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2型糖尿病患者血清鸢尾素、摄食抑制因子-1、3-硝基酪氨酸水平与糖脂代谢和阻塞性睡眠呼吸暂停低通气综合征的关系研究*

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摘要 目的:探讨2型糖尿病(T2DM)患者血清鸢尾素(Irisin)、摄食抑制因子-1(Nesfatin-1)、3-硝基酪氨酸(3-NT)水平与糖脂代谢和阻塞性睡眠呼吸暂停低通气综合征(OSAHS)的关系。**方法:**选择2020年4月~2021年9月期间中国人民解放军总医院京南医疗区收治的T2DM患者80例作为研究对象,根据多导睡眠图(PSG)检查结果,合并OSAHS的51例患者列为T2DM合并OSAHS组,剩余的29例纳为T2DM未合并OSAHS组。选择同期来中国人民解放军总医院京南医疗区体检的40例健康志愿者作为对照组。对比T2DM患者、对照组的Irisin、Nesfatin-1、3-NT水平,采用Pearson相关性分析显示Irisin、Nesfatin-1、3-NT与糖脂代谢指标的相关性。T2DM患者发生OSAHS的影响因素采用多因素Logistic回归分析。**结果:**T2DM合并OSAHS组、T2DM未合并OSAHS组Irisin低于对照组,且T2DM合并OSAHS组低于T2DM未合并OSAHS组($P<0.05$)。T2DM合并OSAHS组、T2DM未合并OSAHS组Nesfatin-1、3-NT高于对照组,且T2DM合并OSAHS组高于T2DM未合并OSAHS组($P<0.05$)。T2DM合并OSAHS组、T2DM未合并OSAHS组糖化血红蛋白(HbA1c)、空腹血糖(FBG)、餐后2h血糖(2hPG)高于对照组,且T2DM合并OSAHS组高于T2DM未合并OSAHS组($P<0.05$)。T2DM合并OSAHS组、T2DM未合并OSAHS组三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)、总胆固醇(TC)较对照组高,高密度脂蛋白胆固醇(HDL-C)低于对照组($P<0.05$)。Pearson相关性分析结果显示,Irisin与HbA1c、FBG、2hPG呈负相关,Nesfatin-1、3-NT与HbA1c、FBG、2hPG呈正相关($P<0.05$)。T2DM合并OSAHS组、T2DM未合并OSAHS组的年龄、合并高血压、体质量指数、AHI、空腹C肽、合并冠心病对比有差异($P<0.05$)。Irisin、Nesfatin-1、3-NT、HbA1c、FBG、2hPG、年龄、合并高血压是T2DM患者发生OSAHS的影响因素($P<0.05$)。**结论:**T2DM合并OSAHS患者的Irisin、Nesfatin-1、3-NT水平表达异常,参与着机体的糖脂代谢过程及OSAHS发生,且OSAHS发生同时还受到HbA1c、FBG、2hPG、年龄、合并高血压的影响,可考虑对上述因素进行早期监测,以进行相关干预。

关键词:2型糖尿病;鸢尾素;摄食抑制因子-1;3-硝基酪氨酸;糖脂代谢;阻塞性睡眠呼吸暂停低通气综合征

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Relationship Study between Serum Irisin, Nesfatin-1 and 3- Nitrotyrosine Levels in Patients with Type 2 Diabetes Mellitus and Glucose and Lipid Metabolism and Obstructive Sleep Apnea Hypopnea Syndrome*

