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OSAHS: Another Independent Risk Factor of Type 2 Diabetes

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Abstract

Obstructive Sleep Apnoea-Hypopnea Syndrome (OSAHS) is a highly prevalent respiratory disorder which can lead to multiple complications and contribute to high morbidity and mortality of cardiovascular disease and high risk of traffic accident. It has aggressively affected the public health and aroused increasing concern in respiratory medicine recently. Current evidence supports an independent association between OSAHS and insulin resistance, glucose intolerance and the risk of type 2 diabetes, independent of obesity. Additionally, OSAHS often leads to worse glycaemic control in diabetics. Efficient CPAP therapy can benefit OSAHS patients with impaired glucose metabolism. In conclusion, diabetics or patients with high risk of diabetes should be routinely screened for early diagnosis, early intervention and individualized treatment for OSAHS.

Keywords

Obstructive Sleep Apnoea-Hypopnea Syndrome, Type 2 Diabetes, Insulin Resistance

OSAHS：2型糖尿病的另一独立危险因素

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摘　要

OSAHS是一种常见的睡眠呼吸疾患，可导致多系统并发症，增加心血管疾病发病率及死亡率，严重影响

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患者健康，甚至引起交通安全隐患，近年来成为呼吸医学界关注的新焦点。大量研究证明OSAHS是2型糖尿病、胰岛素抵抗的独立危险因素。合并OSAHS的2型糖尿病患者血糖控制往往疗效欠佳。有效的持续正压通气治疗(CPAP)在一定程度上能够使OSAHS合并糖代谢紊乱的患者获益。故，糖尿病或糖尿病高风险患者应常规行OSAHS筛查，以便早期诊断、早期干预及个体化治疗。

关键词

阻塞性睡眠呼吸暂停低通气综合征，2型糖尿病，胰岛素抵抗

1. 引言

睡眠呼吸暂停低通气综合征(OSAHS)是睡眠时反复出现上气道塌陷从而引起一系列病理生理紊乱的一种睡眠呼吸疾病，常增加心血管并发症的发病率及死亡率[1]。西方报道 OSAHS 在中年人的发病率为男性 4%~9%，女性 1%~2%，患病率为男性 24%、女性 9% [2]；我国人群 OSAHS 发病率为 3.5%~9.6% [3]，而肥胖男性的患病率高达 33%~77%，女性为 11%~46% [4]。2007 年~2008 年中国糖尿病协会调查结果表明，20 岁以上成人糖尿病患病率达 9.7%，尽管有越来越多的药物选择及有效的生活方式干预，但糖尿病造成的社会负担仍是非常巨大的，且其心脑血管并发症致残率高，成为目前一大公共卫生问题。流行病学研究显示，OSHAS 与 2 型糖尿病密切相关，且独立于肥胖、家族史等危险因素[5] [6]。OSAHS 影响糖尿病发生发展的整个过程。本文就 OSAHS 与糖尿病关系进行综述。

2. OSAHS 与糖尿病前期

糖尿病前期是指血糖增高尚未达到糖尿病诊断标准的糖代谢紊乱状态，通常指空腹血糖受损或糖耐量异常。横断面研究表明 OSAHS 与糖耐量受损、胰岛素抵抗有关，OSAHS 患者糖尿病前期发生率明显高于非 OSAHS 患者[1] [7]。一项队列研究提示 OSAHS 患者平均夜间血氧饱和度与胰岛素抵抗独立相关，OSAHS 是胰岛素抵抗的独立预测因子[8]。另一项纳入 2500 名患者的大样本研究提示，校正年龄、性别、种族、BMI、腹围等的影响后 OSAHS 患者糖耐量异常及空腹血糖受损发生率较非 OSAHS 患者明显增高[9]。Punjabi 等人研究显示在校正性别、年龄、种族、体脂百分比等混杂因素后，对比非 OSAHS 患者，轻、中、重度 OSAHS 组胰岛素敏感性分别下降 26.7%、36.5%、43.7% [10]。

