Observational Study

Medicine

OPEN

Endocrine characteristics and risk factors of type 2 diabetes complicated with gastrointestinal autonomic neuropathy

A single-center retrospective study

Wei Guan, MD[a], Shan Li, MD[b], Wenzao Sun, MD[b], Yuqin Kang, MD[b], Xiaoqin Li, MD[c,*]

Abstract

To analyze endocrine characteristics and risk factors of type 2 diabetes mellitus (T2DM) gastrointestinal autonomic neuropathy. A total of 202 patients with T2DM with obesity who were hospitalized at our institute between January 2019 and June 2021 were selected. Based on adrenocorticotropic hormone (ACTH) levels, 102 patients were placed in the ACTH abnormal group and 100 patients were placed in the non-ACTH abnormal group. Ninety-five healthy adults without diabetes, hyperlipidemia, osteoporosis, or endocrine system abnormalities who were examined at our hospital during the same period were selected as the control group. Fasting plasma glucose (FPG), fasting insulin (FINS), triglycerides (TG), total cholesterol (TC), homeostasis model assessment of insulin resistance (HOMA-IR), ACTH level, body mass index (BMI), and bone mineral density (BMD) were measured to evaluate endocrine characteristics and risk factors. BMI, FPG, FINS, HOMA-IR, TG, TC, and ACTH levels in the abnormal ACTH group were significantly higher than those in the other 2 groups, while BMD was significantly lower than that in the other 2 groups (all $P < .05$). BMI, FPG, FINS, HOMA-IR, TG, TC, and ACTH in the non-ACTH abnormal group were significantly higher than those in the control group, whereas BMD was significantly lower than that in the control group (all $P < .05$). The plasma ACTH level in patients with abnormal ACTH levels was significantly positively correlated with BMI, FPG, FINS, HOMA-IR, TG, and TC and negatively correlated with BMD (all $P < .05$). Multivariate regression analysis showed that BMI, advanced age, FINS, TG, and FPG were risk factors for ACTH abnormalities in patients with diabetes (odds ratio > 1, all $P < .05$). BMI, advanced age, FINS, TG and FPG are the risk factors of abnormal ACTH in T2DM patients with gastrointestinal autonomic neuropathy.

Abbreviations: ACTH = adrenocorticotropic hormone, BMD = bone mineral density, BMI = body mass index, FINS = fasting insulin, FPG = fasting plasma glucose, HOMA-IR = homeostasis model assessment of insulin resistance, HPA = hypothalamic–pituitary–adrenal, OR = odds ratio, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides.

Keywords: ACTH, endocrine, influence factor, T2DM

1. Introduction

In recent years, with the improvement of people's living standards and the increasingly serious aging in China, the incidence rate of type 2 diabetes mellitus (T2DM) with obesity has increased annually; this disease has also become a common medical and health concern worldwide.[1] According to relevant surveys, the incidence of T2DM in China has exceeded 9%, with more than 90 million people suffering from the disease, including more than 30 million obese patients. Gastrointestinal autonomic neuropathy is a type of diabetic neuropathy.[2,3] Patients with diabetes and autonomic neuropathy can suffer from constipation, and some patients experience alternating diarrhea and constipation.[4–6] When the symptoms are serious, the patient can develop gastroparesis, which is difficulty digesting food after eating, accompanied by nausea and vomiting.[7] Some patients are prone to intestinal obstruction and abdominal pain owing to slow intestinal peristalsis. Gastrointestinal autonomic neuropathy in diabetes is common in patients with type 1 diabetes mellitus and those with a long history of T2DM.[8–10] We aimed to analyze the endocrine characteristics and risk factors of patients with T2DM with gastrointestinal autonomic neuropathy.

WG and SL contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Endocrinology, Wuhan Hospital of Traditional Chinese Medicine, Wuhan City, China, [b] Department of Endocrinology, Xiantao First People's Hospital Affiliated to Yangtzeu University, Xiantao City, China, [c] Department of Endocrinology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi City, China.

**Correspondence: Xiaoqin Li, Department of Endocrinology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi City 435001, Hubei Province, China (e-mail: guanwei202211@163.com).*

How to cite this article: Guan W, Li S, Sun W, Kang Y, Li X. Endocrine characteristics and risk factors of type 2 diabetes complicated with gastrointestinal autonomic neuropathy: A single-center retrospective study. Medicine 2023;102:15(e33467).

