doi: 10.13241/j.cnki.pmb.2021.22.016

外周血晚期糖基化终产物、外周血锌转运蛋白 8 与糖尿病脂代谢紊乱的相关性 *

高旭航 张丽婷 卓凤婷 何志杰 蔡泉方

（中国人民解放军联勤保障部队第九一〇医院内分泌科 福建 泉州 362000）

摘要 目的：探讨外周血晚期糖基化终产物 (the Receptor of Advanced Glycation Endproducts，RAGE)、外周血锌转运蛋白 8(Zinc transporter 8，ZnT8)与糖尿病脂代谢紊乱的相关性。**方法：**2015 年 8 月到 2020 年 9 月选择在本院诊治的 2 型糖尿病患者 118 例作为糖尿病组，同期选择在本院体检的健康人 118 例作为对照组。检测两组外周血 RAGE、ZnT8、脂代谢水平，调查患者的一般资料并进行相关性分析。**结果：**糖尿病组的血清 RAGE、ZnT8 含量都高于对照组(P<0.05)。糖尿病组的甘油三酯(Triglycerides，TG)、总胆固醇(Total cholesterol，TC)、低密度脂蛋白(Low-density lipoprotein cholesterol，LDL-C)、视黄醇结合蛋白 4(Retinol binding protein 4，RBP4)、游离脂肪酸(Free fatty acid，FFA)含量高于对照组(P<0.05)，高密度脂蛋白(High density liptein cholesterol，HDL-C)、脂联素(Adiponectin，APN) 含量低于对照组 (P<0.05)。在糖尿病组中，Pearson 分析显示 RAGE、ZnT8 与 TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都存在相关性(P<0.05)。多因素 logistic 回归分析显示 RAGE、ZnT8、TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都为影响患者空腹血糖的重要因素(P<0.05)。**结论：**糖尿病患者的外周血 RAGE、ZnT8 多呈高表达状况，也多伴随有脂代谢紊乱，RAGE、ZnT8 与脂代谢指标存在相关性，也可共同参与调节糖尿病的发生与发展。

关键词：糖尿病；晚期糖基化终产物；锌转运蛋白 8；脂代谢；游离脂肪酸；视黄醇结合蛋白 4

中图分类号：R587.2 **文献标识码：**A **文章编号：**1673-6273(2021)22-4279-04

Correlation between Advanced Glycation end Products in Peripheral Blood, Zinc Transporter 8 in Peripheral Blood and Lipid Metabolism Disorders in Diabetes*

GAO Xu-hang, ZHANG Li-ting, ZHUO Feng-ting, HE Zhi-jie, CAI Quan-fang

(Department of Endocrinology, No. 910 Hospital, Joint Logistics Support Force, Chinese People's Liberation Army, Quanzhou, Fujian, 362000, China)

ABSTRACT Objective: To investigate the relationship between the Receptor of Advanced Glycation Endproducts (RAGE), Zinc transporter 8 (ZnT8) and lipid metabolism disorders in diabetes. **Methods:** From August 2015 to September 2020, 118 cases of patients with type 2 diabetes who were diagnosed and treated in this hospital were selected as the diabetes group, and 118 cases of healthy people who given physical examination in this hospital were selected as the control group during the same period. The levels of RAGE, ZnT8 and lipid metabolism in the peripheral blood of the two groups were detected, the general data of the patients were investigated and the correlation analysis were carried out. **Results:** The serum levels of RAGE and ZnT8 in the diabetes group were higher than those in the control group (P<0.05). The levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), Free fatty acid (FFA). Retinol binding protein 4 (RBP4) in the diabetic group were higher than the control group (P<0.05), the levels of high density lipoprotein (HDL-C) and adiponectin (APN) were lower than the control group (P<0.05). In the diabetes group, Pearson analysis showed that RAGE and ZnT8 were correlated with TG, TC, LDL-C, APN, HDL-C, FFA, RBP4 (P<0.05). Multivariate logistic regression analysis showed that RAGE, ZnT8, TG, TC, LDL-C, APN, HDL-C, FFA, RBP4 were all important factors affected fasting blood glucose (P<0.05). **Conclusion:** Peripheral blood RAGE and ZnT8 of diabetic patients are mostly highly expressed, and most of them are accompanied by lipid metabolism disorders. RAGE and ZnT8 are related to lipid metabolism indicators and can also participate in the regulation of the occurrence and development of diabetes.

