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阻塞性睡眠呼吸暂停低通气综合征合并2型糖尿病患者CXCL13，KIM–1，CTRP5，Klotho表达水平及其临床意义

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[摘　要]　**目的：**探讨阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome，OSAHS)合并2型糖尿病(type 2 diabetes mellitus，T2DM)患者的肾损伤因子-1(kidney injury molecule 1，KIM-1)、趋化因子配体13(chemokine ligand 13，CXCL13)、补体C1q/肿瘤坏死因子相关蛋白5(C1q/tnf-associated protein 5，CTRP5)及Klotho表达水平及临床意义。**方法：**选择2017年3月至2019年1月武汉大学人民医院收治的OSAHS合并T2DM者(合并组)50例、单独OSAHS者(OSAHS组)46例、单独T2DM者(T2DM组)52例，并以同期来我院正常体检的健康人50例作为对照组。比较各组受试者呼吸参数、血脂、血糖、尿KIM-1及血清CXCL13，CTRP5，Klotho水平变化，采用Pearson法对空腹血糖(fasting blood glucose，FBG)、呼吸紊乱指数(apnea hypopnea index，AHI)与尿KIM-1及血清CXCL13，CTRP5，Klotho指标相关性进行分析，并通过受试者工作特征曲线(ROC)分析KIM-1，CXCL13，CTRP5及Klotho对OSAHS合并T2DM患者的诊断价值。**结果：**与对照组比较，合并组、OSAHS组以及T2DM组尿KIM-1及血清CXCL13，CTRP5升高，血清Klotho水平降低(均P<0.001)；与OSAHS组以及T2DM组比较，合并组患者上述指标改变明显(P<0.05)。与T2DM组比较，合并组和OSAHS组患者M-SaO_2，L-SaO_2明显降低，SIT_{90}，AHI明显升高(P<0.001)；与OSAHS组比较，合并组患者FBG和HbA1c水平明显升高(均P<0.001)。OSAHS合并T2DM患者FBG，AHI均与尿KIM-1及血清CXCL13，CTRP5水平呈现正相关，与Klotho水平呈现负相关(P<0.001)。**结论：**尿KIM-1及血清CXCL13，CTRP5，Klotho指标与OSAHS和T2DM患者发生发展关系密切，对OSAHS合并T2DM均具有一定的诊断价值，但联合诊断价值更高。

[关键词]　阻塞性睡眠呼吸暂停低通气综合征合并2型糖尿病；趋化因子配体13；肾损伤因子-1；补体C1q/肿瘤坏死因子相关蛋白5；Klotho

Expressions of CXCL13, KIM-1, CTRP5 and Klotho in OSAHS patients with type 2 diabetes mellitus and their clinical significance

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Abstract　**Objective:** To investigate the expression levels of kidney injury molecule 1 (KIM-1), chemokine ligand 13

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(CXCL13), complement C1q/tnf-associated protein 5 (CTRP5) and Klotho in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) complicated with type 2 diabetes mellitus (T2DM) patients and their clinical significance. **Methods:** Fifty cases of OSAHS combined with T2DM (combined group), 46 cases of OSAHS alone (OSAHS group), 52 cases of T2DM alone (T2DM group) and 50 cases healthy persons admitted to the department of otolaryngology of our hospital from March 2017 to January 2019 were selected as the control group. Comparing the respiratory parameters, blood fat and blood sugar, urine KIM-1 serum CXCL13, CTRP5, Klotho level change of each groups of. Then using the method of Pearson, fasting blood glucose (FBG), apnea hypopnea index (AHI) and urine and serum CXCL13, CTRP5, KIM-1 Klotho index correlation analysis, and through the receiver-operating characteristic curve (ROC) analysis, CXCL13, CTRP5 and KIM-1 Klotho value to the diagnosis of OSAHS combined T2DM patients. **Results:** Compared with the control group, urine kim-1, serum CXCL13 and CTRP5 in the combined group, OSAHS group and T2DM group were increased, and serum Klotho level was decreased (all $P<0.001$). Compared with OSAHS group and T2DM group, patients in the combined group showed significant improvement in the above indicators ($P<0.05$). Compared with T2DM group, M-SaO_2 and L-SaO_2 were significantly decreased in the combined group and OSAHS group, while SIT_{90} and AHI were significantly increased (all $P<0.001$). Compared with OSAHS group, FBG and HbA1c levels of patients in the combined group were significantly increased (all $P<0.001$). FBG, AHI OSAHS combined T2DM patients with urine and serum CXCL13 KIM-1, rendering is related to the level of CTRP5 is negatively related to the level of Klotho. **Conclusion:** Urinary KIM-1 and serum CXCL13, CTRP5, Klotho indicators are closely related to the occurrence and development of OSAHS and T2DM disease, and have certain diagnostic value for OSAHS combined with T2DM, and the combined diagnosis value is higher.