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ABSTRACT Objective: To investigate the relationship between serum Irisin (Irisin), Nesfatin-1 (Nesfatin-1) and 3-nitrotyrosine (3-NT) levels in type 2 diabetes mellitus (T2DM) and glucose and lipid metabolism and obstructive sleep apnea hypopnea syndrome (OSAHS). **Methods:** 80 patients with T2DM who were treated in Jingnan Medical College of the General Hospital of the Chinese people's Liberation Army from April 2020 to September 2021 were selected as the research object. According to the results of polysomnography (PSG), 51 patients with OSAHS were identified as T2DM combined with OSAHS group, and the remaining 29 patients were included as T2DM without OSAHS group. 40 healthy volunteers who came to Jingnan Medical College of the General Hospital of the Chinese people's Liberation Army for physical examination in the same period were selected as the control group. The Irisin, Nesfatin-1 and 3-NT levels in T2DM patients and control group were compared. Pearson correlation analysis showed the correlation between Irisin, Nesfatin-1 and 3-NT and glucose and lipid metabolism indexes. The influencing factors of OSAHS in patients with T2DM were analyzed by multivariate Logistic regression. **Results:** Irisin in T2DM combined with OSAHS group and T2DM without OSAHS group was lower than that in the control group, and irisin in T2DM combined with OSAHS group was lower than that in T2DM

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without OSAHS group ($P<0.05$). Nesfatin-1 and 3-NT in T2DM combined with OSAHS group and T2DM without OSAHS group were higher than those in the control group, and those in T2DM combined with OSAHS group were higher than those in T2DM without OSAHS group ($P<0.05$). Glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG) and 2h postprandial blood glucose (2hPG) in T2DM combined with OSAHS group and T2DM without OSAHS group were higher than those in control group, and those in T2DM combined with OSAHS group were higher than those in T2DM without OSAHS group ($P<0.05$). Triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) in T2DM combined with OSAHS group and T2DM without OSAHS group were higher than those in control group, while high density lipoprotein cholesterol (HDL-C) was lower than those in control group ($P<0.05$). Pearson correlation analysis showed that Irisin was negatively correlated with HbA1c, FBG and 2hPG, while Nesfatin-1 and 3-NT were positively correlated with HbA1c, FBG and 2hPG ($P<0.05$). There were significant differences in age, hypertension, body mass index, AHI, fasting C-peptide and Complicated coronary heart disease between T2DM combined with OSAHS group and T2DM without OSAHS group ($P<0.05$). Irisin, Nesfatin-1, 3-NT, HbA1c, FBG, 2hPG, age and combined with hypertension were the influencing factors of OSAHS in T2DM patients ($P<0.05$). **Conclusion:** The abnormal expression of Irisin, Nesfatin-1 and 3-NT in T2DM patients with OSAHS is involved in the process of glucose and lipid metabolism, OSAHS occurrence. At the same time, OSAHS occurrence also affected by HbA1c, FBG, 2hPG, age, hypertension. Early detection of the above indicators can be considered for relevant intervention.

Key words: Type 2 diabetes mellitus; Iridin; Nesfatin-1; 3-nitrotyrosine; Glucose and lipid metabolism; Obstructive sleep apnea hypopnea syndrome

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前言

2型糖尿病(T2DM)是临床常见的非传染性疾病,国际糖尿病联盟预计至2045年T2DM患者将增加到6.93亿^[1]。阻塞性睡眠呼吸暂停低通气综合征(OSAHS)是常见的呼吸系统疾病,以睡眠中呼吸暂停、打鼾、高碳酸血症和夜间低氧血症为主要特征^[2]。近年来的研究发现 OSAHS 与机体的糖代谢关系密切,且 T2DM 患者与 OSAHS 并存患病较常见,并且在病程进展中相互影响可导致全身多系统功能障碍^[3]。鸢尾素(Irisin)是代谢性疾病的研究热点指标,可对脂肪组织的耗能产热发挥刺激作用,而 T2DM 属于常见的代谢性疾病,考虑 Irisin 可能参与着 T2DM 的进展^[4]。摄食抑制因子-1(Nesfatin-1)参与摄食、能量代谢等生理过程,既往有研究发现 T2DM 患者体内 Nesfatin-1 水平呈现异常状态^[5]。3-硝基酪氨酸(3-NT)是体内酪氨酸残基与活性氮簇等物质发生硝基化反应形成的产物,可反映体内氧化应激状况,而氧化应激又是 T2DM 发病的主要病理机制之一,考虑 3-NT 可能参与着 T2DM 的进展^[6]。本次研究旨在探讨 T2DM 合并 OSAHS 患者 Irisin、Nesfatin-1、3-NT 的水平变化及 T2DM 合并 OSAHS 的影响因素,进一步分析其临床特点及相关因素,以期临床工作提供一定参考,研究如下。