Received: 10 November 2022 / Received in final form: 9 March 2023 / Accepted: 16 March 2023

http://dx.doi.org/10.1097/MD.0000000000033467

2. Materials and methods

2.1. Study population

A total of 202 patients with T2DM treated at our hospital from January 2019 to June 2021 were selected as research participants, and the inclusion criteria were as follows: the diagnostic criteria of T2DM in line with the Chinese guidelines for the prevention and treatment of T2DM[11]; the diagnostic criteria of gastrointestinal autonomic neuropathy according to the clinical symptoms: esophageal dysmotility, gastroparesis diabeticorum, constipation, diarrhea, and fecal incontinence[12]; body mass index (BMI) ≥ 28 kg/m^2; and complete and reliable clinical data. Exclusion criteria were: serious complications such as diabetic ketoacidosis and diabetic hyperosmolar coma; primary diseases of the hypothalamic–pituitary–adrenal (HPA) axis such as pituitary adenoma and primary hypercortisolism or receipt of hormone or immunosuppressant treatment in the recent year; lactation or pregnancy; and serious primary disease or malignant tumor of the heart, liver, kidney, gastrointestinal tract, and other organs. The 202 T2DM patients were classified into the adrenocorticotropic hormone (ACTH) abnormal group (n = 102) and non-ACTH abnormal group (n = 100) according to ACTH level (cutoff for abnormal level was >22 pg/mL at 8 AM and > 9.6 pg/mL at 10 PM). In addition, 95 healthy adults without diabetes, hyperlipidemia, osteoporosis, endocrine system abnormalities, who underwent physical examination at our hospital during the same period were selected as the control group. This study was approved by the ethics committee of the Wuhan Hospital of Traditional Chinese Medicine (approval no.: 2018030), and all participants signed an informed consent form.

2.2. Methods

Fasting elbow venous blood samples were collected from all participants, and fasting plasma glucose (FPG), fasting insulin (FINS), triglycerides (TG), and total cholesterol (TC) were detected using the chemical reagent method. Based on this, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [FPG (mmol/l) × FINS (mIU/L)]/22.5. At 8:00, 16:00, and 24:00 hours, blood was extracted from the elbow vein of all participants, and the plasma ACTH levels were detected using an enzyme-linked immunosorbent assay. The average of 3 values was taken as the final value for the calculation and analysis. Dual-energy X-ray absorptiometry Pro II was used to detect the bone mineral density (BMD) of the lumbar spine (L2–L4). A lower BMD value indicated more severe osteoporosis.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM SPSS Statistics for Windows). The qualitative data (sex) were expressed as n (%) and assessed using χ^2 test, and the quantitative data (including age, BMI, FPG, FINS, HOMA-IR, TG, TC, ACTH, and BMD) were expressed as mean ± standard deviation and assessed using *t* test. The 3 groups were compared using an analysis of variance and a *t* test. Pearson's correlation analysis was used to explore the correlation between plasma ACTH levels and various indicators in patients with T2DM with obesity. Logistic regression analysis was used to analyze the risk factors of patients with T2DM with abnormal ACTH levels caused by influenza. $P < .05$ indicated a significant difference.

3. Results

3.1. Clinical characteristics of participants

The ACTH abnormal group comprised 63 (61.80%) males and 39 (38.20%) females, the non-ACTH abnormal group comprised 60 (60.00%) males and 40 (40.00%) females, and the control group comprised 56 (58.90%) males and 39 (41.10%) females. The mean age was 66.36 ± 12.34 years, 67.69 ± 9.93 years, and 65.68 ± 11.54 years in the ACTH abnormal, non-ACTH abnormal, and control groups, respectively. There was no significant difference in the baseline sex and age data among the 3 groups (all $P > .05$) (Table 1).

