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Original Article

The relationship between islet β-cell dysfunction and major organ dysfunction in patients with severe traumatic MODS

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Abstract: Background: There is a lack of clinical evidence on the relationship between islet β-cell dysfunction with the prognosis and the major organ dysfunction in the patients with severe traumatic MODS. Methods: 170 cases of surviving and dead traumatic MODS patients and 90 normal healthy individuals were selected as research subjects. The declined indexes of the HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ were evaluated as indicators of β-cell dysfunction, the elevated levels of blood ALT, CRE, and CK-MB were evaluated as liver, kidney and myocardium dysfunction indicators, and the elevated levels of blood sTREM-1, TNF-α, IL-6 and HMGB1 were analyzed as indicators of inflammation in all the subjects. Results: The indexes of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ in all the MODS patients were significantly lower than those of the normal control subjects, and the indexes of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ in the dead MODS patients were significantly lower than those of the surviving MODS patients, respectively ($P<0.01$). There was a significant negative correlation between either the HOMA-β or $\Delta INS_{30}/\Delta GLU_{30}$ with the ALT, CRE, and CK-MB, as well as the sTREM-1, TNF-α, IL-6, and HMGB1 levels in all the MODS patients, respectively ($P<0.01$). Conclusion: Islet β-cell dysfunction occurs in patients with severe traumatic MODS and it predicts a poor outcome. Islet β-cell dysfunction is positively related to liver, kidney, and myocardium dysfunction, and excessive inflammation may be an important cause of islet β-cell dysfunction.

Keywords: Trauma, MODS, Islet β-cell dysfunction, multiple organ dysfunction, prognosis, inflammation

Introduction

Multiple organ dysfunction syndrome (MODS) is characterized by secondary dysfunction or disorders of two or more organs or tissues (excluding primary organ or tissue dysfunction) that occur concurrently or consecutively following severe trauma (including postoperative hemorrhage and other primary physical injuries). In hospitalized patients with severe trauma, MODS often involves dysfunction of the liver, kidney and myocardium, and in the advanced stage of MODS, multiple organ failure (MOF) occurs and causes high mortality [1]. MOF is considered to be the leading cause of death among hospitalized patients with severe trauma. The post-traumatic hyperglycemia promotes the development of MODS, and islet β-cell dysfunction plays an important role in the hyperglycemic response [2-4].

The soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) in the blood may serve as an early marker for post-traumatic infection and inflammation, and elevated sTREM-1 induced by endotoxin could trigger the inflammatory response and enhance the levels of a variety of inflammatory cytokines, such as

the tumor necrosis factor α (TNF-α), high-mobility group box-1 (HMGB1) and interleukin 6 (IL-6) [5]. In critically traumatic patients, hyperglycemia is often associated with MODS, indicating a poor prognosis [6, 7]. The mutual promotion of the excessive inflammation and the hyperglycemia caused by islet β-cell dysfunction enhances the development of traumatic MODS, and the inflammation plays a key role in the development of β-cell dysfunction in type 2 diabetes [8].

The homeostasis model assessment of isletβ-cell function (HOMA-β) and the ratio of insulin increase to blood glucose increase at 30 min after a glucose load ($\Delta INS_{30}/\Delta GLU_{30}$) are used as indexes to evaluate the basal and rapid insulin secretion function of islet β-cells, respectively. The declined indexes of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ represent islet β-cell dysfunction. The novel traumatic MODS diagnostic scheme using the indexes of islet β-cell dysfunction is able to diagnose MODS early without excessively extending the diagnostic scope [9]. However, there is no clinical evidence on the relationship between islet β-cell dysfunction with the prognosis and major organ dysfunction in the patients with severe traumatic MODS.