3. OSAHS 与 2 型糖尿病

2 型糖尿病患者中 OSAHS 的患病率可达 18%~77%，而 OSAHS 患者中糖尿病的患病率高达 32.9% [6] [11] [12]，远高于一般人群糖尿病的患病率。多项纵向队列研究均发现 OSAHS 可增加糖尿病发生的整体风险，特别是在中重度 OSAHS 更明显[13] [14]。国内有人对 6 个前瞻性队列研究跟踪 2.7~16 年后进行荟萃分析结果提示 OSAHS 患者糖尿病发病率约为 5.6%，中重度 OSAHS 患者糖尿病发病率较非 OSAHS 增加 63% [6]。2010 年 Aronsohn 等人随机从门诊抽取的 60 名糖尿病进行标准多导睡眠监测(PSG)后发现 OSAHS 患病率高达 77%，在消除混杂因素影响后，睡眠呼吸暂停低通气指数(AHI)、快速动眼睡眠期 AHI 及氧减指数均与糖化血红蛋白(HbA1c)明显正相关[12]，且随着 OSAHS 病情加重 HbA1c 明显升高，提示

OSAHS 通过夜间间歇低氧显著影响血糖稳态，且间歇低氧越严重血糖波动越大。法国一项多中心横断面研究纳入 762 名患者，其中 497 名为既往即已诊断 2 型糖尿病且已接受药物治疗，另外 265 名患者为新诊断的未治疗患者，通过多元回归分析糖尿病治疗组及新近糖尿病未治疗组患者 OSAHS 严重程度与糖化血红蛋白的关系，新诊断未治疗患者 HbA1c 与 AHI 和氧减指数正相关，且随着病情程度加重，HbA1c 升高；但在糖尿病治疗组，HbA1c 与年龄、代谢异常及胰岛素的使用相关，与 OSAHS 病情严重程度无明显关系[15]，提示 OSAHS 对新诊断未治疗的 2 型糖尿病的血糖控制影响更明显，而当进行药物或胰岛素干预治疗后，这种影响可能会被抵消。

4. OSAHS 增加 2 型糖尿病并发症风险

OSAHS 通过间歇低氧、高二氧化碳血症、微觉醒导致交感神经兴奋及氧化应激，进而引起 NO 等舒张血管活性物质合成减少、促炎因子释放、血液高凝状态等介导血管内皮损伤[16] [17]，增加 2 型糖尿病患者心脑血管并发症风险[18]。另有研究显示 OSAHS 可加重 2 型糖尿病患者的肾脏损害[19] [20]，甚至 OSAHS 严重程度与糖尿病肾病风险正相关[21]。OSAHS 亦可加重糖尿病患者周围神经病变、视网膜病变及黄斑病变[22] [23] [24]。

5. OSAHS 影响糖代谢的机制

OSAHS 引起糖代谢紊乱的具体机制尚未阐明，但有大量临床及相关动物实验提示 OSAHS 主要通过间歇低氧(IH)及睡眠片段化引发交感神经兴奋性增强、氧化应激、下丘脑-垂体-肾上腺功能失调、全身炎症反应、脂肪细胞因子改变等病理生理紊乱介导胰岛细胞功能损伤、胰岛素抵抗进而影响糖代谢。

Louis 和 Punjabi [25]在健康成年人做常氧和间歇低氧实验对比，每日 24 次的间歇低氧模拟中度 OSAHS，OGTT 实验结果显示胰岛素敏感性和高糖反应下降(血糖升高所致肝脏糖异生减少及组织糖摄取增加)，心率变异率增加提示交感神经兴奋性增强，但胰腺的胰岛素分泌和血清皮质醇水平保持不变。动物模型试验提示间歇性低氧可降低胰岛素敏感性，使胰岛素稳态模型参数升高[26] [27]。另外间歇性低氧亦可以直接影响肝细胞，导致非酒精性脂肪肝[28]，引起肝糖原增加及糖异生活跃[26]。睡眠片段化或睡眠剥夺亦可影响糖代谢，睡眠片段化啮齿动物模型显示睡眠紊乱通过增加炎症、氧化应激、血清激素水平而导致肥胖、胰岛素抵抗及高血糖[27]。健康成年人予人工睡眠片段化及减少慢波睡眠干预后可出现胰岛素敏感性下降[29] [30]，对于 OSAHS 及 2 型糖尿病患者，睡眠片段化同样的会影响血糖稳态[31] [32]。