Key words: Diabetes; Advanced glycation end products; Zinc transporter 8; Lipid metabolism; Free fatty acids; Retinol binding protein 4

Chinese Library Classification(CLC): R587.2 Document code: A

Article ID: 1673-6273(2021)22-4279-04

* 基金项目：福建省自然科学基金计划项目(13161134)

作者简介：高旭航(1986-)，男，本科，住院医师，研究方向：内分泌相关疾病，电话：13905004543，E-mail：gaoyuhanggg86@163.com

（收稿日期：2021-05-02 接受日期：2021-05-25）

前言

当前由于各种因素的影响，2 型糖尿病患者的发病率逐年增高，其由遗传和环境因素共同引起的一组以糖代谢紊乱为主要表现的临床疾病[1]。随着病情及病程进展，糖尿病可并发各种代谢紊乱疾病，其中脂代谢紊乱与微血管病变存在相关性[2,3]。比如机体长期血糖升高可导致 LDL-C 水平升高，从而加重微血管损害，因此早期分析脂代谢紊乱与糖尿病疾病直接的相关性，便于提出对症治疗，以改善患者的预后效果[4-6]。RAGE 是一种信号转导受体，可表现于神经元、内皮细胞、平滑肌细胞上，此受体可与晚期糖基化终末产物、S100 蛋白、淀粉样蛋白结合，从而介导多种疾病的生理与病理过程[7,8]。ZnT8 是糖尿病的关键抗原，定位于胰岛β 细胞分泌囊膜上，可使锌掺入到胰岛素囊泡中，参与调节胰岛素的旁分泌和自分泌[9,10]。ZnT8 由 369 个氨基酸组成，不仅表达于胰岛β 细胞，在胰岛素合成与分泌中起着重要作用[11,12]。本文具体探讨了外周血 RAGE、ZnT8 与糖尿病脂代谢紊乱的相关性，希望明确 RAGE、ZnT8 在糖尿病脂代谢紊乱中的作用，进一步探索糖尿病脂代谢紊乱的信号传导机制。

1 资料与方法

1.1 研究对象

2015 年 8 月到 2020 年 9 月选择在本院诊治的 2 型糖尿病患者 118 例作为糖尿病组，同期选择在本院体检的健康人 118 例作为对照组。纳入标准：糖尿病组符合 2 型糖尿病的诊断标准；对照组均无糖尿病家族史及自身免疫疾病史，空腹及餐后 2 h 血糖正常；年龄 20-75 岁；患者签署了知情同意书；本院伦理委员会批准了此次研究。排除标准：合并恶性肿瘤者；精神异常者；妊娠、哺乳期患者；1 型糖尿病患者；调查资料缺乏者。

两组入选者一般资料对比差异无统计学意义（$P>0.05$），见表 1。糖尿病患者中空腹血糖（8.24± 1.22）mmol/L。

表 1 两组一般资料对比

Table 1 Comparison of two sets of general information

Groups	n	Gender (M/F)	Age(years)	BMI(kg/m²)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Diabetes group	118	58/60	54.87± 4.67	24.72± 2.15	124.77± 10.47	75.83± 6.78
Control group	118	59/59	54.66± 5.19	24.22± 1.77	125.01± 13.47	75.98± 5.55