Keywords obstructive sleep apnea hypopnea syndrome combined with type 2 diabetes mellitus; chemokine ligand 13; kidney injury molecule 1; C1q/tnf-associated protein 5; Klotho

阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome，OSAHS)是由多种因素引起的睡眠中上气道阻塞的一种全身性疾病，主要以夜间睡眠时有打鼾的症状，同时伴有不同程度的呼吸暂停，以疲乏、白天嗜睡及记忆力减退、睡眠障碍等为主要临床表现的一种睡眠障碍性综合征[1]。OSAHS患者在夜间睡眠时由于会出现一定程度的上气道不完全性或者是完全性阻塞，从而造成通气受阻，最终引发高碳酸血症以及低氧血症等一系列生理病理性改变，严重者可能引起猝死[2]。调查[3]显示：OSAHS疾病临床上常常与T2DM共存，其并发T2DM的概率不低于40%，T2DM中并发OSAHS的概率也有25%左右。T2DM可一定程度加速OSAHS疾病的进展，而OSAHS也可通过诱导机体糖代谢紊乱以及相关并发症的发生加速T2DM疾病的进展[4]。近年研究[5]显示：OSAHS患者常常并发慢性肾功能损伤，而KIM-1是一种新型的I型跨膜蛋白，当机体肾组织发生损伤时，呈现高水平表达，是OSAHS患者肾损伤的特异性标志物。Klotho蛋白也可通过抑制机体氧化应激反应，从而对机体肾功能进行调控，保护肾组织[6]。研究[7]显示：CXCL13和CTRP5在OSAHS合并T2DM的病发过程发挥重要的作用。基于此，现对OSAHS合并T2DM患者尿KIM-1及血清CXCL13，CTRP5及Klotho表达水平及其联合诊断的临床意义进行观察，以期为其临床诊治提供早期参考价值。

1 对象与方法

1.1 对象

选择2017年3月至2019年1月武汉大学人民医院收治的OSAHS合并T2DM者(合并组)50例、单独OSAHS者(OSAHS组46例)、单独T2DM者(T2DM组52例)，并以同期来我院正常体检的健康人50例作为对照组。合并组：男36例，女14例，年龄35~75(51.25±8.64)岁，BMI为(22.35±1.12) kg/m^2，合并高血压15例；OSAHS组：男34例，女12例，年龄37~76(50.65±7.78)岁，BMI为(22.42±1.09) kg/m^2，合并高血压16例；T2DM组：男35例，女17例，年龄36~76(51.32±7.92)岁，BMI为(21.89±1.20) kg/m^2，合并高血压14例；对照组：男34例，女16例，年龄35~74(52.09±8.19)岁，BMI为(22.29±1.13) kg/m^2，合并高血压13例。4组受试者的年龄、性别、BMI及合并症比较差异无统计学意义($P>0.05$)，