This study observed the changes of the indexes of islet β-cell dysfunction in surviving and dead patients with severe traumatic MODS and analyzed the relationship between islet β-cell dysfunction with liver, kidney and myocardium dysfunction as well as inflammatory factors. The objective was to provide a reference for the application of indicators of islet β-cell dysfunction to predict the prognosis of traumatic MODS patients and to discuss the possible causes of islet β-cell dysfunction.

Materials and methods

Subjects

Data were collected from patients with various types of traumatic MODS (including hemorrhagic MODS after major surgery) who were hospitalized and treated at our hospital between June 2014 and June 2016. The causes of traumatic hemorrhage mainly included traffic accidents, knife wounds, high-altitude falls and severe postpartum hemorrhage.

Inclusion and exclusion criteria

Inclusion criteria: A patient was included in the present study if the patient developed MODS following severe traumatic hemorrhage, was hospitalized for more than 3 days, lost more than 1500 ml of blood or 30% of total blood volume in a 24-hour period, or suffered varying degrees of hypovolemic shock. None of the subjects included in the present study suffered from diabetes. In addition, there was no dysfunction of the major organs or tissues prior to the injury. Fasting was defined as abstaining from all food, glucose infusion and nutrient infusion for more than 12 hours. Traumatic hemorrhagic MODS was diagnosed according to the criteria described in the literature [10] and was based on the combination of laboratory indicators of organ functions and clinical manifestations. Brain death was used as the basis for declaring a patient dead. The research protocol was approved by the ethics committee of our hospital. All study subjects (or their lineal relative) signed informed consent documents and actively participated in the study.

Exclusion criteria: The following patients were excluded from the present study: patients with hypovolemic shock who died within 3 days after severe or massive uncontrollable hemorrhage despite rescue efforts; patients who suffered from diabetes or impaired glucose tolerance prior to the injury; patients who had undergone insulin therapy; patients who had a fasting blood glucose level ≤ 3.5 mmol/L; and patients who suffered from pre-injury single or multiple organ dysfunction (including dysfunction of liver, kidney, heart and other major organs).

General information and grouping of the subjects

A total of 170 patients with various types of traumatic MODS (including hemorrhagic MODS following major surgery) who met the inclusion criteria and did not meet the exclusion criteria were selected for the present study. All the patients were hospitalized and treated at our hospital, and their ages ranged from 11 to 65 years. Among the 170 patients, 96 survived, and 74 died. The 96 surviving patients (54 males and 42 females, aged (36.31±18.24) years) constituted the severe traumatic MODS-survival (MODS-S) group (n=96), while the 74 dead patients (40 males and 34 females, aged

(38.13±26.40) years) constituted the severe traumatic MODS-death (MODS-D) group (n=74). In addition, 90 healthy individuals who underwent physical examinations at the medical examination center of our hospital (50 males and 40 females, aged (35.20±33.10) years) served as the normal control group (C group, n=90). No statistically significant differences existed between the groups in basic clinicodemographic factors, including the body mass index (body weight (kg)/height (m^2)), male to female ratio, age, and cause of injury (P>0.05).