1 资料与方法

1.1 一般资料

选择2020年4月~2021年9月间中国人民解放军总医院京南医疗区收治的80例T2DM患者,T2DM诊断标准:参考《中国2型糖尿病防治指南》^[7],出现多饮、多食、多尿、体重减轻等症状,餐后2h血糖(2hPG)≥11.1mmol/L,空腹血糖(FBG)≥7.0mmol/L,糖化血红蛋白(HbA1c)≥6.5%。OSAHS诊断标准:参考《阻塞性睡眠呼吸暂停低通气综合征诊治指南》^[8]:睡眠呼吸暂停低通气指数(AHI)≥5次/h,临床上有典型的呼吸暂停、夜间睡眠打鼾伴日间嗜睡等症状。近三个月无手术及其他

严重应激病史。所有研究对象均排除严重心肝肾疾病、风湿免疫性疾病、急性慢性感染性疾病、肿瘤、结缔组织疾病、糖尿病其他严重并发症。根据多导睡眠图(PSG)检查结果,合并 OSAHS 的 51 例患者列为 T2DM 合并 OSAHS 组,剩余的 29 例纳入 T2DM 未合并 OSAHS 组。选择同期来中国人民解放军总医院京南医疗区体检的 40 例健康志愿者作为对照组。对照组同时排除睡眠呼吸暂停、糖尿病、高血脂、高血压、肺部疾病等。

1.2 方法

1.2.1 临床资料 记录所有患者的体质量指数、舒张压、空腹 C 肽、HbA1c、AHI、收缩压、FBG、三酰甘油(TG)、2hPG、总胆固醇(TC)、性别、低密度脂蛋白胆固醇(LDL-C)、年龄、高密度脂蛋白胆固醇(HDL-C)、合并基础性疾病(包括高血压、冠心病、高血脂)。其中 FBG、2hPG 采用血糖仪(罗氏诊断公司生产)检测,空腹 C 肽、HbA1c、TG、TC、LDL-C、HDL-C 采用 NSA-400 全自动生物化学分析仪(沈阳东软医疗电子股份有限公司生产)检测,AHI 采用飞利浦 Alice PDx 便携式睡眠呼吸监测仪检测。**1.2.2 Irisin、Nesfatin-1、3-NT 检测** T2DM 患者入院次日采血 5 mL,对照组于体检当天采血 5 mL,血液标本经离心处理,离心半径 10 cm,3500 r/min 离心 13 min,分离上清液。采用酶联免疫吸附法(试剂盒为上海酶联生物科技有限公司)检测血清 Irisin、Nesfatin-1、3-NT 水平。

1.3 统计学方法

应用 SPSS 26.0 进行数据分析,计量资料经 Kolmogorov-Smirnov 检验,均呈正态分布,且具备方差齐性,以($\bar{x} \pm s$)表示,两组数据比较采用 t 检验,多组数据比较采用 F 检验及 LSD-t 检验。以例(%)表示计数资料,采用 χ^2 检验。采用 Pearson 相关性分析显示 Irisin、Nesfatin-1、3-NT 与糖脂代谢指标的相关性。T2DM 患者发生 OSAHS 的影响因素采用多因素 Logistic 回归分析。 $\alpha=0.05$ 为检验水准。

2 结果

2.1 T2DM 患者、对照组的 Irisin、Nesfatin-1、3-NT 水平对比

T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组 Irisin 低于对照组，且 T2DM 合并 OSAHS 组低于 T2DM 未合并 OSAHS

组 ($P < 0.05$)。T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组 Nesfatin-1、3-NT 高于对照组，且 T2DM 合并 OSAHS 组高于 T2DM 未合并 OSAHS 组 ($P < 0.05$)。见表 1。

