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Original Article

Liraglutide improves postprandial blood glucose, blood glucose levels, insulin resistance and physical distribution of T2DM patients with MS

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Abstract: Objective: This study aimed to investigate the efficacy of Liraglutide on insulin resistance, physical distribution and oxidative stress level in patients with type 2 diabetes mellitus (T2DM) complicated with metabolic syndrome (MS). Methods: In total, 86 patients with T2DM complicated with MS in our hospital were selected as the study subjects. The patients were divided into control group (CG) (n = 43) and research group (RG) (n = 43) in accordance with a random number table. The patients in the CG received metformin. The patients in RG received Liraglutide. Blood glucose levels, blood lipid levels, insulin resistance, physical distribution, oxidative stress levels were compared between the two groups. Results: FBG, 2hPPG and HbA1c in both groups dramatically decreased after treatment. The three measures in RG were lower than those in CG ($P < 0.05$). TG, TC and LDL-C levels reduced and HDL-C level increased. The TG, TC and LDL-C levels in CG were higher than those in RG ($P < 0.05$). HOMA-IR reduced and HOMA-β increased. The level of HOMA-IR in RG was lower than that in CG ($P < 0.05$). The level of HOMA-β was higher than that in CG ($P < 0.05$). Weight, body mass index and waistline reduced. The three measures in CG were higher than those in RG ($P < 0.05$). Urine 8-isoprostaines F2α and MDA remarkably reduced and T-AOC significantly increased compared with those before treatment. The 8-isoprostaines F2α and MDA in RG were lower than those in CG ($P < 0.05$). The level of T-AOC was higher than that in CG ($P < 0.05$). Conclusion: Liraglutide can significantly improve the postprandial blood glucose, blood glucose level, insulin resistance and physical distribution of T2DM patients with MS. Its effect may be related to the improvement of oxidative stress levels in the body.

Keywords: Liraglutide, type 2 diabetes mellitus complicated with metabolic syndrome, insulin resistance, oxidative stress, physical distribution

Introduction

Type 2 diabetes mellitus (T2DM) is a common endocrine system disease found clinically. The clinical features of T2DM are increased blood glucose levels in patients. T2DM belongs to a systemic chronic metabolic disease. Insulin resistance is an important factor leading to the onset of type 2 diabetes. Metabolic syndrome (MS) is a group of metabolic disorder syndromes, including abnormal lipid metabolism, insulin resistance, hypertension, hyperglycemia, etc. [1, 2]. T2DM is often complicated with metabolic syndrome. The two diseases often interact with each other. As a result, lipid and blood glucose metabolism disorders are caused. Insulin-producing β-cells are destroyed and their function is impaired. At the same time, vascular endothelial function is also impaired. Important organs such as the heart, brain and kidney are damaged [3, 4]. Thus, cure difficulty is increased. Therefore, T2DM combined with MS is an independent risk factor of cardiovascular and cerebrovascular diseases. How to actively and effectively control the blood glucose and lipids become a difficulty in treatment of the disease.

Oxidative stress means the synthesis and release and clearance of active-oxygen radicals are out of balance. As a result, the oxygen radical level increases. Meanwhile, body and cellular injury can be caused [5]. Relevant studies [6, 7] have shown that oxidative stress exists in

patients with T2DM complicated with MS. Liraglutide is the analogue of glucagon-like peptide-1. It has the role of stimulating insulin secretion, decreasing blood glucose and reducing blood pressure. In this study, the efficacy of Liraglutide in the treatment of T2DM complicated with MS and its effect on insulin resistance, physical distribution and oxidative stress levels were observed.

Material and methods

General information

In total, 86 T2DM patients with MS in our hospital from February 2018 to November 2018 were selected for observation, including 44 males and 42 females. The patients were 18-79 years old, with an average age of 61.95 ± 7.09 years. The mean body mass index was 31.12 ± 1.62 kg/m^2. The course of disease was 3-4 years, and the average course was 3.6 ± 0.4 years. The inclusion criteria were as follows: (1) the Diagnostic Criteria of Metabolic Syndrome formulated by International Diabetes Federation in 2005 [8] and Diagnostic Criteria of Diabetes Mellitus in the Guidelines for Prevention and Treatment of Chinese Type 2 Diabetes Mellitus (Edition 2013) [9] were met. (2) There was no contraindication for the study drug. (3) Informed consent form was signed. The exclusion criteria were shown below: (1) patients with acute and chronic complications of inflammation diabetes mellitus; (2) Patients with serious cardiovascular events within a half a year, such as myocardial infarction and cerebral infarction; (3) Patients with hypertension and blood pressure still > 180/110 mmHg after anti-hypertensive treatment; (4) Patients with severe liver and kidney dysfunction; (5) Women who were pregnant and lactating. The patients were categorized as control group (CG) and research group (RG) in accordance with a random number table, 43 patients in each group. This study has been approved by the Ethics Committee of Geriatric Hospital of Zhejiang Province.