具有可比性。

1.2 诊断标准

1)T2DM诊断标准：参考美国糖尿病协会(ADA)于2010年制定的糖尿病诊断标准[8]，患者空腹血糖(8 h内无热量摄入) >7.0 mmol/L；伴有典型的高血糖以及高血糖危象症状者，随机测定血糖量>11 mmol/L；2 h耐糖试验血糖含量>11 mmol/L；糖化血红蛋白(HbA1c)含量>6.5%者。2)OSAHS诊断标准：参考2011年修订的《OSAHS诊治指南》中关于OSAHS的诊断标准[9]，患者每晚呼吸暂停反复发作>30次；呼吸紊乱指数(apnea hypopnea index，AHI)>5次/h。3)肾损害的诊断标准依据临床和病理检查。本研究获得武汉大学人民医院临床医学伦理委员会批准，患者签署知情同意。

1.3 纳入和排除标准

纳入标准：1)符合上述T2DM或者OSAHS的诊断标准；2)临床资料完整者；3)患者及家属同意，并签署知情协议书。排除标准：1)合并肝炎、慢性肾炎、脑血管疾病以及高血压等脏器功能障碍者；2)合并肿瘤、周围血管病以及凝血功能障碍者；3)合并中枢性睡眠呼吸暂停综合征、风湿性免疫疾病以及感染性疾病者；4)合并精神疾病；5)合并糖尿病并发症者；6)3个月内有重大创伤或者外科手术者；7)近期使用抗炎药物或者使用类固醇激素者；8)鼻息肉、扁桃体肥大等呼吸道解剖性狭窄者；9)依从性差，中途退出者。

1.4 观测指标与方法

1.4.1 血氧饱和度

检测前24 h内受试者均禁止服用咖啡、茶、酒以及各类镇静类药物等。采用多导睡眠仪(飞利浦伟康Alice 6型)对所有受试者进行>7 h监测：夜间平均血氧饱和度(M-SaO_2)、夜间最低外周血氧饱和度(L-SaO_2)、血氧饱和度<90%时间占监测时间的百分比(SIT_{90})以及AHI。

1.4.2 血脂、血糖测定

受试者清晨空腹抽取肘静脉血5 mL，离心分离血清，于−75 ℃下保存待测。HbAlc，FBG采用葡萄糖氧化酶法测定，严格按照试剂盒(上海申能德赛诊断技术有限公司)说明书进行操作。氧化物酶法测定血清LDL-C，TC及TG，试剂盒购于北京百奥莱博科技有限公司，严格按照试剂盒说明书执行。

1.4.3 血清 CXCL13，CTRP5，Klotho 水平测定

采用酶联免疫吸附试验测定血清CXCL13，CTRP5，Klotho，严格按照试剂盒(艾恩斯生物科技有限公司)说明书操作。

1.4.4 尿 KIM-1 水平测定

留取所有受试者中段晨尿10 mL，低温高速离心留取上清液，−20 ℃条件下保存待测。采用双抗体夹心酶标免疫分析法测定尿KIM-1，试剂盒购于上海通蔚生物科技有限公司。

1.5 统计学处理

采用SPSS 20.00软件进行数据分析。计数资料以频数(率)表示，比较行卡方检验；计量资料以均数±标准差($\bar{x}\pm s$)表示，多组间比较采用方差分析，相关性分析采用Pearson法进行。以阴性血清测定结果的2倍为cut-off值的基准值，采用受试者工作特征曲线(receiver operating characteristic，ROC)分析CXCL13，KIM-1，CTRP5及Klotho对OSAHS合并T2DM患者的诊断价值。P<0.05为差异具有统计学意义。

2 结果

2.1 临床资料比较

各组受试者在年龄、性别、TC以及LDL-C等方面差异无统计学意义(P>0.05)；与对照组相比，合并组、OSAHS组和T2DM组的BMI、病程、TG、HDL-C均明显升高，差异有统计学意义(P<0.05)；但是合并组、OSAHS组和T2DM组组内比较差异无统计学意义(P>0.05)。各组具有可比性(表1)。