表 1 T2DM 患者、对照组的 Irisin、Nesfatin-1、3-NT 水平对比 ($\bar{x} \pm s$)

Table 1 Comparison of Irisin, Nesfatin-1 and 3-NT levels between T2DM patients and control group ($\bar{x} \pm s$)

Groups	Irisin(ng/mL)	Nesfatin-1(μ g/L)	3-NT(nmol/L)
Control group(n=40)	297.81 \pm 21.24	1.23 \pm 0.28	186.93 \pm 24.12
T2DM without OSAHS group (n=29)	216.74 \pm 18.31*	2.19 \pm 0.33*	291.74 \pm 19.13*
T2DM combined with OSAHS group(n=51)	147.33 \pm 14.58*#	3.38 \pm 0.41*#	417.26 \pm 28.37*#
F	38.234	31.482	48.917
P	0.000	0.000	0.000

Note: compared with the control group, * $P < 0.05$. Compared with T2DM without OSAHS group, # $P < 0.05$.

2.2 T2DM 患者、对照组糖脂代谢指标水平对比

T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组 HbA1c、FBG、2hPG 高于对照组，且 T2DM 合并 OSAHS 组高于 T2DM 未合并 OSAHS 组 ($P < 0.05$)。T2DM 合并 OSAHS 组、T2DM 未

合并 OSAHS 组 TG、TC、LDL-C 均高于对照组，HDL-C 低于对照组 ($P < 0.05$)。T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组 TG、TC、LDL-C、HDL-C 组间对比未见明显差异 ($P > 0.05$)，见表 2。

表 2 T2DM 患者、对照组糖脂代谢指标水平对比 ($\bar{x} \pm s$)

Table 2 Comparison of glucose and lipid metabolism indexes between T2DM patients and control group ($\bar{x} \pm s$)

Groups	HbA1c(%)	FBG(mmol/L)	2hPG(mmol/L)	TG(mmol/L)	TC(mmol/L)	LDL-C(mmol/L)	HDL-C(mmol/L)
Control group(n=40)	5.79 \pm 0.42	6.03 \pm 0.48	6.91 \pm 0.38	1.37 \pm 0.26	3.71 \pm 0.56	2.85 \pm 0.33	1.79 \pm 0.33
T2DM without OSAHS group (n=29)	8.73 \pm 0.54*	7.21 \pm 0.16*	11.68 \pm 0.44*	1.92 \pm 0.37*	4.93 \pm 0.62*	3.93 \pm 0.49*	1.44 \pm 0.73*
T2DM combined with OSAHS group(n=51)	9.71 \pm 0.62*#	8.63 \pm 0.47*#	15.93 \pm 0.49*#	1.91 \pm 0.38*	4.99 \pm 0.96*	3.98 \pm 0.55*	1.41 \pm 0.68*
F	41.293	38.271	30.283	33.685	30.817	29.813	22.418
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: compared with the control group, * $P < 0.05$. Compared with T2DM without OSAHS group, # $P < 0.05$.

2.3 Irisin、Nesfatin-1、3-NT 与糖脂代谢指标的相关性

Pearson 相关性分析结果显示，Irisin 与 HbA1c、FBG、2hPG 呈负相关，Nesfatin-1、3-NT 与 HbA1c、FBG、2hPG 呈正相关

($P < 0.05$)。Irisin、Nesfatin-1、3-NT 与 TG、TC、LDL-C、HDL-C 均无相关性 ($P > 0.05$)，见表 3。

表 3 Irisin、Nesfatin-1、3-NT 与糖脂代谢指标的相关性

Table 3 Correlation between Irisin, Nesfatin-1, 3-NT and glucose and lipid metabolism indexes

Factors	Irisin		Nesfatin-1		3-NT	
	r	P	r	P	r	P
HbA1c	-4.529	0.000	3.998	0.007	4.637	0.000
FBG	-4.284	0.000	4.182	0.002	4.456	0.000
2hPG	-4.371	0.000	4.273	0.000	4.374	0.000
TC	-2.384	0.173	1.024	0.298	2.156	0.182
TG	-1.923	0.216	1.382	0.246	2.472	0.171
LDL-C	-2.056	0.195	1.474	0.231	2.943	0.136
HDL-C	-1.884	0.237	1.638	0.209	1.384	0.241