(一) IH 通过氧化应激直接影响胰岛细胞功能

氧化应激可直接导致胰岛细胞凋亡，抗氧化剂对 IH 暴露的胰岛细胞有一定保护作用[33]。小鼠实验观察到短时间 IH 暴露可导致胰腺 β 细胞增殖和凋亡并存，抗氧化剂可逆转 IH 引起的 β 细胞凋亡，但对细胞增殖无明显影响[34] [35]。芝加哥大学一项研究提示，小鼠 CIH 暴露 30 天(5% O25 秒/常氧 5 分钟，8 小时/天)，可导致空腹胰岛素水平明显增加、胰岛素抵抗，胰岛 β 细胞胰岛素储备明显下降，血糖刺激的胰岛细胞分泌功能受损，胰岛素原转化酶-1 表达下调，胰岛素原转化率降低，同时观察到胰岛细胞线粒体活性氧生成明显增加，而抗氧化剂处理可逆转空腹胰岛素升高、胰岛素抵抗及胰岛素原转化障碍，但 CIH 对血糖无明显影响，胰岛细胞形态学亦无明显改变，提示 CIH 通过线粒体氧化应激产生活性氧直接影响胰岛 β 细胞，引起胰岛细胞基础胰岛素分泌增强、胰岛素抵抗、胰岛素转化障碍，并损害胰岛细胞对血糖的反应，但由于存在代偿性基础胰岛素分泌增强，血糖尚可维持在正常水平[36]。另有研究显示短时间 IH 暴露可诱导胰岛细胞代偿性增殖以抵抗胰岛素抵抗、维持血糖稳态，这种效应可持续 4 至 8 周，而随着时间延长，CIH 将引起胰岛细胞凋亡，最终导致胰岛细胞功能障碍，而同时存在高糖状态时可增加胰岛细胞对低氧的敏感性，使胰岛细胞凋亡进一步加重[37] [38]。

(二) 全身炎症反应激活

大量临床研究及动物实验均显示 OSAHS 或间歇性低氧可通过激活 NF-κB 上调 TNF-α、IL-6、IL-1 等炎性因子表达，且有研究提示炎症因子水平升高与病情严重程度相关[39] [40] [41]，经 CPAP 治疗后上调的 NF-κB 及其下游炎症因子显著下降[39] [41]。间歇低氧处理的脂肪细胞及大鼠 IL-6 及 TNF-α 的水平较持续缺氧组明显升高，重度间歇缺氧组最高，与缺氧程度呈剂量依赖性关系[42]。TNF-α 具有强烈的脂解作用，并可刺激瘦素分泌，导致明显的胰岛素抵抗[43]。有研究提示 TNF-α 可能通过下调肌肉组织胰岛素介导的胰岛素受体(IR)磷酸化而介导胰岛素抵抗[44]，但 TNF-α 对肌肉胰岛素信号的调节是直接作用于胰岛素信号通路还是通过游离脂肪酸(FFA)等代谢产物进行调节尚不可知，因为该研究结果提示 TNF-α 增高亦伴随有 FFA 明显增高，FFA 暴露后胰岛素结合及胰岛素受体的内化可能会减少，但胰岛素受体激酶却不受影响[45] [46]，同时该研究也观察到 TNF-α 抑制剂处理后可逆转胰岛素介导的肝脏葡萄糖输出减少，但其对肝脏葡萄糖代谢的影响却不是通过胰岛素受体激酶，故认为 TNF-α 可能是通过影响其下游的信号通路或刺激脂解作用产生 FAA 进而影响肝脏糖代谢。IL-6 在胰岛素抵抗中同样发挥重要的作用，血浆中 IL-6 的升高与肥胖和糖尿病的发病率呈正相关，同时 IL-6 在多种组织(如肝脏、肌肉、脂肪组织、大脑等)中对血糖代谢发挥着交互作用[47] [48]。美国一项临床研究显示，在血糖异常的对象中，OSAHS 患者夜间反复低氧程度与 IL-6 密切相关，而在血糖正常对象中，反复夜间低氧仅仅与 TNF-α 相关，且这两种炎症因子在个体内存在相互联系，这表现在 IL-6/TNF-α 比值与夜间低氧严重程度亦呈相关性[49] [50]，这提示上述两种细胞因子之间可能存在某种相互调控机制。JNK 通路是 MAPK 家族成员之一，是氧化应激重要信号通路，在 2 型糖尿病胰岛素抵抗中发挥重要作用，可通过 IKK(IκB 激酶)与 NF-κB 通路互相联系。有研究提示 IL-6、TNF-α 可能通过 JNK 和 NF-κB 途径激活信号级联反应，从而介导氧化应激及炎症的病理生理过程，进而影响胰岛素信号转导及糖代谢，其中 IKK 甚至可直接磷酸化胰岛素受体底物-1(IRS-1)，因构象变化而干扰胰岛素作用下的酪氨酸磷酸化，从而阻断下游 PI3K 信号途径引起胰岛素抵抗[51] [52] [53]。另有研究提示 CIH 可直接激活 ERK、JNK、P38 等 MAPK 家族成员导致炎症反应、干扰胰腺胰岛素分泌、导致胰岛细胞损伤及凋亡[54]。