1.2 外周血 RAGE、ZnT8 检测

所有入选者均禁食 8 h 以上晨起空腹抽取静脉血 2-3 mL，2 h 内离心 20 min 后分离上层血清，保存在 -80℃冰箱备用，采用酶联免疫法检测血清 RAGE 与 ZnT8 含量。

1.3 脂代谢指标检测

取 1.2 中的血液样本，采用全自动生化分析仪检测 TG、TC、HDL-C、LDL-C 含量，采用酶法检测 RBP4、FFA、APN 含量，严格按照操作说明书操作。

1.4 统计方法

选择 SPSS20.00 软件进行数据分析，计量数据选择($\bar{x}\pm s$)差表示，计数数据采用(%)表示，对比方法分别为 t 检验与卡方 x^2 检验等，相关性分析采用 Pearson 分析，影响因素分析采用多因素 logistic 回归分析，检验水准为α=0.05。

2 结果

2.1 血清 RAGE、ZnT8 含量对比

糖尿病组的血清 RAGE、ZnT8 含量都高于对照组(P<0.05)。见表 2。

表 2 两组血清 RAGE、ZnT8 含量对比(pg/mL，$\bar{x}\pm s$)

Table 2 Comparison of serum RAGE, ZnT8 contents between two groups(pg/mL, $\bar{x}\pm s$)

Groups	n	RAGE	ZnT8
Diabetes group	118	1782.44± 253.82*	98.76± 5.55*
Control group	118	198.72± 16.30	10.76± 1.11

Note: Compared with the control group, *P<0.05.

2.2 脂代谢指标对比

糖尿病组的 TG、TC、LDL-C、FFA、RBP4 含量高于对照组，HDL-C、APN 含量低于对照组(P<0.05)。见表 3。

表 3 两组脂代谢指标对比($\bar{x}\pm s$)

Table 3 Comparison of lipid metabolism indexes between two groups($\bar{x}\pm s$)

Groups	n	TG(mmol/L)	TC(mmol/L)	LDL-C (mmol/L)	APN(μg/mL)	HDL-C (mmol/L)	FFA(mmol/L)	RBP4(mg/L)
Diabetes group	118	2.28± 0.21*	5.19± 0.34*	3.33± 0.18*	8.92± 0.37*	1.06± .22*	1.87± 0.23*	42.13± 2.47*
Control group	118	1.48± 0.18	4.14± 0.38	2.87± 0.34	14.28± 1.57	1.38± 0.15	0.68± 0.09	31.39± 3.33

Note: Compared with the control group, *P<0.05.

2.3 相关性分析

在糖尿病组中，Pearson 分析显示 RAGE、ZnT8 与 TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都存在相关性(P<0.05)。见表4。

2.4 影响因素分析

在糖尿病组中，多因素 logistic 回归分析显示 RAGE、ZnT8、TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都为影响患者空腹血糖的重要因素(P<0.05)。见表 5。

表 4 外周血晚 RAGE、ZnT8 与糖尿病脂代谢紊乱的相关性(n=118)

Table 4 Correlation of Late RAGE, ZnT8 in Peripheral Blood with Diabetic Lipid Metabolism Disorder (n=118)

Index		TG	TC	LDL-C	APN	HDL-C	FFA	RBP4
RAGE	r	0.533	0.495	0.555	0.596	0.432	0.672	0.611
	P	0.005	0.010	0.004	0.001	0.017	0.000	0.000
ZnT8	r	0.535	0.501	0.598	0.611	0.456	0.699	0.622
	P	0.006	0.010	0.001	0.000	0.015	0.000	0.000

表 5 影响糖尿病患者空腹血糖的多因素 logistic 回归分析(n=118)

Table 5 Multivariate regression analysis of fasting blood glucose logistic diabetic patients (n=118)

