Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Effect of Liraglutide combined with Jinlida granules on glycolipid metabolism and islet function of type 2 diabetes mellitus

Xianjuan Wang#, Kun He#, Jing Li, Ying Liu, Zhaokang Peng, Lijuan Zhao, Shumin Ji*

Department of Endocrinology, Xingtai Third Hospital, Xingtai City, Hebei Province, 054000, China

Article Info

Article history:

Received: October 25, 2023
Accepted: January 18, 2024
Published: February 29, 2024

Use your device to scan and read the article online

Abstract

To investigate whether Liraglutide combined with Jinlida granules affects glycolipid metabolism and islet function in the treatment of type 2 diabetes mellitus (T2DM), a control group and an observation group were established with 90 T2DM patients. The control group was given Jinlida treatment and the observation group was given liraglutide combined treatment for 12 weeks. The clinical efficacy, glycolipid metabolism, bone metabolism, islet function, and endothelial function. The curative effect of the observation group was better than that of the control group. After treatment, FBG, 2hPG, HbAlc, TC, TG, and LDL-C in the observation group were lower and HDL-C was higher than those in the control group (P<0.05). After treatment, the observation group showed higher bone mineral density, osteocalcin, FINS, and HOMA-β and lower HOMA-IR than the control group (P<0.05). After treatment, endothelin-1 level in the observation group was lower than that in the control group, and the NO level was higher (P<0.05). No significant difference was found in the incidence of adverse reactions between the two groups (P>0.05). Liraglutide combined with Jinlida in T2DM can improve glucose, lipid, and bone metabolism, promote the recovery of islet function, and enhance vascular endothelial function.

Keywords: Combination therapy, Islet function, Jinlida, Lipid metabolism, Liraglutide, Type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes that usually occurs in adulthood and often as a result of a wrong lifestyle. Obesity, abdominal fat, lack of exercise and family history of diabetes are risk factors for this disease. Urinary frequency, feeling of extreme hunger and thirst, weakness and fatigue, dry skin and unwanted weight loss are the main symptoms of this disease [1, 2].

T2DM is a serious disease in which the insulin produced by the pancreas does not work properly or the pancreas is not able to produce enough insulin. As a result, the level of blood sugar (glucose) becomes higher than the standard state. The body cells of a person with T2DM are not able to absorb sugar from food. Failure to treat this disease, which is also called adult diabetes, causes problems and diseases such as heart disease, kidney disease, and stroke. The best way to control the disease is through lifestyle changes, medication or insulin, and regular periodic checkups [1-3].

T2DM is mainly caused by insulin resistance and is accompanied by insufficient insulin secretion. High glucose and high lipid toxicity in patients will aggravate insulin resistance and inhibit insulin secretion by islet beta cells, resulting in insufficient insulin secretion [1]. In the past, T2DM was primarily treated with metformin with poor clinical efficacy [2]. Jinlida granule is a proprietary Chinese medicine that can regulate blood lipids, glucose, and triglycerides in the body, thus alleviating T2DM and reducing blood glucose and insulin levels in diabetic patients to a certain extent. However, the clinical efficacy of monotherapy is not satisfactory [3, 4]. Liraglutide is a glucagon-like peptide-1 receptor agonist, which can control blood glucose, reduce body weight, and improve islet function. It has been reported in the past that Liraglutide has a high therapeutic effect on T2DM [5]. Based on this, this study was to explore the effects of liraglutide combined with Jinlida in T2DM on glycolipid metabolism and islet function.

2. Materials and methods

2.1. Clinical data

90 patients with T2DM from October 2021 to February 2023 were selected. A control group and an observation group were established by the random number table method. In the control group, there were 26 males and 19 females, aged from 41 to 78 years with an average age of (59.67±5.31) years. The course of disease ranged from 6 months to 9 years, with an average of (2.58 ± 0.56) years. BMI ranges from 18.5 to 28.3 kg/m^2, with an average of (23.01 ± 1.26) kg/m^2. The observation group included 24

* Corresponding author.
E-mail address: jishumin123456@hotmail.com (S. Ji).
# These authors contributed equally
Doi: http://dx.doi.org/10.14715/cmb/2024.70.2.22

males and 21 females, with an average age of (58.53±5.68) years, ranging from 40 to 75 years. The course of disease ranged from 5 months to 9 years, with an average of (2.54 ± 0.59) years. BMI ranges from 18.1-27.9 kg/m^2, with an average of (22.98 ± 1.42) kg/m^2. The above data indicated no significant difference between the two groups (P>0.05).