(三) 脂肪细胞因子改变

学者普遍认为脂肪组织分泌的脂肪细胞因子被认为是代谢综合征、2 型糖尿病、心血管疾病的重要致病因子[55] [56]。脂肪组织也受可到 IH 影响，IH 可导致脂联素(一种胰岛素增敏剂)下调、抵抗素及瘦素上调[57] [58]。

瘦素在下丘脑核、炎症及内皮系统起调节作用[59]，可下调胰腺胰岛素基因的表达及胰岛素分泌，在外周组织促进糖摄取[60]，可作为促炎因子调节 IL-6、TNF-α，同时本身亦受促炎因子的调节[61]，通常在肥胖患者体内明显增高，但有研究显示 OSAHS 患者体内瘦素水平亦明显增高，且经 CPAP 治疗后显著下降[62]。人体脂肪组织体外实验及大鼠实验提示瘦素升高水平与间歇缺氧的时间呈剂量依赖关系，可导致空腹胰岛素增高及糖耐量受损[42]，且经 CPAP 治疗后可下降[63]，但也有实验提示持续缺氧处理比间歇缺氧升高更明显[64]，甚至短时间间歇缺氧处理瘦素水平可轻度下降的报道[65]。瘦素受低氧诱导因子-1(HIF-1)调节，瘦素增高可能伴随 HIF-1 升高，作为 IH 引起的系统性炎症反应的适应性反应过程[66]。国内有人进行脂肪细胞体外实验提示亦提示间歇缺氧暴露可导致瘦素上调、脂联素下调，同时伴有 HIF-1α 和 Glut-1 表达升高，提示 HIF-1α 和 Glut-1 亦可能是引起 OSAHS 患者血糖升高及胰岛素抵抗的机制之一[38] [42]。

脂联素是一种不具有促炎作用的脂肪细胞因子，反而具有抗炎作用和胰岛素增敏作用[56]，是调节能量平衡、血糖和血脂代谢的重要因子[67]，其通过增加骨骼肌对游离脂肪酸的氧化而降低循环游离脂肪酸

水平及骨骼肌甘油三酯水平，从而改善胰岛素敏感性和胰岛素抵抗，另外脂联素可抑制单核细胞活性及巨噬细胞吞噬活性，抑制巨噬细胞产生 TNF-α、抑制 NF-κB 及其下游炎症因子的产生，还可以促进抗炎因子 IL-10 的产生，反过来氧化应激、TNF-α、IL-6 抑制脂联素的生成[61] [68]。OSAHS 患者血清脂联素水平有争议，有人观察到重度 OSAHS 患者血清脂联素水平受抑制，且独立于肥胖的影响[42] [69]，经过 2-3 个月 CPAP 治疗后血清脂联素水平明显升高[70]。但也有观察到 OSAHS 患者血清脂联素水平较非 OSAHS 高[71]。Kanbay 等人的研究提示排除肥胖的影响后 OSAHS 患者血清脂联素下降、TNF-α 明显增高，血清脂联素水平与 AHI、TNF-α 呈负相关，并认为脂联素下调可能是 OSAHS 患者发生心血管并发症及代谢紊乱的重要机制[57]。OSAHS 患者脂联素水平下降的可能原因是间歇性低氧抑制组蛋白去乙酰化酶 3(HDAC3)转位进入细胞核，从而抑制过氧化物酶体增殖物激活受体 γ(PPAR-γ)依赖的信号通路，PPAR-γ 是脂联素合成的重要转录调节因子，可被 TNF-α 抑制，PPAR-γ 受抑制后脂联素的合成和分泌将减少[72]。