Methods of measuring

Fasting blood was collected from all patients, and a variety of indices were analyzed: fasting blood glucose (GLU_0), fasting blood insulin (INS_0), sTREM-1, TNFα, HMGB1, IL-6, ALT, CRE and CK-MB. In addition, the patients were given a rapid intravenous injection of glucose solution at 75 g glucose/kg body weight, and then, at 30 min after administration of the glucose solution, blood samples were collected, and the blood levels of glucose (GLU_{30}) and insulin (INS_{30}) were examined again. HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ values were calculated using the following formulas [11]: HOMA-β = ($INS_0 \times 20$)/(GLU_0-3.5); $\Delta INS_{30}/\Delta GLU_{30} = (INS_{30}\text{-}INS_0)/(GLU_{30}\text{-}GLU_0)$. The levels of a number of indices were recorded and statistically analyzed in the patients with severe traumatic MODS during their hospitalization period when the fasting blood glucose levels were highest, including HOMA-β, $\Delta INS_{30}/\Delta GLU_{30}$, sTREM-1, TNFα, HMGB1, IL-6, ALT, CRE and CK-MB. The blood glucose, ALT, CRE, and CK-MB levels were determined by enzymatic assays on a Beckman AU2700 automatic biochemical analyzer (Beckman Instruments Inc., USA), and the determination kits were purchased from Shenzhen Mindray Bio-Medical Electronics Co., Ltd. (Shenzhen, China). Blood insulin was measured using an Electrochemiluminescence Kit (Roche Diagnostics(Shanghai) Co., Ltd.) on a Roche e601 automatic electrochemiluminescence immunoassay analyzer (Roche Diagnostics Co., Ltd. Basel, Switzerland). Blood sTREM-1, TNF-α, HMGB1 and IL-6 were measured by an enzyme-linked immunosorbent assay (ELISA) on a BIO-RAD 550 microplate spectrophotometer (BIO-RAD Co., Ltd., Hercules, California, USA). The ELISA kits were purchased from the Sigma-Aldrich Corporation (Sigma-Aldrich Corporation, USA). All indicators were measured according to the instructions provided by the manufacturers of the kits.

Statistical analysis

All statistical analyses were performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA).The enumeration data were presented as a rate and compared using an χ^2 test. The measurement data were presented as the mean ± SD, and multiple comparisons of group means were performed using one-way analysis of variance (ANOVA), and further comparisons between each two groups were conducted using Newman-Keuls tests. The significance of the correlation coefficients was tested using Spearman's correlation analysis. The significance level was set at p<0.05.

Results

Comparisons of islet β-cell dysfunction among the three groups

The indexes of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ in both the dead MODS group and the survival MODS group were significantly lower than those of the normal control group, respectively (P<0.01), and the indexes of HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$ in the dead MODS group were significantly lower than those of the survival MODS group, respectively (P<0.01). These results indicated that all the patients with severe traumatic MODS had islet β-cell dysfunction compared with the normal control group. The more severe the islet β-cell dysfunction was, the worse the prognosis of severe traumatic MODS was (**Figure 1A**, **1B**).

Correlations between the islet β-cell dysfunction with the major organ dysfunction in patients with severe traumatic MODS

The index of the HOMA-β was negatively correlated with the level of ALT, CRE, and CK-MB; the correlation coefficients between the HOMA-β with ALT, CRE and CK-MB were -0.7852, -0.6019 and -0.5985, respectively (P<0.01) (**Table 1**). The index of the $\Delta INS_{30}/\Delta GLU_{30}$ was negatively correlated with the level of ALT, CRE and CK-MB; the correlation coefficients between the $\Delta INS_{30}/\Delta GLU_{30}$ with the ALT, CRE, and CK-MB were -0.7181, -0.5191 and -0.6076, respectively (P<0.01) (**Table 2**). These results

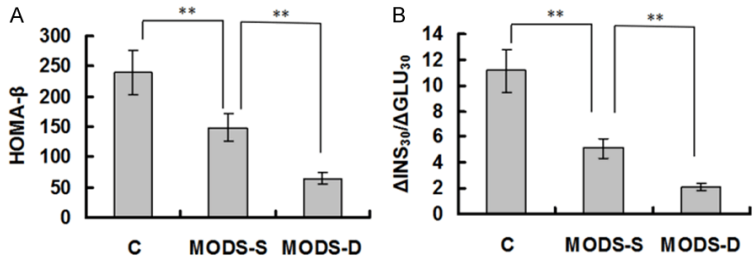

Figure 1. Comparison of HOMA-β (A) and $\Delta INS_{30}/\Delta GLU_{30}$ (B) among three groups.**P<0.01. (C) Normal control group. MODS-S, MODS-Survival group. MODS-D, MODS-Death group. HOMA-β, Homeostasis model assessment of β cell function. $\Delta INS_{30}/\Delta GLU_{30}$, $(INS_{30}\text{-}INS_0)/(GLU_{30}\text{-}GLU_0)$.

showed that the more severe the islet β-cell dysfunction was, the worse the liver, kidney, and myocardium dysfunction in severe traumatic MODS patients was.