2.4 T2DM 患者发生 OSAHS 的单因素分析

T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组的性别、合并高血脂、收缩压、舒张压组间对比无统计学差异($P>0.05$)。

T2DM 合并 OSAHS 组、T2DM 未合并 OSAHS 组的年龄、合并高血压、体质量指数、AHI、空腹 C 肽、合并冠心病对比有差异($P<0.05$),见表 4。

表 4 T2DM 患者发生 OSAHS 的单因素分析
Table 4 Univariate analysis of OSAHS in T2DM patients

Factors	T2DM combined with OSAHS group(n=51)	T2DM without OSAHS group(n=29)	t/ χ^2	P
Gender(male/female)	29/22	16/13	0.021	0.884
Age(years)	61.78±4.28	54.69±5.22	6.571	0.000
Body mass index(kg/m ²)	29.18±1.21	26.93±1.16	8.114	0.000
Systolic pressure(mmHg)	128.57±6.49	129.06±10.22	-0.262	0.794
Diastolic pressure(mmHg)	87.31±6.29	86.49±7.15	-0.117	0.907
Fasting C-peptide(ng/mL)	2.75±0.62	3.96±0.42	-9.348	0.000
AHI	22.47±2.46	1.42±0.38	45.649	0.000
Combined with hypertension	19(37.25)	3(10.34)	6.715	0.010
Combined with coronary heart disease	15(29.41)	2(6.90)	5.600	0.018
Combined with hyperlipidemia	6(11.76)	1(3.45)	1.601	0.216

2.5 T2DM 患者发生 OSAHS 的多因素 Logistic 回归分析

以表 1、表 2、表 4 中有统计学意义的因素为自变量,以 T2DM 患者是否发生 OSAHS 为自变量(未发生 =0,发生 =1)。Irisin、Nesfatin-1、3-NT、HbA1c、FBG、2hPG、年龄、体质量指数、空腹 C 肽、AHI 为原值输入,合并高血压(赋值:0= 未合并,1=

合并)、合并冠心病(赋值:0= 未合并,1= 合并)。构建多因素 Logistic 回归模型,采用 ENTER 法,最终分析结果显示:Irisin、Nesfatin-1、3-NT、HbA1c、FBG、2hPG、年龄、合并高血压是 T2DM 患者发生 OSAHS 的影响因素($P<0.05$),见表 5。

表 5 T2DM 患者发生 OSAHS 的多因素 Logistic 回归分析
Table 5 Multivariate Logistic regression analysis of OSAHS in T2DM patients

Variables	β	SE	Wald χ^2	OR	95%CI	P
Irisin	0.412	0.386	13.291	2.091	1.473~2.886	0.000
Nesfatin-1	0.389	0.291	10.323	1.953	1.318~2.406	0.000
3-NT	0.433	0.337	7.364	1.886	1.415~2.617	0.001
HbA1c	0.456	0.374	9.027	2.381	1.762~2.973	0.000
FBG	0.349	0.389	8.536	1.727	1.296~2.408	0.000
2hPG	0.362	0.307	12.482	1.916	1.684~2.472	0.000
Age	0.411	0.297	10.317	1.892	1.485~2.417	0.000
Combined with hypertension	0.426	0.357	9.633	1.906	1.526~2.551	0.000

3 讨论

T2DM 以慢性高血糖为特征,其慢性并发症是患者预后不良或死亡的主要原因之一。OSAHS 则是指睡眠期间出现气流消失或者减弱的临床综合征^[9]。目前的研究认为 OSAHS 可以导致多种炎症因子的分泌增加,而炎症因子的大量分泌会导致内皮通透性下降,血流速度下降,进而减少外周组织对葡萄糖的摄取,加重胰岛素抵抗^[10]。此外,T2DM 与 OSAHS 之间发病机制的内在联系还与人体的氧化应激反应有关^[11]。OSAHS 患者睡眠中反复的呼吸暂停,可引发氧化应激的发生,对机体