3.2. Comparison of BMI, blood glucose, blood lipids, BMD, and plasma ACTH levels in the 3 groups

BMI, FPG, FINS, HOMA-IR, TG, TC, and ACTH levels in the ACTH abnormal group were significantly higher than those in the other 2 groups, and BMD was significantly lower than those in the other 2 groups. BMI, blood FPG, FINS, HOMA-IR, TG, TC, and ACTH in the non-ACTH abnormal group were significantly higher than those in the control group, and BMD was significantly lower than that in the control group (all $P < .001$) (Table 2).

3.3. Pearson correlation analysis between plasma ACTH level and various indicators in the ACTH abnormal group

The plasma ACTH levels in patients with abnormal ACTH were significantly positively correlated with BMI ($r = 0.369$, $P < .001$), FPG ($r = 0.289$, $P = .003$), FINS ($r = 0.216$, $P = .029$), HOMA-IR ($r = 0.323$, $P < .001$), TG ($r = 0.230$, $P = .020$), and TC ($r = 0.216$, $P = .029$) and significantly negatively correlated with BMD ($r = -0.260$, $P = .008$) (Table 3).

3.4. Potential influencing factors of abnormal ACTH in patients with T2DM

Logistic regression analysis was used to explore potential influencing factors. In the multivariate regression analysis, BMI (odds ratio [OR] = 3.315, $P = .005$), advanced age (OR = 3.028, $P = .008$), TG (OR = 3.452, $P < .001$), FINS (OR = 2.158, $P = .008$), and FPG (OR = 2.854, $P = .001$) were risk factors for abnormal ACTH levels in patients with diabetes (Table 4).

4. Discussion

There is a large amount of fat in obese people, and this fat will produce insulin resistance and then induce pancreatic β cells to secrete more insulin, leading to hyperinsulinemia. Excessive insulin leads to pancreatic β cell failure, eventually leading to insufficient insulin secretion in patients and an inability to control blood glucose levels, resulting in diabetes. In the clinic, there have been in-depth studies on the pathogenesis of diabetes complicated by cardiovascular events; however, there is no definitive conclusion.

The HPA axis is one of the most important endocrine axes in the body. It plays an important role in physiological stress regulation and maintenance of basic life activities. In recent years, many studies have found that changes in the HPA axis function are related to the occurrence and development of diabetes,

Table 1

Comparison of 3 groups of baseline data.

Group	Male, n (%)	Age (yr)
ACTH abnormal group (n = 102)	63 (61.8)	66.36 ± 12.34
Non-ACTH abnormal group (n = 100)	60 (60.0)	67.69 ± 9.93
Control group (n = 95)	56 (58.9)	65.68 ± 11.54
t/χ^2	0.146	0.623
P	.954	.543

ACTH = adrenocorticotropic hormone.

Table 2

Comparison of BMI, blood glucose, blood lipids, BMD, and plasma ACTH levels in the 3 groups.

Group	BMI (kg/m²)	FPG (mmol/L)	FINS (mIU/L)	HOMA-IR	TG (mmol/L)	TC (mmol/L)	BMD (g/cm²)	ACTH (pg/mL)
ACTH abnormal group (n = 102)	30.09 ± 0.69*†	9.36 ± 2.06*†	10.66 ± 2.89*†	4.03 ± 1.26*†	2.69 ± 0.90*†	5.80 ± 1.36*†	1.03 ± 0.19*†	58.66 ± 12.29*†
Non-ACTH abnormal group (n = 100)	25.03 ± 1.86*	8.63 ± 1.50*	8.32 ± 2.09*	3.36 ± 0.98*	2.16 ± 0.83*	5.28 ± 0.93*	1.13 ± 0.23*	52.29 ± 11.36*
Control group (n = 95)	23.39 ± 2.66	5.03 ± 0.69	5.56 ± 1.63	1.20 ± 0.68	1.16 ± 0.36	4.26 ± 0.69	1.25 ± 0.30	35.56 ± 9.98
t	11.933	13.083	18.669	20.089	16.693	15.039	8.193	18.833
P	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Data are presented as mean ± standard deviation.

ACTH = adrenocorticotropic hormone, BMD = bone mineral density, BMI = body mass index, FINS = fasting insulin, FPG = fasting plasma glucose, HOMA-IR = homeostasis model assessment of insulin resistance, TC = total cholesterol, TG = triglycerides.

*Compared with the control group, $P < .05$.