Methods

The patients in CG were given Metformin Hydrochloride Tablets (China Associate Pharmaceutical Co., Ltd., GYZZ H44024853) 0.85 g twice daily by oral administration. The patients in RG received Liraglutide Injection (Novo Nordisk, GYZZ J20160037). The initial treatment dose was 0.6 mg once daily by subcutaneous injection. The daily dose was increased to 1.2 mg after 7 d if the patient did not feel discomfort. Meanwhile, it was adjusted in accordance with blood glucose level. The highest dose did not exceed 1.8 mg daily. Patients in both groups were given a 6-month treatment cycle.

Outcome measures

(1) Blood glucose level: fasting blood glucose (FBG) and 2 h postprandial blood glucose (2hPG) were determined with the hexokinase method before and after treatment. Glycosylated hemoglobin HbA1C was tested with high performance liquid chromatography (HPLC) (All kits were provided by Bio-Rad Laboratories). In very small amounts, the sample mixture to be separated and tested is sent into a stream of mobile phase percolating via a column. The mixture moves through the column at varying velocities and interacts with the sorbent. The time at which a specific analyte emerges from the column is termed as its retention time. The retention time is measured under specific conditions and considered as the identifying characteristic of a given analyte.

(2) Blood lipid level: fasting without solids and liquids was performed for at least 8 h before and after treatment. The fasting venous blood was extracted. Abbott AEROSET automatic biochemical analyzer was used to test the levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL-C) and low density lipoprotein (LDL-C).

(3) Insulin resistance: chemiluminescence immunoassay was adopted to measure the fasting insulin level (Bio-Rad kit). Insulin resistance index (HOMA-IR) = 20× fasting blood glucose * fasting insulin/22.5. Insulin β cell function index (HOMA-β) = Fasting insulin *20/(Fasting blood glucose-3.5).

(4) Physical distribution: body Weight, body mass index (BMI) and waistline were measured before and after treatment. The formula for BMI is weight in kilograms divided by height in meters squared.

Table 1. Comparison of clinical data

Group	*n*	Gender n/% Males	Females	Age (years)	(Body mass index) (kg/m^2)	Duration of diabetes mellitus (years)
Research group	43	23 (69.05)	20 (30.95)	62.17 ± 7.22	31.18 ± 1.53	3.3 ± 0.6
Control group	43	21 (71.43)	32 (28.57)	61.83 ± 7.65	31.06 ± 1.71	3.5 ± 0.5
t			3.44	5.76	11.23	5.21
P			< 0.05	< 0.05	< 0.05	< 0.05