2.2. Inclusion criteria

Inclusion criteria included: The relevant diagnostic criteria for T2DM were met [6]; All patients signed the consent form; Patients with no previous treatment history of liraglutide or Jinlida.

2.3. Exclusion criteria

Exclusion criteria included: Type 1 diabetes mellitus; Patients with diabetic nephropathy; Patients with heart, liver, and kidney dysfunction; Patients with ketoacidosis; Patients with other diseases that affect glucose metabolism, such as pituitary growth hormone tumor and hypercortisolism; Patients who have recently taken drugs that affect blood glucose.

2.4. Methods

The control group was treated with Jinlida granules (Z20050845, specification: 9 g/packet; Yiling Pharmaceutical, Shijiazhuang, China) and taken with boiling water, 9 g/time, 3 times/day. The observation group was given subcutaneous injections of Liraglutide injection (J20160037, specification: 3mL:18mg; Novo NordiskA/S) combined treatment, 1.2 mg/time, once/day. Both groups were treated continuously for 12 weeks.

2.5. Outcome measures

(1) Clinical efficacy [7] was measured after 12 weeks. Obviously efficacy: FPG < 7.0 mmol/L or reduced by > 30%; effective: FPG < 8.5 mmol/L or reduced by 10-29%; ineffective: FPG showed no significant change or decreased by less than 10%.

(2) Glycolipid metabolism index: Before treatment and 12 weeks after treatment, 3 ml fasting venous blood was collected to measure fasting blood glucose and 2 h postprandial blood glucose by OneTouch Ultra (Johnson, Shanghai, China), HbAlc was determined by high-performance liquid chromatography using variant II analyzer (BioRad), and insulin was determined by radioimmunoassay. All kits were purchased from Diagnostic Systems Laboratories. TC, TG, LDL-C, and HDL-C were detected by an automatic biochemical analyzer (Hitachi, Japan).

(3) Islet function indicators: Fasting insulin (FINS) before treatment and 12 weeks after treatment were detected by radioimmunoimmunoassay, and HOMA-IR and HOMA-β were evaluated by homeostasis model assessment.

(4) Bone metabolism indices: Bone mineral density (BMD) of lumbar vertebra l-4 was measured with GE DXA dual-energy X-ray bone densitometer. Serum osteocalcin (BGP) levels were measured by radioimmunoassay.

(5) Vascular endothelial function: Serum endothelin (ET) level was detected by enzyme-linked immunosorbent assay and NO level by nitric acid reduction colorimetry.

2.6. Statistical analysis

Data were processed by SPSS22.0 software. Enumeration data were expressed as percentages and compared by χ^2 test. Measurement data were expressed as (±s) after the normality test and compared by t-test. P<0.05 meant that the difference was statistically significant.

3. Results

3.1. Clinical efficacy

Table 1 shows that the therapeutic efficacy of the observation group was better than that of the control group (P<0.05).

3.2. Glucose metabolism indices

Glucose metabolism indices showed no significant difference in the two groups before treatment (P>0.05). After treatment, observation group had reduced FBG, 2hPG, and HbAlc versus control group (P<0.05, Figure 1).

3.3. Lipid metabolism indices

Lipid metabolism indices indicated no significant difference between the two groups before treatment (P>0.05). After treatment, observation group showed reduced TC, TG and LDL-C and enhanced HDL-C versus control group (P<0.05, Figure 2).

3.4. Islet function indices

Pre-treatment islet function indices showed no significant difference between the two groups (P>0.05). After treatment, higher FINS and HOMA-β and lower HOMA-IR were measured in observation group rather than control group (P<0.05, Figure 3).

3.5. Bone metabolic indices

No significant difference could be seen in pre-treatment bone metabolic indices between the two groups (P>0.05). Observation group expressed higher BMD value and BGP level than control group (P<0.05, Figure 4).