†Compared with the group without abnormal ACTH, $P < .05$.

Table 3

Pearson correlation coefficient between plasma ACTH level and various indicators in ACTH abnormal group.

Group	BMI (kg/m²)	FPG (mmol/L)	FINS (mIU/L)	HOMA-IR	TG (mmol/L)	TC (mmol/L)	BMD (g/cm²)
r	0.369	0.289	0.216	0.323	0.230	0.216	–0.260
P	<.001	.003	.029	<.001	.020	.029	.008

ACTH = adrenocorticotropic hormone, BMD = bone mineral density, BMI = body mass index, FINS = fasting insulin, FPG = fasting plasma glucose, OMA-IR = homeostasis model assessment of insulin resistance, TC = total cholesterol, TG = triglycerides.

Table 4

Potential influencing factors of abnormal ACTH in patients with type 2 diabetes.

Factors	β	SE	Wald	*P*	OR	95% CI
BMI	1.245	0.535	9.012	.005	3.315	1.789–5.257
Advanced age (>85)	1.105	0.511	7.053	.008	3.028	2.141–4.256
FINS	1.321	0.603	12.258	<.001	3.452	1.943–4.925
FPG	0.885	0.410	6.155	.008	2.158	1.423–3.252
TG	1.094	0.501	10.265	.001	2.854	1.123–3.846

ACTH = adrenocorticotropic hormone, BMI = body mass index, CI = confidence interval, FINS = fasting insulin, FPG = fasting plasma glucose, OR = odds ratio, SE = standard error, TG = triglycerides.

and the level of blood cortisol is the most studied. Fu et al[13] showed that elevated nocturnal cortisol levels in overweight or obese patients with T2DM may be a risk factor for microvascular complications. In this study, ACTH, another important hormone in the HPA axis, was used as the research target. Considering the circadian rhythm of hormone secretion, we collected plasma ACTH levels at 8:00, 16:00, and 24:00 hours, and took the average as the final value for analysis. We found that BMI, FPG, FINS, HOMA-IR, TG, TC, and ACTH in the abnormal ACTH group were significantly higher than those in the other 2 groups; BMD was significantly lower than that in the other 2 groups; BMI FPG, FINS, HOMA-IR, TG, TC, and ACTH were significantly higher than those in the control group; and BMD was significantly lower than that in the control group (all $P < .05$).

The internal environment of the human body is a complex system, and various hormones have complex associations with cytokines. ACTH is the main secretory hormone of glucocorticoids, and the latter induces insulin resistance. It can affect the body's sensitivity to insulin, promote protein and fat decomposition in peripheral tissues, and activate lipolytic enzymes together with glucagon and catecholamine, resulting in an increase in amino acids, free fatty acids, and glycerol. This not only increases the raw materials for gluconeogenesis, weakens the role of insulin, and increases blood glucose but also aggravates insulin resistance and leads to blood lipid disorders, participating in the disorder of glucose and lipid metabolism.[14,15] Several studies have shown obesity can lead to an increase in blood cortisol levels and disorders of glucose and lipid metabolism in patients with diabetes and that blood cortisol levels are involved in the process of glucose and lipid metabolism disorders in patients with diabetes.[16,17] In addition, glucocorticoids can also inhibit the formation and function of osteoblasts, induce apoptosis or death, directly act on the bone matrix, reduce the expression of osteocalcin genes, and reduce bone mineral density, increasing the risk of osteoporosis.[18] Wu et al[19] showed that the early-morning ACTH level in elderly female patients with osteoporosis and vertebral compression fractures can reflect the BMD level of the lumbar spine, and ACTH may also affect bone metabolism, which is one of the pathogenic factors of osteoporosis in elderly women.