Correlations of the islet β-cell function with the inflammatory factors in patients with severe traumatic MODS

The index of the HOMA-β was negatively correlated with the level of sTREM-1, TNF-α, IL-6 and HMGB-1; the correlation coefficients between the HOMA-β with the sTREM-1, TNF-α, IL-6 and HMGB-1 were -0.7173, -0.8062, -0.7591 and -0.6783, respectively (P<0.01) (**Table 3**). The index of the $\Delta INS_{30}/\Delta GLU_{30}$ was negatively correlated with the sTREM-1, TNF-α, IL-6, and HMGB-1 levels; the correlation coefficients between the $\Delta INS_{30}/\Delta GLU_{30}$ and the sTREM-1, TNF-α, IL-6, and HMGB-1 were -0.6010, -0.7154, -0.7263 and -0.5970, respectively (P<0.01) (**Table 4**). These results implied that the elevated inflammatory factors may account for the islet β-cell dysfunction in patients with severe traumatic MODS.

Discussion

Severe traumatic patients are usually in a hypermetabolic state, and as a result, hyperglycemic responses develope. Insulin is an important irreplaceable hormone that reduces blood glucose levels, and severe trauma-induced hyperglycemia is caused by not only insulin resistance but also insufficient insulin secretion by islet β-cells stimulated by the blood glucose, and that the insufficient insulin secretion by islet β-cells is considered to be islet β-cell dysfuntion [9, 12-14]. Hyperglycemia following severe trauma is related to MODS and inflammation. The incidence of MODS and infection in severe traumatic patients with hyperglycemia is significantly higher than it is in patients with normal blood glucose levels, and the blood glucose level in severe traumatic patients can be used as a diagnostic indicator to determine the severity and prognosis of MODS [15, 16].

Severe traumatic MODS refers to multiple organ dysfunction rather than multiple organ failure. Dysfunction means that the organ is not fully functional and does not mean that the organ has completely lost its function. Liver, kidney and the myocardium of heart are the major organs that are most often dysfunctional in severe traumatic MODS, as represented by an elevated blood level of the ALT, CRE, and CK-MB, respectively.

Pancreatic islets are important cells in the body. Islet β-cells may be the only cell type capable of secreting insulin, which is strictly regulated by the blood glucose level. Therefore, a scientific assessment of islet β-cell function should take into account not only insulin secretion levels but also the level of blood glucose stimulation [9]. Normal islet β-cells may compensate for the insulin resistance and control the blood glucose level in the normal range. Therefore, a sustained elevation of fasting blood glucose is generally considered to be a manifestation of islet β-cell dysfunction. Patients with type 1 or type 2 diabetes all suffer from islet β-cell dysfunction [17, 18].

The dysfunctions of islet β-cells include a decrease of basal insulin secretion (HOMA-β) and a decrease of rapid insulin secretion after a glucose load ($\Delta INS_{30}/\Delta GLU_{30}$). This study found that the indexes of islet β-cell function (HOMA-β and $\Delta INS_{30}/\Delta GLU_{30}$) were decreased in all the traumatic MODS patients, indicating that severe traumatic MODS involves islet β-cell dysfunction, and that β-cell dysfunction should be a constituent part of MODS caused by severe trauma. This study also found that the HOMA-β and the $\Delta INS_{30}/\Delta GLU_{30}$ values were significantly lower in the dead patients than they were in the surviving patients, which implies that islet β-cell dysfunction predicts a poor outcome for severe traumatic MODS

Table 1. The correlation coefficient of the HOMA-β with ALT, CRE and CK-MB in 170 patients with severe traumatic MODS