Index	Wald	*P*	OR	95%CI
RAGE	4.053	0.023	0.922	0.865-0.998
ZnT8	5.495	0.014	0.782	0.492-0.888
TG	3.775	0.029	0.812	0.673-0.992
TC	3.882	0.026	0.888	0.714-0.981
LDL-C	5.677	0.010	0.913	0.583-0.995
APN	0.555	0.000	3.572	1.227-6.255
HDL-C	0.567	0.021	1.874	1.222-3.722
FFA	7.398	0.000	0.376	0.033-0.874
RBP4	8.372	0.001	0.456	0.145-0.821

3 讨论

2 型糖尿病是近年来患病率迅速增加的内分泌科疾病，其发病周期较长，并具有迁延难愈、反复发作等特点，未接受及时治疗则易引起各种并发症，对患者日常生活造成不利影响，甚至危及生命[14]。现代研究表明空腹血糖的调节有赖于足量基础胰岛素的分泌和肝脏对胰岛素正常的敏感性，若此过程存在异常，则可诱发糖尿病的发生[15]。

本研究显示糖尿病组的血清 RAGE、ZnT8 含量都高于对照组(P<0.05)，结合 Jayaraj RL[16]和 Johansson KS[17]研究结果分析：RAGE 可通过淀粉样蛋白、两性霉素、晚期糖基化终末产物等配体对多种疾病的发生与发展进行调整，因此在糖尿病患者血清中其水平显著上升。RAGE 可促使机体细胞内氧化应激的产生，并且可进一步激活分裂原激活的蛋白激酶家族成员，引起细胞内自由基产生增多，从而导致炎症因子的大量释放，诱发糖尿病的形成[18]。并且 RAGE 与受体的相互作用引起的氧化应激也会直接导致相关神经元死亡，激活小胶质细胞，也可间接地导致相关神经元死亡[19]。ZnT8 为一种糖尿病自身抗原，对自身免疫糖尿病的诊断和预测具有应用价值。ZnT8 蛋白属于阳离子扩散易化家族，含 369 个氨基酸，为此一种 6 次跨膜蛋白，在进化过程中比较保守[20]。ZnT8 定位于胰岛β 细胞分泌囊膜上，能调节胰岛素分泌，ZnT8 表达升高可导致电压敏感性钙通道开放，使得机体内血糖升高[21,22]。

糖尿病为一种代谢性疾病，该病患者长期呈高血糖状态导致患者表现为消瘦、多饮多食等症状[23]。糖尿病患者多伴随有脂代谢紊乱，糖毒性与脂毒性协同作用可导致胰岛β 细胞功能障碍与胰岛素抵抗加重，特别是脂代谢紊乱被视为是导致糖尿病病情进展的重要因素 [24]。本研究显示糖尿病组的 TG、TC、LDL-C、FFA、RBP4 含量高于对照组 (P<0.05)，HDL-C、APN 含量低于对照组(P<0.05)。从机制上分析，FFA、RBP4 具有相对较强的组织、细胞毒性，可抑制葡萄糖的氧化和转运，导致细胞生长周期调控紊乱与细胞转运机制改变，进而引起胰岛素抵抗的发生[25,26]。Maula A 等[27]研究提出：人体内血清 FFA、RBP4 水平相对较低，糖尿病可导致 FFA、RBP4 表达量升高，导致其毒性作用相应增大，致使神经与血管受损，导致患者的疾病恶化，与本研究结果一致。脂肪组织作为 TG 的储库，可分泌多种脂代谢相关细胞因子，也可释放游离脂肪酸，并参与机体葡糖糖、脂肪代谢等过程[28]。相关研究显示：APN 是机体脂肪细胞分泌的最丰富的肽，能加快血浆游离脂肪酸的清除、减轻炎症反应、组织血管损伤，也为一种具有负性调节功能的蛋白质，其血清含量降低可导致机体糖、脂代谢异常，使得体脂分布异常及胰岛素抵抗，也可导致代谢综合征的发生与发展，与本研究结果一致[29]。