Previous studies have shown that inflammatory factors, including interleukins, C-reactive protein, and plasminogen activators, are important risk factors for cardiovascular events in patients with T2DM.[20,21] Adipokine has a certain effect on promoting the occurrence of diabetes with cardiovascular events.[22,23] Adipokines include lipase, leptin, and tumor necrosis factors. Leptin participates in carbohydrate energy metabolism, inhibits fat synthesis, and promotes weight loss. A disorder of leptin function is one of the important reasons for insulin resistance. Tumor necrosis factor is mainly secreted by adipose tissue and lymphocytes and participates in insulin resistance, which is closely related to the incidence of diabetes and cardiovascular events. Lipase is a protease secreted by adipocytes and is mainly involved in the regulation of energy, glucose, and lipid metabolism; it is closely related to obesity and insulin.[24,25]

Obesity in T2DM is caused by fat accumulation due to daily excess calories in patients, which leads to diabetes.[26] Therefore, when treating patients with diabetes with cardiovascular events, we need to strengthen the intervention of patients' lifestyles.[27,28] First, we should strengthen health education for patients because many patients do not understand their diseases and do not know the mechanism of disease, related complications, or the importance of their management. Therefore, during medical treatment, medical staff need to strengthen lifestyle interventions for patients so that patients can understand the effective significance of these interventions in alleviating diabetes. Simultaneously, we should guide them into developing good living habits, working and resting normally, and avoiding staying

up late. Second, we need to strengthen the dietary intervention for patients, reducing their daily calorie intake, and achieve the goal of regulating their condition. Patients need to be guided to choose a low-fat, low-calorie, and low-carbohydrate diet. Daily calorie intake should be controlled between 800 and 1500 kcal/d, and weight control should be strengthened to avoid continuous weight gain. In addition to controlling the patient's diet, we also need to strengthen the healthy exercise guidance for patients, such that the calories are burned appropriately, and help them to reduce weight and alleviate the disease. Reasonable exercise increases the basal metabolic rate and improves insulin sensitivity to better control blood glucose levels and reduce the occurrence of complications.

To the best of our knowledge, this is the first study to analyze the endocrine characteristics and risk factors of patients with T2DM with gastrointestinal autonomic neuropathy. However, this study has several limitations. One of the limitations is that it was based on retrospective data; therefore, causality cannot be inferred. Large-scale, multicenter, prospective studies are required to confirm our results. Another limitation is that the small sample size may have weakened the generalizability of the results.

In summary, endocrine abnormalities in patients with T2DM with gastrointestinal autonomic neuropathy are mainly the abnormalities of ACTH. BMI, advanced age, FINS, TG, and FPG are risk factors for abnormal ACTH levels in these patients. Future research should focus on the effect of abnormal ACTH levels on the prognosis of patients with T2DM with gastrointestinal autonomic neuropathy. In addition, the sample size of this study was relatively small; further, it was a single-center study. In future studies, the sample size should be increased and many study sites should be included to further assess the feasibility and effect.

Author contributions

Conceptualization: Wei Guan, Shan Li, Xiaoqin Li.
Data curation: Wei Guan.
Formal analysis: Wei Guan, Yuqin Kang.
Funding acquisition: Wei Guan.
Investigation: Wei Guan.
Methodology: Wei Guan, Yuqin Kang.
Project administration: Wei Guan, Yuqin Kang.
Software: Shan Li, Wenzao Sun.
Validation: Shan Li, Wenzao Sun, Yuqin Kang, Xiaoqin Li.
Visualization: Shan Li, Wenzao Sun, Yuqin Kang, Xiaoqin Li.
Resources: Wenzao Sun.
Supervision: Wenzao Sun.
Writing – original draft: Wenzao Sun, Xiaoqin Li.
Writing – review & editing: Wenzao Sun, Xiaoqin Li.