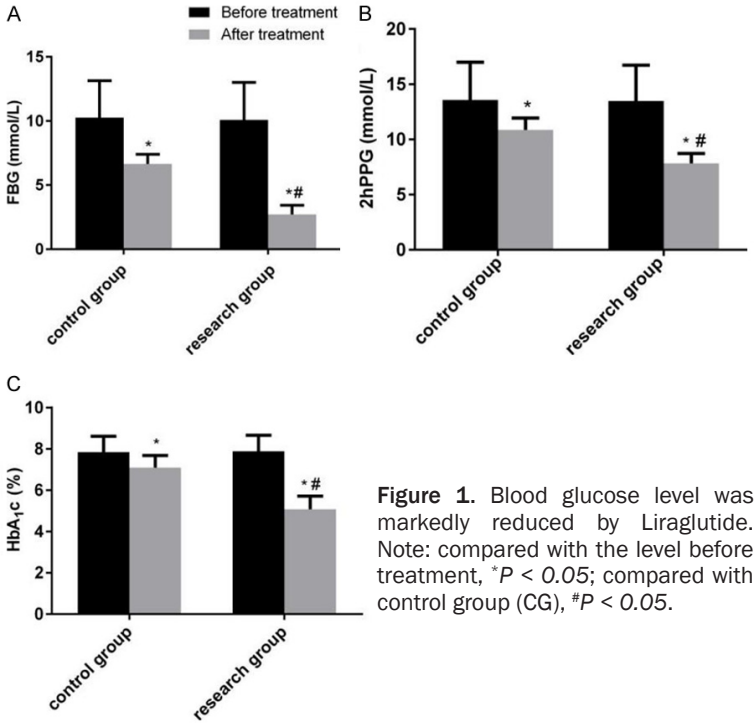

Figure 1. Blood glucose level was markedly reduced by Liraglutide. Note: compared with the level before treatment, $^{*}P < 0.05$; compared with control group (CG), $^{\#}P < 0.05$.

(5) Oxidative stress: enzyme-linked immunosorbent assay was introduced to determine urine 8-isoprostanes F2α (kit was provided by R&D Company).

Statistical analysis

SPSS 19.0 was used to analyze the data obtained in this study. The measurement data was analyzed by t test. The figures were plotted with Graphpad prism 8. The enumeration data was analyzed by χ^2 test. $P < 0.05$ implied significant difference.

Results

The general information was not different between the two groups

There were 23 males and 20 females in the RG, and 21 males and 32 females in the CG, which showed no significant difference. The clinical data of mean age, body mass index and duration of diabetes mellitus were 62.17 ± 7.22 years, 31.18 ± 1.53 kg/m^2 and 3.3 ± 0.6 years, respectively in RG; and 61.83 ± 7.65 years, 31.06 ± 1.71 kg/m^2 and 3.5 ± 0.5 years, respectively in CG, which showed no significant differences (**Table 1**).

The reduction of blood glucose level by liraglutide

Before treatment, the levels of FBG, 2hPPG and HbA1c in both groups were not significantly different ($P > 0.05$). FBG, 2hPPG and HbA1c in both groups dramatically decreased after treatment. The three measures in RG were lower than those in CG ($P < 0.05$). This indicated that Liraglutide can significantly reduce the level of blood glucose compared to metformin (**Figure 1**).

Liraglutide reduces the levels of blood lipid

Before treatment, the levels of TG, TC and LDL-C in both groups were not significantly different ($P > 0.05$). TG, TC and LDL-C in both groups remarkably decreased and HDL-C increased after treatment. The former three measures in the RG group were lower than those in CG after treatment ($P < 0.05$). The HDL-C level was higher than that in CG ($P < 0.05$). This implied that Liraglutide can clearly reduce the level of blood lipid compared with metformin (**Figure 2**).

Liraglutide improves insulin resistance

Before treatment, the levels of HOMA-IR in both groups was not significantly different ($P > 0.05$). HOMA-IR in both groups reduced and HOMA-β increased after treatment ($P < 0.05$). HOMA-IR

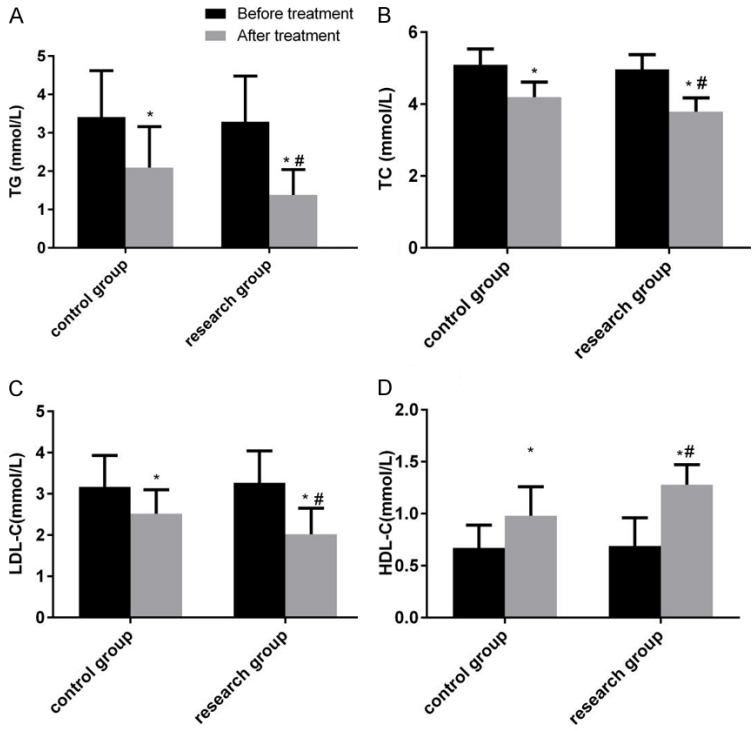

Figure 2. The blood lipid level was observably reduced by Liraglutide. Note: compared with the level before treatment, $^{*}P < 0.05$. Compared with CG, $^{\#}P < 0.05$.