糖尿病是一种由环境因素、多种遗传因子共同作用所引起

的以慢性高血糖为特征的代谢紊乱性疾病，患者体内常存在有多种自身抗体，这些自身抗体是自身免疫反应的重要检测指标[30]。RAGE 是免疫蛋白样跨膜受体，也是晚期糖基化终末产物的受体，其表达水平下降可有效保护机体内的神经元及突触[31]。锌在胰岛β 细胞中含量最高，存在形式为锌胰岛素结晶，包括 6 个胰岛素和 2 个锌离子结合的六聚物。低锌血症是糖尿病患者普遍症状，锌的转运需要大量高效的锌转运蛋白抗体来完成，锌转运蛋白抗体高表达说明锌含量增强，同时胰岛素分泌功能增强[32]。本研究 Pearson 分析显示糖尿病患者的 RAGE、ZnT8 与 TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都存在相关性（P<0.05）；多因素 logistic 回归分析显示 RAGE、ZnT8、TG、TC、LDL-C、APN、HDL-C、FFA、RBP4 都为影响患者空腹血糖的重要因素(P<0.05)。从机制上分析，APN 能加快血浆游离脂肪酸的清除与降低 TG 水平，也可减轻炎症反应与组织血管损伤，增加胰岛素的敏感性等作用。RBP4 是由肝脏及脂肪组织分泌，RBP4 表达水平上升可影响机体糖、脂代谢异常，导致体脂分布异常及胰岛素抵抗。RAGE、ZnT8 的大量表达可引起红细胞膜携带的负电荷下降，引起血液浓缩，增加血液粘度，结合载脂蛋白 A 形成载脂蛋白 A，导致机体内脂代谢指标异常，可对机体其他器官造成直接或间接损害，从而导致患者的病情恶化[33,34]。本研究也存在一定的不足，没有设置不同病情的糖尿病组，也没有进行 RAGE、ZnT8 表达阳性分析，将在后续研究中进行探讨。

总之，糖尿病患者的外周血 RAGE、ZnT8 多呈高表达状况，也多伴随有脂代谢紊乱，RAGE、ZnT8 与脂代谢指标存在相关性，也可共同参与调节糖尿病的发生与发展，可考虑作为临床上糖尿病患者病情监测的参考指标。

参 考 文 献（References）

[1] Valerio C M, Ekta, Gupta M, et al. Pathobiological and molecular connections involved in the high fructose and high fat diet induced diabetes associated nonalcoholic fatty liver disease [J]. Diabetol Metab Syndr, 2020, 69(9): 851-867

[2] Wali J A, Jarzebska N, Raubenheimer D, et al. Cardio-Metabolic Effects of High-Fat Diets and Their Underlying Mechanisms-A Narrative Review[J]. Nutrients, 2020, 12(5): 113-119

[3] Watanabe M. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature [J]. Diabetes Metab J, 2020, 21(8): e13024

[4] Wilson A S, Koller K R, Ramaboli M C, et al. Diet and the Human Gut Microbiome: An International Review [J]. Inflamm Res, 2020, 65(3): 723-740

[5] Yari Z, Behrouz V, Zand H, et al. New Insight into Diabetes Management: From Glycemic Index to Dietary Insulin Index [J]. Curr Diabetes Rev, 2020, 16(4): 293-300

[6] Alessi J, De Oliveira G B, Schaan B D, et al. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes[J]. Nutrients, 2020, 12(9): 80

[7] Chiang J Y L, Ferrell J M. Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy [J]. Am J Physiol Gastrointest Liver Physiol, 2020, 318(3): G554-g573

[8] Dinda B, Dinda M, Roy A, et al. Dietary plant flavonoids in prevention of obesity and diabetes [J]. Adv Protein Chem Struct Biol, 2020, 120 (12): 159-235

[9] Feng Q Q, Ojo O O, Wang X H, et al. Intermittent Fasting as Part of the Management for T2DM: from Animal Models to Human Clinical Studies[J]. Nutrients, 2020, 20(4): 13