Index with HOMA-β	ALT	CRE	CK-MB
Correlation coefficient	-0.7852	-0.6019	-0.5985
P	<0.01	<0.01	<0.01

Table 2. The correlation coefficient of the $\Delta INS_{30}/\Delta GLU_{30}$ with ALT, CRE and CK-MB in 170 patients with severe traumatic MODS

Index with $\Delta INS_{30}/\Delta GLU_{30}$	ALT	CRE	CK-MB
Correlation coefficient	-0.7181	-0.5191	-0.6076
P	<0.01	<0.01	<0.01

Table 3. The correlation coefficient of the HOMA-β with sTREM-1, TNFα, IL-6 and HMGB-1 in 170 patients with severe traumatic MODS

Index with HOMA-β	sTREM-1	TNFα	IL-6	HMGB-1
Correlation coefficient	-0.6010	-0.7154	-0.7263	-0.5970
P	<0.01	<0.01	<0.01	<0.01

Table 4. The correlation coefficient of the $\Delta INS_{30}/\Delta GLU_{30}$ with sTREM-1, TNFα, IL-6 and HMGB-1 in 170 patients with severe traumatic MODS

Index with Δ $INS_{30}/\Delta GLU_{30}$	sTREM-1	TNFα	IL-6	HMGB-1
Correlation coefficient	-0.7173	-0.8062	-0.7591	-0.6783
P	<0.01	<0.01	<0.01	<0.01

patients. Islet β-cell dysfunction promotes the development and progression of severe traumatic MODS.

It is reported that there is a relationship between islet β-cell dysfunction and the severity of disease among critically ill children, and that islet β-cell dysfunction reflects the severity of the disease of critically ill children [19]. This study found that islet β-cell dysfunction was not an isolated event in patients with severe traumatic MODS. In these patients, β-cell insufficiency was accompanied by liver, kidney, and myocardium dysfunction. Moreover, islet β-cell dysfunction was positively correlated with the dysfunction of the liver, kidney, and myocardium,indicating that the more severe the islet β-cell dysfunction was, the more severe the dysfunction of the liver, kidney and myocardium. Perhaps the dysfunction of islet β-cells may be just as important as liver, kidney and myocardium dysfunction are for the diagnosis of MODS caused by severe trauma. Islet β-cell dysfunction may play an important role in the occurrence and development of severe traumatic MODS.

Islet β-cell dysfunction in patients with diabetes is related to an increased expression of inflammatory factors [20-22]. The blood levels of the inflammatory factors of sTREM-1, TNF-α, IL-6 and HMGB1 are increased in severe traumatic infection subjects [23, 24], and the inflammation response can induce the dysfunction and damage of islet β-cells [14, 25, 26]. This study found that the severity degree of islet β-cell dysfunction was positively correlated with the blood levels of sTREM-1, TNF-α, IL-6, and HMGB1 in patients with severe traumatic MODS. The higher the levels of inflammatory factors were, the more severe the degree of islet β-cell dysfunction was, and the elevated blood inflammatory factors may be the main cause for islet β-cell dysfunction in patients with traumatic MODS.

Islet β-cell dysfunction following severe trauma is characterized by a persistent hyperglycemic response as indicated by laboratory data, and islet β-cell dysfunction may not display typical clinical symptoms. However, severe β-cell dysfunction in the patients with traumatic MODS may cause a glycometabolism disorder, which can induce metabolic acidosis and an electrolyte disturbance, resulting in the death of the patient. Therefore, the danger of post-traumatic islet β-cell dysfunction should draw great attention in clinical practice.

The protection of islet β-cell function after severe trauma may be an important measure to prevent and control MODS. The administration of insulin or glucose-insulin-potassium can protect the islet β-cell function and other major organs dysfunction, and the anti-inflammatory effects may be of great significance in the prevention and treatment of severe traumatic MODS in patients [27-30]. However, the causal relationship between islet β-cell dysfunction and dysfunction in other organs, the detailed mechanisms of islet β-cell dysfunction, and

whether islet β-cell dysfunction occurs before the dysfunction in other organs is not fully understood so these questions are worthy of further investigation in patients with traumatic MODS.