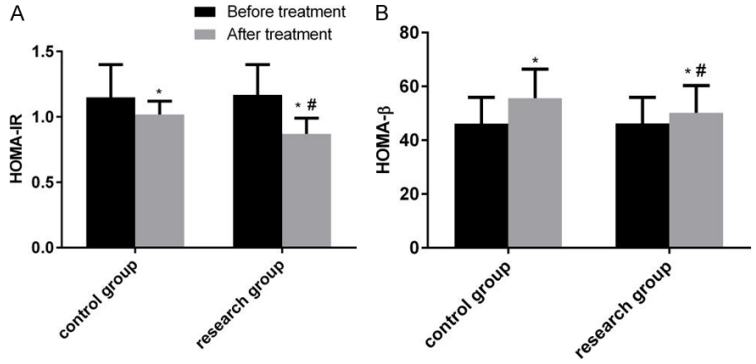

Figure 3. The insulin resistance status was remarkably improved by Liraglutide. Note: compared with the status before treatment, $^{*}P < 0.05$. $^{\#}P < 0.05$ compared to CG.

in RG after treatment was lower than that in CG ($P < 0.05$). HOMA-β after treatment was higher than that in CG ($P < 0.05$). This suggested that Liraglutide can clearly improve insulin resistance (**Figure 3**).

Liraglutide improves the physical distribution of body mass

Before treatment, the levels of weight, body mass index and waistline in both groups were not significantly different ($P > 0.05$). Weight, body mass index and waistline in both groups decreased after treatment. The three measures in CG were higher than those in RG ($P < 0.05$). This implied that Liraglutide can markedly improve the physical distribution of body mass (**Figure 4**).

Liraglutide improves oxidative stress levels

Before treatment, the levels of urine 8-isoprostanes F2α and MDA in both groups were not significantly different ($P > 0.05$). The levels of urine 8-isoprostanes F2α and MDA in both groups decreased and T-AOC level increased after treatment ($P < 0.05$). The levels of urine 8-isoprostanes F2α and MDA in RG after treatment were lower than those in CG ($P < 0.05$). The level of T-AOC after treatment was higher than that in CG ($P < 0.05$). It indicated that Liraglutide can remarkably improve the oxidative stress level (**Figure 5**).

Discussion

Many factors are involved the progress of T2DM, including genetic factors and environmental factors. The clinical manifestations are elevated blood glucose and insulin resistance [10, 11]. In recent years, with the aging of the population in China, the incidence of T2DM complicated with MS is increasing. It seriously endangers the health of patients. Although intensive drug therapy is given to the patients with T2DM complicated with MS, the central obesity, hypertension and other abnormal conditions are still likely to cause cardiovascular disease [12, 13]. Meanwhile, oxidative stress exists in T2DM patients with MS. Excessive free radicals are produced. It leads to biological film lipid peroxidation, enzyme denaturation,