[10] Francque S. Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors[J]. Diabet Med, 2021, 18(1): 24-39

[11] Garcia-Serrano A M, Duarte J M N. Brain Metabolism Alterations in Type 2 Diabetes: What Did We Learn From Diet-Induced Diabetes Models?[J]. Front Neurosci, 2020, 14(9): 229

[12] Gemmink A, Schrauwen P, Hesselink M K C. Exercising your fat (metabolism) into shape: a muscle-centred view [J]. Diabetologia, 2020, 63(8): 1453-1463

[13] Groβkopf A, Simm A. Carbohydrates in nutrition: friend or foe?[J]. Z Gerontol Geriatr, 2020, 53(4): 290-294

[14] Henry C J, Kaur B, Quek R Y C. Chrononutrition in the management of diabetes[J]. Nutr Diabetes, 2020, 10(1): 6

[15] Inaishi J, Saisho Y. Beta-Cell Mass in Obesity and Type 2 Diabetes, and Its Relation to Pancreas Fat: A Mini-Review [J]. Nutrients, 2020, 12(12): 878-879

[16] Jayaraj RL, Azimullah S, Beiram R. Diabetes as a risk factor for Alzheimer's disease in the Middle East and its shared pathological mediators[J]. Saudi J Biol Sci, 2020, 27(2): 736-750

[17] Johansson KS, Brønden A, Knop FK, et al. Clinical pharmacology of imeglimin for the treatment of type 2 diabetes [J]. Expert Opin Pharmacother, 2020, 21(8): 871-882

[18] Banday M Z, Sameer A S, Nissar S. Pathophysiology of diabetes: An overview[J]. Avicenna J Med, 2020, 10(4): 174-188

[19] Batch J T, Lamsal S P, Adkins M, et al. Advantages and Disadvantages of the Ketogenic Diet: A Review Article [J]. Diabetes Obes Metab, 2020, 12(8): e9639

[20] Berbudi A, Rahmadika N, Tjahjadi A I, et al. Type 2 Diabetes and its Impact on the Immune System [J]. Curr Diabetes Rev, 2020, 16(5): 442-449

[21] Brichard S M, Maykish A, Sikalidis A K. Utilization of Hydroxyl-Methyl Butyrate, Leucine, Glutamine and Arginine Supplementation in Nutritional Management of Sarcopenia-Implications and Clinical Considerations for Type 2 Diabetes Mellitus Risk Modulation[J]. Int J Mol Sci, 2020, 10(1): 456-459

[22] Lin C H, Shao L, Zhang Y M, et al. An evaluation of liraglutide including its efficacy and safety for the treatment of obesity[J]. 2020, 21 (3): 275-285

[23] Sheu W H H, Chan S P, Matawaran B J, et al. Use of SGLT-2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Abdominal Obesity: An Asian Perspective and Expert Recommendations [J]. 2020, 44(1): 11-32

[24] Shukla L, Yuan Y, Shayan R, et al. Fat Therapeutics: The Clinical Capacity of Adipose-Derived Stem Cells and Exosomes for Human Disease and Tissue Regeneration [J]. Nat Rev Endocrinol, 2020, 11 (9): 158

[25] Thakkinstian A, Sorop O, Van De Wouw J, et al. Experimental animal models of coronary microvascular dysfunc tion [J]. Nutri ents, 2020, 116(4): 756-770

（下转第 4330 页）

[18] Xu A C, Broome D T, James M S, et al. Predictors for Adverse Outcomes in Diabetic Ketoacidosis in a Multihospital Health System - ScienceDirect[J]. Endocrine Practice, 2020, 26(3): 259-266

[19] Javed S, Singh P, Paliwal S K. Correlation of severity of dengue with serum aminotransferase levels [J]. International Journal of Advances in Medicine, 2021, 8(3): 415