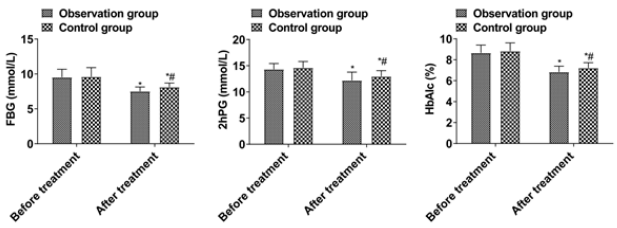

Fig. 1. Glucose metabolism indices. * P<0.05 indicated comparison with before treatment; # P<0.05 indicated comparison with observation group.

Table 1. Comparison of clinical efficacy between the two groups (e.g., %).

Groups	N	Obviously effective	Effective	Ineffective	Total effective rates
Observation group	45	20	23	2	95.56 (43)
Control group	45	16	21	8	82.22 (37)
χ^2					4.05
P					0.044

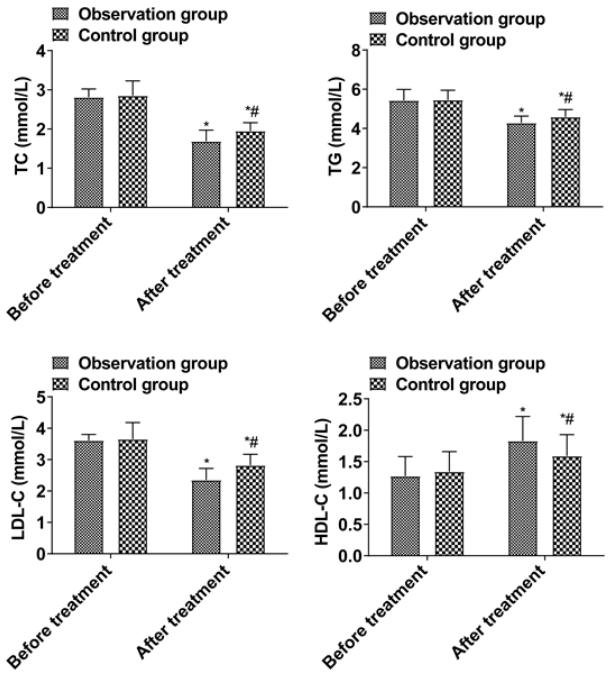

Fig. 2. Lipid metabolism indices. * P<0.05 indicated comparison with before treatment; # P < 0.05 indicated comparison with observation group.

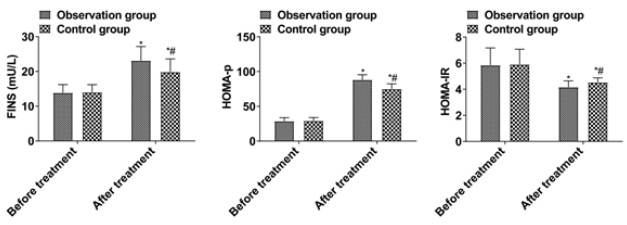

Fig. 3. Islet function indices. * P<0.05 indicated comparison with before treatment; # P<0.05 indicated comparison with observation group.

3.6. Endothelial function indices

Before treatment, there was no significant difference in endothelial function indices between the two groups (P>0.05). After treatment, ET-1 level in the observation group was lower and NO level was higher than that in the control group (P<0.05, Figure 5).

3.7. Incidence of adverse reactions

There was no statistical significance in the incidence of adverse reactions between the two groups (P>0.05, Table 2).

4. Discussion

T2DM has shown increasing incidence. High glucose and high lipid toxicity in T2DM patients will aggravate insulin resistance and inhibit insulin secretion [8, 9]. Jinlida being composed of ginseng, Polygonatum sibiricum Red., Coptis chinensis, radix aspartame, Radix Pueraria rhizome, and atractylodes has protective effects on hypoglycemia and islet beta cells in T2DM patients mainly relying on multi-flavor Chinese medicine with multi-target and multi-link effects to improve insulin resistance and thus reduce blood glucose [10]. However, according to relevant reports, single-drug therapy is not effective [11]. Liraglutide can well control blood glucose, reduce patients' weight, and improve islet function [12]. This study found that lilaglutide combined with Jinlida achieved a better therapeutic effect, lowered FBG, 2hPG, HbAlc, TC, TG, and LDL-C and elevated FINS, HOMA-β, and HDL-C, indicating that lilaglutide combined with Jinlida can improve the body glucose and lipid metabolism. The reason is that liraglutide can promote the secretion of insulin, improve the sensitivity of body tissue cells to insulin, inhibit the apoptosis of islet beta cells, and restore the function of islet beta cells. In addition, liraglutide has a long half-life when injected subcutaneously, which can prolong its action time, make patients feel full for a certain period, and continuously control blood glucose levels [13, 14]. In addition, this study showed that liraglutide combi-