In conclusion, islet β-cell dysfunction in patients with traumatic MODS is often accompanied by major organ dysfunction. There is a positive correlation between islet β-cell dysfunction and major organ dysfunction. Islet β-cell dysfunction may serve as a prognostic indicator for patients with traumatic MODS, and elevated blood inflammatory factors may be the major cause of islet β-cell dysfunction.

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Disclosure of conflict of interest

None.

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References

[1] Fueglistaler P, Amsler F, Schuepp M, Fueglistaler-Montali I, Attenberger C, Pargger H, Jacob AL, Gross T. Prognostic value of sequential organ failure assessment and simplified acute physiology II score compared with trauma scores in the outcome of multiple-trauma patients. Am J Surg 2010; 200: 204-14.

[2] Sperry JL, Frankel HL, Vanek SL, Nathens AB, Moore EE, Maier RV, Minei JP. Early hyperglycemia predicts multiple organ failure and mortality but not infection. J Trauma 2007; 63: 487-93.

[3] Louis K, Netea MG, Carrer DP, Kotsaki A, Mylona V, Pistiki A, Savva A, Roditis K, Alexis A, Van der Meer JW, Giamarellos-Bourboulis EJ. Bacterial translocation in an experimental model of multiple organ dysfunctions. J Surg Res 2013; 183: 686-94.

[4] Wang ZK, Hu XY, Chai CC, Chen ZL, Pan XQ, Wang BL, Xu LS. [Clinical significance of changes in insulin resistance and secretion in multiple organ dysfunction syndrome patients complicated by trauma and hemorrhage]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2003; 15: 43-4.

[5] Li Z, Zhang E, Hu Y, Liu Y, Chen B. High serum sTREM-1 correlates with myocardial dysfunction and predicts prognosis in septic patients. Am J Med Sci 2016; 351: 555-62.

[6] Kyle UG, Coss Bu JA, Kennedy CE, Jefferson LS. Organ dysfunction is associated with hyperglycemia in critically ill children. Intensive Care Med 2010; 36: 312-20.

[7] Jeschke MG, Pinto R, Herndon DN, Finnerty CC, Kraft R. Hypoglycemia is associated with increased postburn morbidity and mortality in pediatric patients. Crit Care Med 2014; 42: 1221-31.

[8] Eguchi K, Manabe I. Macrophages and islet inflammation in type 2 diabetes. Diabetes Obes Metab 2013; 3: 152-8.

[9] Wang ZK, Chen RJ, Wang SL, Li GW, Zhu ZZ, Huang Q, Chen ZL, Chen FC, Deng L, Lan XP, Hu T. Clinical application of a novel diagnostic scheme including pancreatic betacell dysfunction for traumatic multiple organ dysfunction syndrome. Mol Med Rep 2018; 17: 683-93.

[10] Wang C, Su Q, Zhang SW, Yin CH, Wang H, Wang BE. [A clinical study on the diagnostic criteria of multiple organ dysfunction syndrome]. Zhonghua Wai Ke Za Zhi 2009; 47: 40-3.

[11] Zhu HQ, Yang ZJ, Zhang B, Xiao JZ, Yang WY. [Ageing related changes of insulin secretion and insulin sensitivity among normal glucose tolerance individuals in China]. Zhonghua Yi Xue Za Zhi 2012; 92: 1948-53.

[12] Yu Y, Chai J. The function of miRNAs and their potential as therapeutic targets in burn-induced insulin resistance (review). Int J Mol Med 2015; 35: 305-10.

[13] Rehou S, Mason S, Burnett M, Jeschke MG. Burned adults develop profound glucose intolerance. Crit Care Med 2016; 44: 1059-66.