2.2 呼吸参数及血糖比较

合并组和OSAHS组患者的呼吸参数比较差异无统计学意义(P>0.05)；与T2DM组比较，合并组和OSAHS组患者M-SaO_2，L-SaO_2明显降低，SIT_{90}，AHI明显升高(P<0.05)。合并组和T2DM组在FBG和HbA1c水平比较差异无统计学意义(P>0.05)；与OSAHS组比较，合并组和T2DM组患者FBG和HbA1c水平明显升高(P<0.05，表2)。

2.3 尿 KIM-1 及血清 CXCL13，CTRP5，Klotho 水平比较

与对照组比较，合并组、OSAHS组以及T2DM组尿KIM-1及血清CXCL13，CTRP5升高，血清Klotho水平降低(P<0.05)；与OSAHS组以及T2DM组比较，合并组患者尿KIM-1及血

清CXCL13，CTRP5升高，血清Klotho水平降低(P<0.05)；OSAHS组与T2DM组患者尿KIM-1及血清CXCL13，CTRP5，Klotho水平比较差异无统计学意义(P>0.05，表3)。

2.4 OSAHS 合并 T2DM 患者 FBG，AHI 与尿 KIM-1 及血清 CXCL13，CTRP5，Klotho 指标相关性分析

OSAHS合并T2DM患者FBG，AHI均与尿KIM-1及血清CXCL13，CTRP5水平呈正相关，与Klotho水平呈负相关(P<0.05，表4)。

2.5 KIM-1，CXCL13，CTRP5 及 Klotho 单独和联合诊断 OSAHS 合并 T2DM 的 ROC 曲线分析

联合诊断的AUC为0.945最大，约登指数为0.795，敏感度、特异度和准确度分别为0.856，0.936，93.261，联合诊断各项目均明显高于单指标诊断结果(表5，图1)。

表1 各组受试者一般资料比较

Table 1 Comparison of general data of subjects in each group

组别	n	年龄/岁	男/女	BMI/(kg·m^{-2})	病程/年	TG/(mmol·L^{-1})	TC/(mmol·L^{-1})	LDL-C/(mmol·L^{-1})	HDL-C/(mmol·L^{-1})
合并组	50	51.25 ± 8.64	36/14	28.46 ± 2.13	3.56 ± 0.63	3.28 ± 0.16	4.81 ± 0.96	2.36 ± 0.26	0.91 ± 0.26
OSAHS组	46	50.65 ± 7.78	34/12	26.35 ± 2.06	6.59 ± 1.20	2.51 ± 0.14	4.76 ± 0.88	2.28 ± 0.19	1.12 ± 0.24
T2DM组	52	51.32 ± 7.92	35/17	26.41 ± 2.19	3.89 ± 0.86	2.56 ± 0.16	4.82 ± 0.92	2.34 ± 0.17	1.10 ± 0.26
对照组	50	52.09 ± 8.19	34/16	22.18 ± 1.69	–	1.39 ± 0.08	4.91 ± 0.87	2.20 ± 0.15	1.46 ± 0.23
F/χ^2		0.389	0.203	4.657	5.369	7.653	0.201	0.355	2.587
P		0.349	0.904	<0.001	<0.001	<0.001	0.904	0.837	0.006

表2 各组呼吸参数及血糖比较($\bar{x} \pm s$)

Table 2 Comparison of respiratory parameters and blood glucose among each group ($\bar{x} \pm s$)

组别	n	M-SaO_2/%	L-SaO_2/%	SIT_{90}/%	AHI/(次·h^{-1})	FBG/(mmol·L^{-1})	HbA1c/%
合并组	50	92.45 ± 12.15	79.85 ± 8.63	13.16 ± 9.85	36.89 ± 12.09	10.87 ± 2.54	8.59 ± 2.13
OSAHS组	46	93.01 ± 12.36	80.15 ± 9.03	13.28 ± 10.02	34.01 ± 12.26	5.06 ± 1.06	6.53 ± 1.86
T2DM组	52	96.12 ± 12.56	90.56 ± 9.71	3.15 ± 0.56	2.69 ± 0.41	10.26 ± 2.6	8.42 ± 2.06
F		12.565	1.235	9.597	4.596	8.369	6.548
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