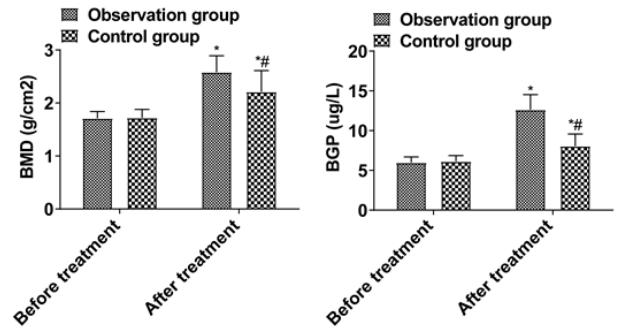

Fig. 4. Bone metabolic indices. * P<0.05 indicated comparison with before treatment; # P<0.05 indicated comparison with observation group.

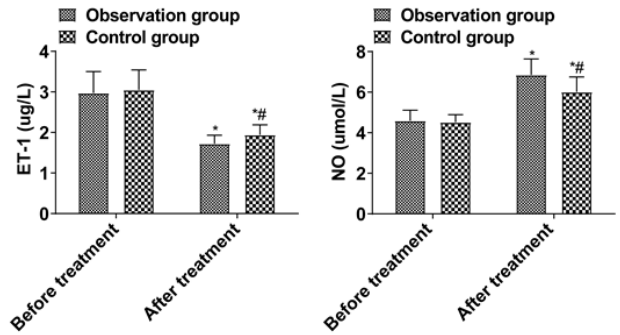

Fig. 5. Endothelial function indices. * P<0.05 indicated comparison with before treatment; # P<0.05 indicated comparison with observation group.

Table 2. Comparison of the incidence of adverse reactions between the two groups (e.g., %)

Groups	N	Nausea and vomiting	Hypoglycemia	Rash	Incidence
Observation group	45	0	1	0	2.22
Control group	45	2	0	1	6.67
χ^2					1.047
P					0.306

ned with Jinlida elevated BMD value and BGP level, thus improving bone metabolism in the body, which is mainly related to the improvement of bone density by liraglutide regulating intestinal calcium and phosphorus metabolism [15].

In the condition of long-term hyperglycemia, the body of T2DM patients gradually presents inflammatory responses, and most diabetic patients also have dyslipidemia, which destroys vascular endothelial function of patients [16]. However, vascular endothelial function impairment is the basic pathological change of various complications in T2DM patients, which will lead to atherosclerosis and thrombosis [17]. NO and ET-1 are a pair of antagonistic vasoactive substances synthesized by vascular endothelial cells and can maintain vascular homeostasis. Hyperglycemia can decrease NO synthesis and activity, weaken the vasodilatory effect, and thus aggravate the disturbance of blood microcirculation. Due to long-term hyperglycemia in diabetic patients, blood viscosity increases, lipid metabolism disorders, and insufficient perfusion of blood microcirculation lead to tissue ischemia and hypoxia, induce vascular endothelial injury, and increase the synthesis and release of ET-1 [4, 18]. In addition to the hypoglycemic effect, liraglutide has the function of protecting vascular endothelia and improving neuromuscular microcirculation [19]. Liraglutide can inhibit vascular adhesion molecules and plasminogen activators in the body, reduce high reactive oxygen species, and then reduce the damage to vascular endothelial cells, thereby improving vascular endothelial function and protecting vascular function in patients. This study indicated that liraglutide combined with Jinlida could improve vascular endothelial function in T2DM patients by reducing ET-1 and elevating NO. This is mainly because liraglutide can protect the blood glucose regulation function of the remaining islet cells, improve the insulin resistance of diabetic patients, reduce or relieve the toxic effect caused by hyperglycemia, thus relieving the oxidative stress reaction in the body, maintaining the normal function of vascular endothelium, promoting NO expression, inhibiting endothelial cell apoptosis and inducing proliferation, thereby reducing vascular endothelial damage and maintaining a stable endothelial environment [20-26]. In addition, this study found that T2DM patients receiving liraglutide treatment based on Jinlida would not increase the incidence of adverse reactions, suggesting that combination therapy is relatively safe.

