 1 diabetes risk prediction: Using ultrasound imaging to assess pancreas inflammation in the inducible autoimmune diabetes BBDR model. *PLoS One* 2017; **12**(6): e0178641.

[10]Bouchi R, Terashima M, Sasahara Y, Asakawa M, Fukuda T, Takeuchi T, et al. Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: a pilot study. *Cardiovasc Diabetol* 2017; **16**(1): 32.

[11]Blindbæk SL, Schlosser A, Green A, Holmskov U, Sorensen GL, Grauslund J. Association between microfibrillar-associated protein 4 (MFAP4) and micro- and macrovascular complications in long-term type 1 diabetes mellitus. *Acta Diabetol* 2017; **54**(4): 367-372.

[12]El-Asrar MA, Elbarbary NS, Ismail EA, Bakr AA. Circulating angiopoietin-2 levels in children and adolescents with type 1 diabetes mellitus: relation to carotid and aortic intima-media thickness. *Angiogenesis* 2016; **19**(3): 421-431.

[13]Kim NH, Kim DL, Kim KJ, Kim NH, Choi KM, Baik SH, et al. Effects of vildagliptin or pioglitazone on glycemic variability and oxidative stress in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a 16-week, randomised, open label, pilot study. *Endocrinol Metab (Seoul)* 2017; **32**(2): 241-247.

[14]Usluo ullari B, Usluogullari CA, Balkan F, Orkmez M. Role of serum levels of irisin and oxidative stress markers in pregnant women with and without gestational diabetes. *Gynecol Endocrinol* 2017; **33**(5): 405-407.

[15]Bernardi L, Gordin D, Bordino M, Rosengard-Barlund M, Sandelin A, Forsblom C, et al. Oxygen-induced impairment in arterial function is corrected by slow breathing in patients with type 1diabetes. *Sci Rep* 2017; **7**(1): 6001.

[16]Tanko Y, Jimoh A, Ahmed A, Adam A, Ejeh L, Mohammed A, et al. Effects of selenium yeast on blood glucose and antioxidant biomarkers in cholesterol fed diet induced type 2 diabetes mellitus in wistar rats. *Niger J Physiol Sci* 2017; **31**(2): 147-152.

[17]Berbecaru-Iovan A, Stanciulescu EC, Andrei AM, Berbecaru-Iovan S, Gird CE, Dumitrescu CI, et al. Hepatoprotective effect of Syringae vulgaris flos ethanolic extracts in streptozotocin-induceddiabetes in rats. *Rom J Morphol Embryol* 2016; **57**(4): 1279-1284.

[18]Cong W, Ruan D, Xuan Y, Niu C, Tao Y, Wang Y, et al. Cardiac-specific overexpression of catalase prevents diabetes-induced pathological changes by inhibiting NF-κB signaling activation in the heart. *J Mol Cell Cardiol* 2015; **89**(Pt B): 314-325.

[19]Kresyun NV, Godlevskii LS. Superoxide dismutase and catalase activities in the retina during experimental diabetes and electric stimulation of the paleocerebellar cortex. *Bull Exp Biol Med* 2014; **158**(2): 206-208.

[20]Pahwa S, Sharma R, Singh B. Role of glutathione s-transferase in coronary artery disease patients with and without type 2 diabetes mellitus. *J Clin Diagn Res* 2017; **11**(1): BC05-BC08.