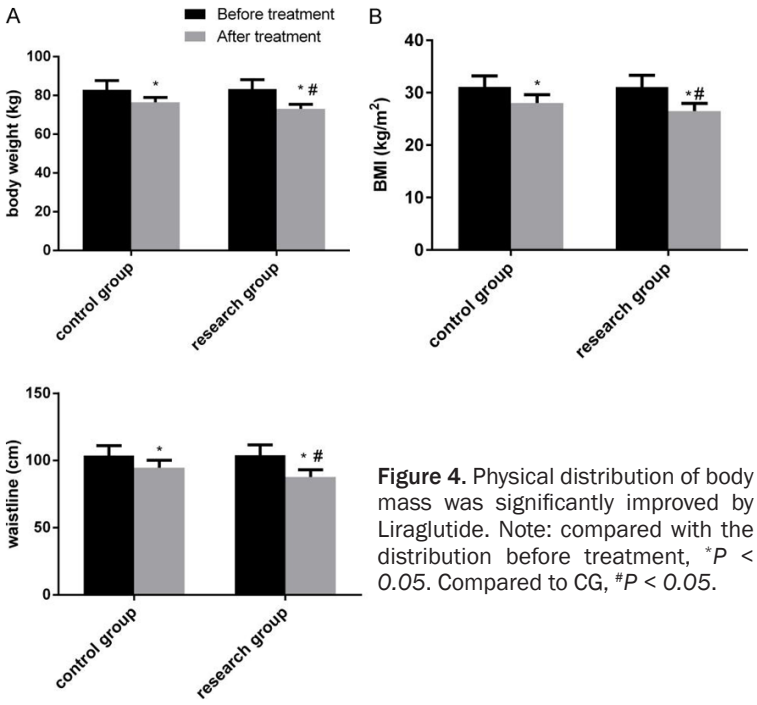

Figure 4. Physical distribution of body mass was significantly improved by Liraglutide. Note: compared with the distribution before treatment, $^{*}P < 0.05$. Compared to CG, $^{\#}P < 0.05$.

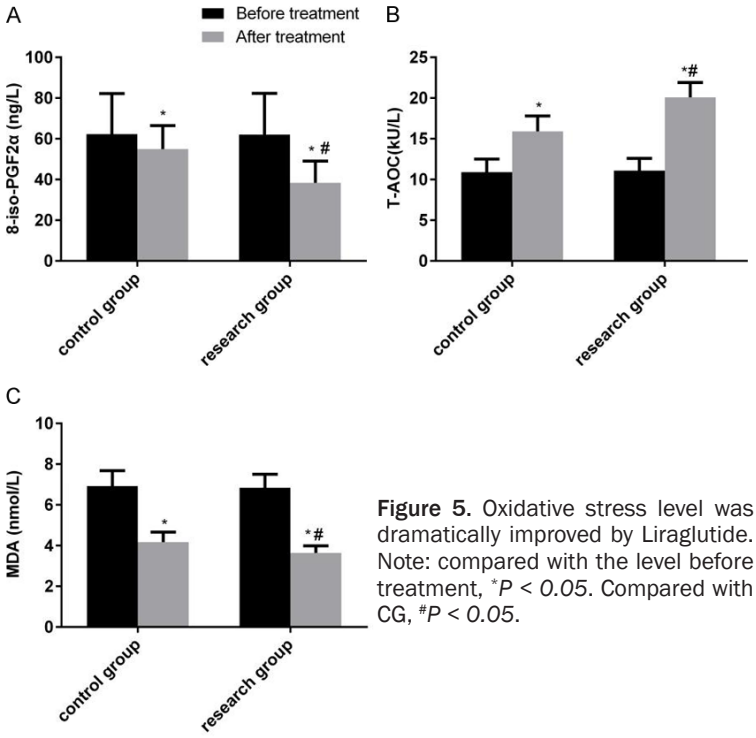

Figure 5. Oxidative stress level was dramatically improved by Liraglutide. Note: compared with the level before treatment, $^{*}P < 0.05$. Compared with CG, $^{\#}P < 0.05$.

etc. As a result, cell damage and death is caused [14-16]. Therefore, improvement of patient's physical distribution, control of blood glucose, improvement of insulin function, alleviation of oxidative stress in clinical treatment are of great significance for control of disease progression of T2DM complicated with MS. In this study, Liraglutide was used for treatment of patients with T2DM and MS. The results showed that Liraglutide can remarkably improve the postprandial blood glucose, blood lipid levels, insulin resistance and physical distribution of body mass. The mechanism may be related to the improvement of oxidative stress levels in patients.

Liraglutide belongs to an analogue obtained by modifying glucagon-like peptide. It can stimulate insulin synthesis and release, regulate glucagon production and control blood glucose fluctuation [17, 18]. However, the specific mechanism has not been clearly elucidated. The effects of Liraglutide, including losing weight, controlling blood glucose, etc. may be related to delaying gastric emptying, increasing satiety and inhibiting the feeding center of thalamus. In this study, the patients in RG were treated with Liraglutide. The patients in CG were given metformin. The results showed that 2hPPG in RG was lower than that in CG. The improvement of HOMA-IR and HOMA-β was more apparent in RG than in CG. This result is consistent with the previous study [19]. It indicated that Liraglutide can better improve insulin resistance, enhance the islet cell function and control postprandial blood glucose and blood lipid level. Our study showed that the weight, body mass index and waistline in RG were lower than those in CG after treatment. It implied that Liraglutide can improve physical distribution of the body, reduce weight and reduce the waistline of patients with T2DM and

MS. The result is consistent with previous studies [20, 21].