In summary, Liraglutide combined with Jinlida in T2DM can improve the body's glucose and lipid metabolism and bone metabolism, promote the recovery of islet function, and improve vascular endothelial function.

Acknowledgments
Not applicable.

Ethics approval and consent to participate
This study was approved by the ethical committees of Xingtai Third Hospital. Written inform consent was obtained from all patients.

Funding Statements
Not applicable.

Conflicts of Interest
The authors declare no conflicts of interest.

Data available
Data is available from the corresponding author on request.

Authors' contributions
XW and KH the initiator of the study conducted the main experimental part, described the results, and wrote the article. JL and SJ performed the statistical calculations and participated in drafting the manuscript. YL, ZP and LZ participated in collecting the research material. SJ supervised the work.

References

1. Ikonomidis I, Pavlidis G, Thymis J, Birba D, Kalogeris A, Kousathana F, et al (2020) Effects of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and their combination on endothelial glycocalyx, arterial function, and myocardial work index in patients with type 2 diabetes mellitus after 12-month treatment. J Am Heart Assoc 9(9):e015716. doi: 10.1161/JAHA.119.015716
2. Ali AM, Martinez R, Al-Jobori H, Adams J, Triplitt C, DeFronzo R, et al (2020) Combination therapy with canagliflozin plus liraglutide exerts additive effect on weight loss, but not on HbA1c, in patients with type 2 diabetes. Diabetes Care 43(6):1234–1241. doi: 10.2337/dc18-2460
3. Zhong X, Chen Z, Chen Q, Zhao W, Chen Z (2019) Novel site-specific fatty chain-modified GLP-1 receptor agonist with potent antidiabetic effects. Molecules 24(4):779. doi: 10.3390/molecules24040779
4. Singh P, Taufeeq M, Pesavento TE, Washburn K, Walsh D, Meng S (2020) Comparison of the glucagon-like-peptide-1 receptor agonists dulaglutide and liraglutide for the management of diabetes in solid organ transplant: A retrospective study. Diabetes Obes Metab 22(5):879–884. doi: 10.1111/dom.13964
5. Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, et al (2020) European society of cardiology/heart failure association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail 22(2):196–213. doi: 10.1002/ejhf.1673
6. Pastor R, Tur JA (2019) Liraglutide for the treatment of obesity: analyzing published reviews. Curr Pharm Des 25(15):1783–1790. doi: 10.2174/1381612825666190701155737
7. Saber SM, Abd El-Rahman HA (2019) Liraglutide treatment effects on rat ovarian and uterine tissues. Reprod Biol 19(3):237–244. doi: 10.1016/j.repbio.2019.07.003
8. Zhao T, Chen H, Cheng C, Zhang J, Yan Z, Kuang J, et al (2019) Liraglutide protects high-glucose-stimulated fibroblasts by activating the CD36-JNK-AP1 pathway to downregulate P4HA1. Biomed Pharmacother 118:109224. doi: 10.1016/j.biopha.2019.109224
9. Mann JFE, Fonseca V, Mosenzon O, Raz I, Goldman B, Idorn T, et al (2018). Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. Circulation 138(25):2908–2918. doi: 10.1161/CIRCULATIONAHA.118.036418
10. Ando Y, Shigiyama F, Hirose T, Kumashiro N (2021) Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: A 24-week randomized controlled trial. J Diabetes Investig 12(10):1816–1826. doi: 10.1111/jdi.13533
11. Baylan U, Korn A, Emmens RW, Schalkwijk CG, Niessen HWM, Krijnen PAJ, Simsek S (2022) Liraglutide treatment attenuates inflammation markers in the cardiac, cerebral and renal microvas-

culature in streptozotocin-induced diabetic rats. Eur J Clin Invest 52(9):e13807. doi: 10.1111/eci.13807