表3 各组受试者尿KIM-1及血清CXCL13，CTRP5，Klotho水平比较($\bar{x} \pm s$)

Table 3 Comparison of urine KIM-1 and serum CXCL13, CTRP5 and Klotho levels of subjects among each group ($\bar{x} \pm s$)

组别	n	KIM-1/(ng·mL^{-1})	CXCL13/(μg·L^{-1})	CTRP5/(μg·mL^{-1})	Klotho/(ng·L^{-1})
合并组	50	6.53 ± 1.26	380.62 ± 26.53	0.89 ± 0.16	89.56 ± 12.36
OSAHS组	46	3.17 ± 0.52	241.82 ± 13.69	0.66 ± 0.11	139.63 ± 19.63
T2DM组	52	2.98 ± 0.35	235.62 ± 11.53	0.51 ± 0.09	135.67 ± 21.56
对照组	50	2.21 ± 0.26	151.32 ± 21.25	0.31 ± 0.05	377.36 ± 25.69
F		4.460	5.892	12.368	8.560
P		<0.001	<0.001	<0.001	<0.001

表4 FBG，AHI与尿KIM-1及血清CXCL13，CTRP5，Klotho指标相关性分析

Table 4 Correlation analysis of FBG and AHI with urinary KIM-1 and serum CXCL13, CTRP5 and Klotho

参数	KIM-1	CXCL13	CTRP5	Klotho
FBG				
r	0.373	0.514	0.451	-0.370
P	0.018	0.000	0.000	0.031
AHI				
r	0.401	0.527	0.355	-0.462
P	0.010	<0.001	0.036	0.000

表5 CXCL13，KIM-1，CTRP5及Klotho单独和联合诊断OSAHS合并T2DM的价值分析

Table 5 Value analysis of CXCL13, KIM-1, CTRP5 and Klotho in diagnosing of OSAHS with T2DM separately and in combination

项目	AUC	约登指数	敏感度	特异度	准确度
KIM-1	0.656	0.372	0.614	0.761	77.362
CXCL13	0.622	0.243	0.598	0.654	76.329
CTRP5	0.810	0.436	0.646	0.791	80.936
Klotho	0.698	0.373	0.598	0.776	79.853
联合诊断	0.945	0.795	0.856	0.936	93.261

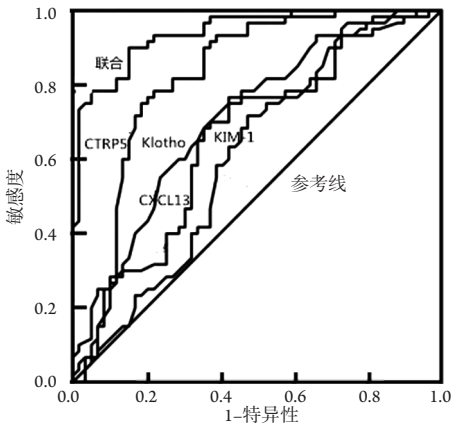

图1 KIM-1，CXCL13，CTRP5及Klotho单独和联合诊断OSAHS合并T2DM的ROC曲线

Figure 1 ROC curve of KIM-1, CXCL13, CTRP5 and Klotho in diagnosing of OSAHS with T2DM separately and in combination