Oxidative stress means the excessive production or reduced loss of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in body. It results in the abnormal increase of free radicals and biological membrane lipid peroxidation. Furthermore, denaturation of intracellular proteins and enzymes, DNA damage and death or apoptosis of cells occur. T-AOC and MDA are important indexes. They indirectly reflect the level of oxidative stress in vivo [22, 23]. MDA is the toxic end product during oxidative stress reactions. Its levels can reflect the severity of free radical imbalance in body cells. T-AOC can reflect the number of known and unknown antioxidants in bodily fluids. It can evaluate the body's antioxidant activity overall. Isoprostanes F2 is a prostaglandin F2 isomer. It can promote the decomposition of oxygen radicals and reduce tissue injury. Urine 8-isoprostanes F2α is an important component of isoprostanes F2. It can directly reflect the degree of oxidative stress [24]. Additional study has found that [25, 26] the high glucose state in diabetes mellitus patients can promote the production of more superoxide anion and excessive ROS by the mitochondria. When the body's scavenging activity is exceeded, ROS can active signal transduction cascade pathways and transcription factors. The glycosylation end product pathway, polyalcohol pathway, hexosamine bypass and protein kinase C (PKC) pathway are activated. It results in oxidative stress injury and intracellular proteins, membrane lipid and nucleic acid damage. Thus, cell death is caused. The study showed that the levels of urine 8-isoprostanes F2α and MDA in RG are significantly reduced after treatment. T-AOC level remarkably increased. The improvement of all measures was better in RG than that in CG. It implied that Liraglutide can alleviate the oxidative stress, reduce the levels of urine 8-isoprostanes F2α and MDA, improve the activity of 8-isoprostanes F2α and MDA and promote the overall antioxidant capacity of patients with T2DM and MS. However, due to the small sample size and short treatment time, the long-term effect of Liraglutide in patients with T2DM complicated with MS and the outcome of cardiovascular improvement still need to be observed by expanding the sample size.

In summary, Liraglutide can remarkably improve the postprandial blood glucose, insulin resistance, physical distribution and oxidative stress of patients with T2DM and MS.

Disclosure of conflict of interest

None.

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References

[1] Lira Neto JC, Xavier MA, Borges JW, Araújo MF, Damasceno MM and Freitas RW. Prevalence of metabolic syndrome in individuals with type 2 diabetes mellitus. Rev Bras Enferm 2017; 70: 265-270.

[2] Nsiah K, Shang VO, Boateng KA and Mensah FO. Prevalence of metabolic syndrome in type 2 diabetes mellitus patients. Int J Appl Basic Med Res 2015; 5: 133-8.

[3] Koopman ADM, Rauh SP, van't Riet E, Groeneveld L, van der Heijden AA, Elders PJ, Dekker JM, Nijpels G, Beulens JW and Rutters F. The association between social Jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the new hoorn study. J Biol Rhythms 2017; 32: 359-368.

[4] Merone L and McDermott R. Nutritional anti-inflammatories in the treatment and prevention of type 2 diabetes mellitus and the metabolic syndrome. Diabetes Res Clin Pract 2017; 127: 238-253.

[5] Chen Z, Zhao GH, Zhang YK, Shen GS, Xu YJ and Xu NW. Research on the correlation of diabetes mellitus complicated with osteoporosis with lipid metabolism, adipokines and inflammatory factors and its regression analysis. Eur Rev Med Pharmacol Sci 2017; 21: 3900-3905.

[6] Yao K, Bian C and Zhao X. Association of polycystic ovary syndrome with metabolic syndrome and gestational diabetes: aggravated complication of pregnancy. Exp Ther Med 2017; 14: 1271-1276.

[7] Kornicka K, Houston J and Marycz K. Dysfunction of mesenchymal stem cells isolated from metabolic syndrome and type 2 diabetic patients as result of oxidative stress and autophagy may limit their potential therapeutic use. Stem Cell Rev 2018; 14: 337-345.