12. Zhuravlyova L, Rogachova T, Sokolnikova N, Filonenko M (2021) The influence of liraglutide on the level of blood pressure in patients with arterial hypertension against the background of obesity and type 2 diabetes mellitus. J Hypertens 39:e207. doi: 10.1097/01.hjh.0000746772.11336.ec
13. Tičinović Kurir T, Miličević T, Novak A, Vilović M, Božić J (2020) Adropin - potential link in cardiovascular protection for obese male type 2 diabetes mellitus patients treated with liraglutide. Acta Clin Croat 59(2):344–350. doi: 10.20471/acc.2020.59.02.19
14. Rafiullah M, Benabdelkamel H, Masood A, Ekhzaimy AA, Musambil M, Joy SS, Alfadda AA (2023) Urinary proteome differences in patients with type 2 diabetes pre and post liraglutide treatment. Curr Issues Mol Biol 45(2):1407–1421. doi: 10.3390/cimb45020092
15. Aoki K, Kamiyama H, Takihata M, Taguri M, Shibata E, Shinoda K, et al (2020) Effect of liraglutide on lipids in patients with type 2 diabetes: a pilot study. Endocr J 67(9):957–962. doi: 10.1507/endocrj.EJ19-0464
16. Wegeberg AM, Meldgaard T, Baek A, Drewes AM, Vyberg M, Jessen N, et al (2021) Subcutaneous adipose tissue composition and function is unaffected by liraglutide-induced weight loss in adults with type 1 diabetes. Basic Clin Pharmacol Toxicol 128(6):773–782. doi: 10.1111/bcpt.13575
17. Moreno-Fernandez J, Garcia-Seco JA, Seco Segura AM, Garcia-Seco F, Rozas Moreno PJ, Aguirre Sanchez-Covisa M (2020) Liraglutide vs. lixisenatide in obese type 2 diabetes mellitus patients: What effect should we expect in routine clinical practice?. Prim Care Diabetes 14(1):68–74. doi: 10.1016/j.pcd.2019.05.006
18. Konwar M, Bose D, Jaiswal SK, Maurya MK, Ravi R (2022) Efficacy and safety of liraglutide 3.0 mg in patients with overweight and obese with or without diabetes: A systematic review and meta-analysis. Int J Clin Pract 2022:1201977. doi: 10.1155/2022/1201977
19. Gordon M, Meagher P, Connelly KA (2021) The effect of empagliflozin and liraglutide on the NLRP3 inflammasome in a rodent model of type 2 diabetes mellitus. Can J Diabetes 45(6):553–556. doi: 10.1016/j.jcjd.2020.11.003
20. Yan W, Pang M, Yu Y, Gou X, Si P, Zhawatibai A, et al (2019) The neuroprotection of liraglutide on diabetic cognitive deficits is associated with improved hippocampal synapses and inhibited neuronal apoptosis. Life Sci 231(8):116566. doi: 10.1016/j.lfs.2019.116566
21. Ramzy MM, Abdalla AM, Zenhom NM, Okasha AM, Abdelkafy AE, Saleh RK (2019) Therapeutic effect of liraglutide on expression of CTGF and BMPin induced diabetic nephropathy. J Cell Biochem 120(10):17512–17519. doi: 10.1002/jcb.29015
22. Fazeli F, Ahanjan M (2022) The capacity of stem cells in treatment of diabetes. Cell Mol Biomed Rep 2(4):230–244. doi: 10.55705/cmbr.2022.357066.1060
23. Dhuldhaj U, Malik N (2022) Global perspective of phosphate solubilizing microbes and phosphatase for improvement of soil, food and human health. Cell Mol Biomed Rep 2(3): 173–186. doi: 10.55705/cmbr.2022.347523.1048
24. Mirzaei A, Shakoory-Moghadam V (2022) Bioinformatics analysis and pharmacological effect of Stevia rebaudiana in the prevention of type-2 diabetes. Cell Mol Biomed Rep 2(2):64–73. doi: 10.55705/cmbr.2022.336232.1035
25. Behzadmehr R, Rezaie-Keikhaie K (2022) Evaluation of Active Pulmonary Tuberculosis Among Women with Diabetes. Cell Mol Biomed Rep 2(1):56–63. doi: 10.55705/cmbr.2022.336572.1036
26. Azeez S, Jafar S, Aziziaram Z, Fang L, Mawlood A, Ercisli M (2021) Insulin-producing cells from bone marrow stem cells versus injectable insulin for the treatment of rats with type I diabetes. Cell Mol Biomed Rep 1(1):42–51. doi: 10.55705/cmbr.2021.138888.1006