References

[1] Yang S, Lin R, Si L, et al. Cod-liver oil improves metabolic indices and hs-CRP levels in gestational diabetes mellitus patients: a double-blind randomized controlled trial. J Diabetes Res. 2019;2019:7074042.
[2] Xu X, Ruan L, Tian X, et al. Calcium inhibitor inhibits high glucose-induced hypertrophy of H9C2 cells. Mol Med Rep. 2020;22:1783–92.
[3] Dasgupta K, Boulé N, Henson J, et al. Remission of type 2 diabetes and improved diastolic function by combining structured exercise with meal replacement and food reintroduction among young adults: the RESET for REMISSION randomised controlled trial protocol. BMJ Open. 2022;12:e063888.
[4] Chen ZG, He H, Luo HB. Correlation analysis between body fat parameters and insulin resistance in obese patients with type 2 diabetes. China Modern Med Appl. 2019;13:30–2.
[5] Mo S, Sun LJ. Correlation between abdominal fat distribution and insulin resistance in overweight/ obese patients with type 2 diabetes. Chin J Exp Diagnostics. 2020;24:57–9.
[6] Xiao L, Zou K, Zhou D, et al. Changes of blink reflex in type 2 diabetes mellitus. J Diabetes Res. 2021;2021:2473193.
[7] Kobori T, Onishi Y, Iwamoto M, et al. Association of insulin treatment with gastric residue during an esophagogastroduodenoscopy. J Diabetes Investig. 2022;13:501–4.
[8] Chen JY, Shan XJ, Liu M, et al. Effect of calcitriol combined with metformin on early nephropathy of abdominal obesity type 2 diabetes. Hebei Med J. 2020;26:602–5.
[9] Liu CL, Jin XP, Wang Y, et al. Relationship between serum cortisol level and blood glucose and lipids in obese patients with type 2 diabetes. J Modern Int Trad Chin Western Med. 2018;27:660–3.
[10] Chang MX, Gu TW, Zhu DL. Study on the correlation between serum cortisol and nonalcoholic fatty liver disease in patients with type 2 diabetes. J Clin Internal Med. 2020;37:166–9.
[11] Association DBoCM. Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus (2013 edition). Chin J Endocrine Metabol. 2013;37:311–98.
[12] Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. Diabetes Care. 2003;26:1553–79.
[13] Fu AB, Xie YT, He BB, et al. Correlation analysis between nocturnal cortisol level and microvascular complications in overweight/ obese patients with type 2 diabetes. Chin J Endocrinol Metabol. 2018;34:834–8.
[14] Zhou WJ, He FP, Yang XK. The diagnostic significance of ACTH in 15508 patients with hypertension, diabetes and dwarfism was analyzed. Chin J Sanitary Inspect. 2021;31:756–60.
[15] Zhu Y, Zhang PZ, Bi Y. Study on the relationship between blood ACTH, cortisol levels and their rhythm and diabetes nephropathy. Chin J Diabetes. 2021;13:597–602.
[16] Wang C, Wang J, Chen K, et al. Caprylic acid (C8:0) promotes bone metastasis of prostate cancer by dysregulated adipo-osteogenic balance in bone marrow. Cancer Sci. 2020;111:3600–12.
[17] Zhang H, Shen Y, Kim IM, et al. The impaired bioenergetics of diabetic cardiac microvascular endothelial cells. Front Endocrinol (Lausanne). 2021;12:642857.
[18] Zhang LY, Zhang HJ. Study on the correlation between cortisol and bone mineral density in patients with type 2 diabetes. Henan Med Res. 2018;27:3083–7.
[19] Wu QM, Wang DH, Liao J, et al. Relationship between early morning glucocorticoid level and bone mineral density in elderly women with osteoporotic vertebral compression fractures. Guizhou Med. 2019;43:1388–9.
[20] Nesto R. C-reactive protein, its role in inflammation, type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. Diabet Med. 2004;21:810–7.
[21] Patrick L, Uzick M. Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha-tocopherol, red yeast rice, and olive oil polyphenols. A review of the literature. Altern Med Rev. 2001;6:248.
[22] Chait A, Den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Fron Cardiovascular Med. 2020;7:22.
[23] Fuster JJ, Ouchi N, Gokce N, et al. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. Circ Res. 2016;118:1786–807.
[24] Havel PJ. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes. 2004;53:S143–51.
[25] Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. Curr Opin Lipidol. 2002;13:51–9.
[26] Sobczak AIS, Blindauer CA, Stewart AJ. Changes in plasma free fatty acids associated with type-2 diabetes. Nutrients. 2019;11:2202.
[27] Wan EYF, Fong DYT, Fung CSC, et al. Classification rule for 5-year cardiovascular diseases risk using decision tree in primary care Chinese patients with type 2 diabetes mellitus. Sci Rep. 2017;7:15238.
[28] Huang MC, Lin KD, Chen HJ, et al. Validity of a short food frequency questionnaire assessing macronutrient and fiber intakes in patients of Han Chinese descent with type 2 diabetes. Int J Environ Res Public Health. 2018;15:1142.