3 讨论

OSAHS是一种对人们生命健康产生严重影响的睡眠障碍性疾病，多合并T2DM，其可通过诸多机制对机体全身多器官和多系统产生损伤，易并发诸如糖尿病、心力衰竭、高血压等心脑血管并发症，睡眠呼吸暂停引发的睡眠结构破坏、高碳酸血症以及低氧血症，对患者的寿命及生存质量产生严重影响[10-11]。另外，机体长期处在高碳酸血症、低氧血症状态，如果得不到及时治疗改善，会引发一系列细胞因子水平的改变，对肾功能产生损伤[12]。当患者肾发生损伤时，临床主要以肾指标异常、蛋白尿以及夜尿增多等为表现[13]。目前临床上通常依据血清肌酐清除率、血清肌酐等进行诊断，但大量研究[14-15]显示：上述指标对早期肾损伤诊断的特异性和敏感性相对较低，同时其还受年龄、药物、肌肉代谢及蛋白摄入等肾外因素的影响，且当上述肾功能常规指标出现异常时，肾功能损伤程度基本已到中晚期，严重者甚至发展到终末期。OSAHS合并T2DM患者早期也会出现典型的糖尿病症状，表现为炎症反应、血糖代谢和胰岛素分泌紊乱、氧化应激反应等，早期发现并纠正较为困难[16]。故寻找合适的特异性指标对OSAHS合并T2DM患者进行早期诊断并纠正越来越受到临床工作者的关注。

本研究结果显示：OSAHS合并T2DM患者KIM水平较高，且与AHI和FBG呈正相关。这可能是

由于FBG反映患者血糖水平，是T2DM诊断的重要指标；AHI是反映患者睡眠呼吸暂停严重程度的重要指标，其水平升高可引起机体下丘脑–垂体–肾上腺轴功能发生紊乱，进而引起患者胰岛素抵抗状态加重，血糖水平升高，影响机体肾功能[17]。而KIM是一种在正常肾组织几乎不表达的新I型跨膜蛋白，肾组织发生损伤后，KIM会被裂解释放，经由尿液排出[18]。Dwijayanti等[19]研究显示：在机体肾组织损伤后2 h，即可在其尿液中发现KIM-1，且与常规肾功能指标比较具有更高的特异性和灵敏度，同时与肾组织实际病理性损伤程度呈现正相关。而对于OSAHS合并T2DM患者，早期由于长期处于低氧状态，会出现一定程度肾功能损伤，进而表现为尿液KIM-1水平升高，且与FBG及AHI水平呈现正相关。但是本研究结果显示：单一KIM-1对OSAHS合并T2DM诊断价值不高，CXCL13是一种具有重要生理作用的趋化因子，在糖尿病的发展过程中是介导机体免疫及炎症反应的重要桥梁，其可对胰岛素分泌产生影响，诱导细胞发生凋亡，从而影响血糖代谢[20]。故OSAHS合并T2DM患者CXCL13水平相对较高，并与FBG呈现一定相关性。CTRP5是一种新型的脂肪因子，与冠心病、代谢性疾病关系密切，参与免疫、细胞分化、炎症反应调节及能量代谢等过程[21]。OSAHS合并T2DM患者由于夜间间歇性低氧状态可激活机体相关炎症通路，出现氧化应激状态，刺激CTRP5的产生[22]。Klotho是由Kuro-0于1997年在*Nature*上阐述的一种新型抗衰老基因，主要于机体大脑脉络丛及肾脏组织中表达[23]。近年，Maltese等[24]研究显示：Klotho可由胰岛β细胞合成分泌，对β细胞具有保护功能，还可一定程度地促进机体胰岛素分泌，降低血糖水平，与本文中Klotho与FBG呈现负相关结果一致。另外，Klotho还可降低对胰岛细胞内的过氧化物水平，改善机体氧化应激状态，延缓T2DM疾病的发展。故KIM-1，CTRP5，Klotho，CXCL13均可作为OSAHS合并T2DM患者诊断的特异性指标，但是单独诊断效率均较低，而联合诊断可提高特异性和灵敏度，有效减少了OSAHS合并T2DM患者漏诊的发生。

综上所述，OSAHS合并T2DM患者尿KIM-1及血清CXCL13，CTRP5，Klotho指标与其疾病发生和发展关系密切，对OSAHS合并T2DM均具有一定的诊断价值，但联合诊断价值更高。

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