(四) 下丘脑-垂体-肾上腺轴激活及交感神经兴奋增强

IH 可引起下丘脑-垂体-肾上腺轴激活[27] [37]，导致糖皮质激素释放，糖皮质激素通过增加脂肪分解、抑制胰岛素依赖的 Glut-4 向肌肉细胞表面易位、抑制肌肉糖摄取及糖原合成和增加糖异生诱导胰岛素抵抗[73] [74]。在动物实验和人体内均可观察到 IH 可激活交感神经[75] [76]，交感神经兴奋后可刺激脂解作用，导致 FFA 生成增多，而 FFA 通过干扰骨骼肌胰岛素信号通路进而减少全身骨骼肌血糖摄取[73]；此外 IH 诱导的交感神经兴奋所释放的儿茶酚胺可直接刺激肝脏糖原动员、抑制肌肉的葡萄糖摄取、刺激胰高血糖素分泌、抑制胰岛素分泌，并增加肝脏中的糖异生作用。

6. CPAP 治疗对 OSAHS 患者糖代谢的影响

OSAHS 治疗措施包括睡眠及生活习惯改变、体重控制、手术及 CPAP 治疗等，有研究显示药物或手术控制体重均可显著改善 OSAHS 的血糖水平，2 型糖尿病患者生活习惯改变诱导体重下降也可显著改善 OSAHS 病情[77] [78]。近年鼻、咽喉、颌面部手术及正畸治疗运用越来越广泛，但 CPAP 仍然是 OSAHS 治疗的首选措施。有研究提示对 OSAHS 合并糖尿病前期患者，无论是否合并肥胖，CPAP 治疗均可改善血糖稳态[79] [80]，并可显著改善 OGTT 实验的胰岛素敏感性[81] [82]，降低 24 小时血压水平[79]，与另一针对非糖尿病患者的荟萃分析结果 CPAP 治疗显著改善胰岛素稳态模型参数结果类似[83]。Guest 等人的研究显示 CPAP 治疗 5 年后 HbA1C 明显下降[84]。然而亦有研究提示经过三个月每晚 6.6 小时的 CPAP 治疗胰岛素敏感性并无明显改善，CPAP 治疗 2 年后 HbA1C 水平无明显下降[85]。虽然相对于口服降糖药物或胰岛素应用来说，CPAP 治疗对糖代谢紊乱的改善效果可能没那么显著，但从目前相关临床实验数据看还是有一定的临床意义，且对于依从性好、中重度患者、合并肥胖、糖尿病前期及血糖控制差患者效果更显著，有望在治疗 3 月后显效[80] [86]。

总之，OSAHS 患者 2 型糖尿病发病率明显高于普通人群，是胰岛素抵抗的独立危险因素，目前 OSAHS 发生糖代谢紊乱的机制尚未完全阐明，有待进一步深入研究。OSAHS 可增加糖尿病心脑血管病变、肾脏损害、糖尿病视网膜病变等并发症的整体风险，影响糖尿病药物治疗效果。有效的 CPAP 治疗可在一定程度上使 OSAHS 合并糖代谢紊乱患者获益，故对于合并 2 型糖尿病或糖尿病发生风险高的患者应针对 OSAHS 进行早期诊断及干预，并实施个体优化治疗。

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参考文献 (References)

[1] Morgenstern, M., Wang, J., Beatty, N., Batemarco, T., Sica, A.L. and Greenberg, H. (2014) Obstructive Sleep Apnea: An Unexpected Cause of Insulin Resistance and Diabetes. Diabetes Mellitus. *Associated Conditions Endocrinology and Metabolism Clinics of North America*, **43**, 187-204.