[20] Saldanha S, L. N, L. D, et al. EP1.16-37 Correlation of Serum Albumin and CRP Levels with Chemotherapy Toxicity in Patients of Metastatic Lung Cancer [J]. Journal of Thoracic Oncology, 2019, 14 (10): S1078-S1079

[21] Cowley E, Miller M R, Yin C, et al. Correlation between Medication Administration-Related Errors in Patients with Parkinson Disease and Timing of Pharmacy-Led Best Possible Medication Histories [J]. The Canadian Journal of Hospital Pharmacy, 2021, 74(1): 15-20

[22] CC Gutiérrez-Ortiz, MJ Concepción-Zavaleta, EJ García-Villasante. Diabetic ketoacidosis treatment during COVID-19 pandemic in a country with scarce health resources [J]. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020, 14(6): 1847-1848

[23] Nw A, Ks A, Ak A, et al. A case of invasive pulmonary aspergillosis diagnosed by transbronchial lung biopsy during treatment for diabetic ketoacidosis in a type 1 diabetic patient [J]. Journal of Infection and Chemotherapy, 2020, 26(2): 274-278

[24] Wei Y, Wu C, Su F, et al. Clinical characteristics and outcomes of patients with diabetic ketoacidosis of different severity [J]. Medicine, 2020, 99(45): e22838

[25] Kaushal T, Lord K, Olsen R, et al. Improving Disposition Decision-Making for Pediatric Diabetic Ketoacidosis[J]. Pediatric Quality and Safety, 2020, 5(2): e260

[26] Wang K M, Isom R T. SGLT2 Inhibitor-Induced Euglycemic Diabetic Ketoacidosis: A Case Report [J]. Kidney Medicine, 2020, 2 (2): 218-221

[27] Hussein M, Kilfoil L. Using your "head backward" in the management of diabetic ketoacidosis[J]. The Nurse practitioner, 2020, 45(1): 7-11

[28] Gr Iffey R T, Schneider R M, Malone N, et al. Diabetic Ketoacidosis Management in the Emergency Department: Implementation of a Protocol to Reduce Variability and Improve Safety [J]. The Journal for Healthcare Quality (JHQ), 2019, 41(6): 1

（上接第 4282 页）

[26] Lopaschuk G D, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review[J]. JACC Basic Transl Sci, 2020, 5(6): 632-644

[27] Maula A. Educational weight loss interventions in obese and overweight adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials [J]. Int J Mol Sci, 2020, 37(4): 623-635

[28] Ojo O. The Role of Dietary Fibre in Modulating Gut Microbiota Dysbiosis in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials[J]. J Pers Med, 2020, 12(11): 223-229

[29] Piché M E, Tchernof A, Després J P. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases[J]. Circ Res, 2020, 126(11): 1477-1500

[30] Roden M, Sacks F, Tacke F, et al. Non-Alcoholic Fatty Liver Disease Treatment in Patients with Type 2 Diabetes Mellitus; New Kids on the Block[J]. Nat Rev Gastroenterol Hepatol, 2020, 18(2): 172-181

[31] Ross L J, Byrnes A, Hay R L, et al. Exploring the highs and lows of very low carbohydrate high fat diets on weight loss and diabetes- and cardiovascular disease-related risk markers: A systematic review [J]. Nutr Diet, 2021, 78(1): 41-56

[32] Thondam S K, Cuthbertson D J, Wilding J P H. The influence of Glucose-dependent Insulinotropic Polypeptide (GIP) on human adipose tissue and fat metabolism: Implications for obesity, type 2 diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD)[J]. Peptides, 2020, 125(9): 170208

[33] Tozzi R, Risi R, Tuccinardi D, et al. Obesity, Bioactive Lipids, and Adipose Tissue Inflammation in Insulin Resistance [J]. Obes Rev, 2020, 12(5): 223-229

[34] Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility [J]. Diabetologia, 2020, 63(3): 453-461