[14] Li DW, Shen CA, Chai JK, Ma L, Shang YR, Li LZ. [Structural and functional changes in islet beta cells in severely scalded rats]. Zhonghua Shao Shang Za Zhi 2013; 29: 355-9.

[15] Bosarge PL, Shoultz TH, Griffin RL, Kerby JD. Stress-induced hyperglycemia is associated with higher mortality in severe traumatic brain injury. J Trauma Acute Care Surg 2015; 79: 289-94.

[16] Kulp GA, Tilton RG, Herndon DN, Jeschke MG. Hyperglycemia exacerbates burn-induced liver inflammation via noncanonical nuclear factor-kappaB pathway activation. Mol Med 2012; 18: 948-56.

[17] Ahren B, Foley JE. Improved glucose regulation in type 2 diabetic patients with DPP-4 inhibitors: focus on alpha and beta cell function and lipid metabolism. Diabetologia 2016; 59: 907-17.
[18] Kramer CK, Choi H, Zinman B, Retnakaran R. Glycemic variability in patients with early type 2 diabetes: the impact of improvement in beta-cell function. Diabetes Care 2014; 37: 1116-23.
[19] Liu PP, Lu XL, Xiao ZH, Qiu J, Zhu YM. Relationship between beta cell dysfunction and severity of disease among critically Ill children: a STROBE-compliant prospective observational study. Medicine (Baltimore) 2016; 95: e3104.
[20] Donath MY, Storling J, Maedler K, Mandrup-Poulsen T. Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. J Mol Med (Berl) 2003; 81: 455-70.
[21] Fatima N, Faisal SM, Zubair S, Ajmal M, Siddiqui SS, Moin S, Owais M. Role of pro-inflammatory cytokines and biochemical markers in the pathogenesis of type 1 diabetes: correlation with age and glycemic condition in diabetic human subjects. PLoS One 2016; 11: e0161548.
[22] Burke SJ, Stadler K, Lu D, Gleason E, Han A, Donohoe DR, Rogers RC, Hermann GE, Karlstad MD, Collier JJ. IL-1beta reciprocally regulates chemokine and insulin secretion in pancreatic beta-cells via NF-kappaB. Am J Physiol Endocrinol Metab 2015; 309: E715-26.
[23] Su L, Liu D, Chai W, Long Y. Role of sTREM-1 in predicting mortality of infection: a systematic review and meta-analysis. BMJ Open 2016; 6: e010314.
[24] Liu M, Zhang Y, Xiong JY, Wang Y, Lv S. Etomidate mitigates lipopolysaccharide-induced CD14 and TREM-1 expression, NF-kappaB activation, and pro-inflammatory cytokine production in rat macrophages. Inflammation 2016; 39: 327-35.
[25] Berchtold LA, Prause M, Storling J, Mandrup-Poulsen T. Cytokines and pancreatic beta-cell apoptosis. Adv Clin Chem 2016; 75: 99-158.
[26] Cieslak M, Wojtczak A. Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. Acta Biochim Pol 2015; 62: 15-21.
[27] Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, Liu J, Li M, Fu Z, Cheng H. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008; 371: 1753-60.
[28] Wang Z, Liu L, Hu T, Lei W, Wan F, Zhang P, Wang Z, Xu J, Zhu H, Zhu Z, Yang Y, Hu X, Xu L, Wang S. Protective effect of glucose-insulin-potassium (GIK) on intestinal tissues after severe burn in experimental rats. Burns 2012; 38: 846-854.
[29] Sun Q, Li J, Gao F. New insights into insulin: The anti-inflammatory effect and its clinical relevance. World J Diabetes 2014; 5: 89-96.
[30] Zhu Z, Hu T, Wang Z, Wang J, Liu R, Yang Q, Zhang X, Xiong Y. Anti-inflammatory and organ protective effect of insulin in scalded MODS rats without controlling hyperglycemia. Am J Emerg Med 2018; 36: 202-207.