[8] Zimmet P, M M Alberti KG and Serrano Ríos M. [A new international diabetes federation world-

wide definition of the metabolic syndrome: the rationale and the results]. Rev Esp Cardiol 2005; 58: 1371-6.
[9] Gahagan S and Silverstein J; American Academy of pediatrics committee on native American Child Health; American academy of pediatrics section on endocrinology. Prevention and treatment of type 2 diabetes mellitus in children, with special emphasis on American Indian and Alaska native children. American academy of pediatrics committee on native American Child Health. Pediatrics 2003; 112: e328.
[10] Li HX, Han SY, Wang XW, Ma X, Zhang K, Wang L, Ma ZZ and Tu PF. Effect of the carthamins yellow from Carthamus tinctorius L. on hemorheological disorders of blood stasis in rats. Food Chem Toxicol 2009; 47: 1797-802.
[11] Roy C, Tremblay PY and Ayotte P. Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature. Environ Res 2017; 156: 747-760.
[12] Katsoulis K, Paschou SA, Hatzi E, Tigas S, Georgiou I and Tsatsoulis A. TCF7L2 gene variants predispose to the development of type 2 diabetes mellitus among individuals with metabolic syndrome. Hormones (Athens) 2018; 17: 359-365.
[13] Shinkov A, Borissova AM, Kovatcheva R, Vlahov J, Dakovska L, Atanassova I and Petkova P. Increased prevalence of depression and anxiety among subjects with metabolic syndrome and known type 2 diabetes mellitus-a population-based study. Postgrad Med 2018; 130: 251-257.
[14] Meijnikman AS, De Block CEM, Verrijken A, Mertens I and Van Gaal LF. Predicting type 2 diabetes mellitus: a comparison between the FINDRISC score and the metabolic syndrome. Diabetol Metab Syndr 2018; 10: 12.
[15] Yang J, Han R, Chen M, Yuan Y, Hu X, Ma Y, Wu M, Zhang X, Wang M, Jiang S and Pan F. Associations of estrogen receptor alpha gene polymorphisms with type 2 diabetes mellitus and metabolic syndrome: a systematic review and meta-analysis. Horm Metab Res 2018; 50: 469-477.
[16] Davies MJ, Merton KW, Vijapurkar U, Balis DA and Desai M. Canagliflozin improves risk factors of metabolic syndrome in patients with type 2 diabetes mellitus and metabolic syndrome. Diabetes Metab Syndr Obes 2017; 10: 47-55.
[17] Lacobellis G, Mohseni M, Bianco SD and Banga PK. Liraglutide causes large and rapid epicardial fat reduction. Obesity (Silver Spring) 2017; 25: 311-316.
[18] Hu SY, Zhang Y, Zhu PJ, Zhou H and Chen YD. Liraglutide directly protects cardiomyocytes against reperfusion injury possibly via modulation of intracellular calcium homeostasis. J Geriatr Cardiol 2017; 14: 57-66.
[19] Chen P, Huang Q, Xu XJ, Shao ZL, Huang LH, Yang XZ, Guo W, Li CM and Chen C. The effect of liraglutide in combination with human umbilical cord mesenchymal stem cells treatment on glucose metabolism and beta cell function in type 2 diabetes mellitus. Zhonghua Nei Ke Za Zhi 2016; 55: 349-54.
[20] Gao DM and Bao SDJJoHMU. Regulating effect of liraglutide therapy on metabolic disorders in patients with newly diagnosed type 2 diabetes complicated with obesity. 2017; 23.
[21] Rigato M and Fadini GP. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. Diabetes Metab Syndr Obes 2014; 7: 107-20.
[22] Qiao Y, Sun J, Ding Y, Le G and Shi Y. Alterations of the gut microbiota in high-fat diet mice is strongly linked to oxidative stress. Appl Microbiol Biotechnol 2013; 97: 1689-97.
[23] Fan WT, Zhao XN, Cheng J, Liu YH and Liu JZ. Oxidative stress and hepatocellular injury induced by oral administration of Cr(3+) in chicken. J Biochem Mol Toxicol 2015; 29: 280-7.
[24] Tang WHW, Mcgee P, Lachin JM, Li DY, Hoogwerf B and Hazen SL; DCCT/EDIC Research Group. Oxidative stress and cardiovascular risk in type 1 diabetes mellitus: insights from the DCCT/EDIC study. J Am Heart Assoc 2018; 7: e008368.
[25] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414: 813-20.
[26] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS and Lazar MA. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-12.