组织及细胞造成损伤,进而导致代谢异常,T2DM 疾病进展^[12]。因此,深入分析 T2DM 合并 OSAHS 患者的影响因素对于临床干预具有较好的借鉴意义。

Irisin 具有调节能量代谢、改善胰岛素抵抗等作用^[13]。目前国内外不少研究认为 Irisin 与 T2DM 有显著相关性^[14、15]。本次研究显示,T2DM 患者的 Irisin 水平下降,且合并 OSAHS 的患者下降更明显,且与 HbA1c、FBG、2hPG 水平呈负相关,多因素 Logistic 回归分析结果显示 Irisin 是 T2DM 合并 OSAHS 的影响因素之一,提示低水平的 Irisin 参与着 T2DM 合并 OSAHS 的发生。OSAHS 患者睡眠时,由于呼吸暂停,导致低氧血症的

慢性炎症状态。而 Irisin 参与了调节糖脂代谢紊乱及组织器官损伤这一过程,引起过度消耗,致使水平下降^[16]。Nesfatin-1 在能量平衡、摄食调节中发挥重要作用,已被不少研究证实^[17,18]。既往的基础试验表明^[19],Nesfatin-1 可促进胰岛素代偿性分泌,可与胰岛 β 细胞存在共表达。本次研究显示,T2DM 合并 OSAHS 患者 Nesfatin-1 水平升高,且与 HbA1c、FBG、2hPG 呈正相关,同时 Nesfatin-1 还是 T2DM 并发 OSAHS 的影响因素。说明 Nesfatin-1 参与着 T2DM 合并 OSAHS 的病情发生。分析可能是因为 T2DM 患者体内胰岛 β 细胞处于代偿阶段,随胰岛素代偿性分泌,Nesfatin-1 可伴随性增加并释放入血,导致水平升高^[20,21]。而 OSAHS 可刺激胰岛素分泌、刺激机体处于高血糖环境,从而导致代偿性胰岛素分泌增加,Nesfatin-1 随之增多^[22,23]。3-NT 是反映机体氧化应激新的生物标志。3-NT 本身可能作为一种新的致病介质,参与着 T2DM 及其并发症的发生过程^[24]。研究发现,T2DM 合并 OSAHS 的 3-NT 水平异常升高,与 HbA1c、FBG、2hPG 呈正相关,也是 T2DM 并发 OSAHS 的影响因素。证实了 3-NT 参与 T2DM 及其并发症的发生发展过程。OSAHS 患者缺氧后引起血清氧化应激指标(如 3-NT)升高,加重了机体的胰岛素抵抗,进而引起糖脂代谢紊乱^[25]。研究结果还发现,HbA1c、FBG、2hPG、年龄、合并高血压同时也是 T2DM 患者发生 OSAHS 的影响因素。HbA1c、FBG、2hPG 水平偏高可提示患者长期处于高血糖环境,而高血糖环境极易造成控制呼吸的中枢或周围神经发生病变,极易引起 OSAHS 的发生,而 OSAHS 的间歇性低氧和睡眠中断又可使胰岛素敏感性降低,造成恶性循环^[26,27]。年龄越大的患者身体机能减退,缺乏对呼吸的清醒驱动,使得睡眠中的呼吸严重依赖于机械感受器和化学感受器刺激的水平,因此容易出现 OSAHS^[28]。而高血压是一种靶器官损伤类疾病,高血压可导致机体血管活性物质增多,损伤血管内皮,影响机体的正常循环,从而增加 OSAHS 的发生几率^[29,30]。

综上所述,T2DM 合并 OSAHS 患者的 Irisin、Nesfatin-1、3-NT 水平表达异常,影响着机体的糖脂代谢过程及 OSAHS 发生,且 OSAHS 发生还受到 HbA1c、FBG、2hPG 等因素的影响,可考虑对上述因素进行早期监测,以为制定针对性干预措施提供参考。

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