[2] Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. and Badr, S. (1993) The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. *The New England Journal of Medicine*, **328**, 1230-1235. https://doi.org/10.1056/NEJM199304293281704

[3] 魏永祥, 付春华, 杨非衡, 肖明明, 林莎. 北京市朝阳区成人打鼾及阻塞性睡眠呼吸暂停低通气综合征流行病学调查[J]. 中国医药导报, 2013, 10(27): 108-111.

[4] Young, T., Peppard, P.E. and Taheri, S. (2005) Excess Weight and Sleep-Disordered Breathing. *Journal of Applied Physiology*, **99**, 1592-1599.

[5] Rajan, P. and Greenberg, H. (2015) Obstructive Sleep Apnea as a Risk Factor for Type 2 Diabetes Mellitus. *Nature and Science of Sleep*, **7**, 113-125.

[6] Wang, X., Bi, Y., Zhang, Q. and Pan, F. (2013) Obstructive Sleep Apnoea and the Risk of Type 2 Diabetes: A Meta-Analysis of Prospective Cohort Studies. *Respirology*, **18**, 140-146. https://doi.org/10.1111/j.1440-1843.2012.02267.x

[7] Araújo, L.S., Fernandes, J.F.R., Klein, M.R.S.T. and Sanjuliani, A.F. (2015) Obstructive Sleep Apnea Is Independently Associated with Inflammation and Insulin Resistance, But Not with Blood Pressure, Plasma Catecholamines, and Endothelial Function in Obese Subjects. *Nutrition*, **31**, 1351-1357.

[8] Borel, A., Monneret, D., Tamisier, R., *et al*. (2013) The Severity of Nocturnal Hypoxia But Not Abdominal Adiposity Is Associated with Insulin Resistance in Non-Obese Men with Sleep Apnea. *PLoS ONE*, **8**, e71000. https://doi.org/10.1371/journal.pone.0071000

[9] Seicean, S., Kirchner, H.L., Gottlieb, D.J., *et al*. (2008) Sleep-Disordered Breathing and Impaired Glucose Metabolism in Normal-Weight and Overweight/Obese Individuals: The Sleep Heart Health Study. *Diabetes Care*, **31**, 1001-1006. https://doi.org/10.2337/dc07-2003

[10] Punjabi, N.M. and Beamer, B.A. (2009) Alterations in Glucose Disposal in Sleep-Disordered Breathing. *American Journal of Respiratory and Critical Care Medicine*, **179**, 235-240. https://doi.org/10.1164/rccm.200809-1392OC

[11] Sharafkhaneh, A., Richardson, P. and Hirshkowitz, M. (2004) Sleep Apnea in a High Risk Population: A Study of Veterans Health Administration Beneficiaries. *Sleep Medicine*, **5**, 345-350.

[12] Aronsohn, R.S., Whitmore, H., Van Cauter, E. and Tasali, E. (2010) Impact of Untreated Obstructive Sleep Apnea on Glucose Control in Type 2 Diabetes. *American Journal of Respiratory and Critical Care Medicine*, **181**, 507-513. https://doi.org/10.1164/rccm.200909-1423OC

[13] Botros, N., Concato, J., Mohsenin, V., Selim, B., Doctor, K. and Yaggi, K. (2009) Obstructive Sleep Apnea as a Risk Factor for Type II Diabetes. *American Journal of Medicine*, **122**, 1122-1127.

[14] Celen, Y.T., Hedner, J., Carlson, J. and Peker, Y. (2010) Impact of Gender on Incident Diabetes Mellitus in Obstructive Sleep Apnea: A 16-Year Follow-Up. *Journal of Clinical Sleep Medicine: Official Publication of the American Academy of Sleep Medicine*, **6**, 244-250.

[15] Priou, P., Le Vaillant, M., Meslier, N., *et al*. (2015) Association between Obstructive Sleep Apnea Severity and Glucose Control in Patients with Untreated versus Treated Diabetes. *Journal of Sleep Research*, **24**, 425-431. https://doi.org/10.1111/jsr.12278

[16] Drager, L.F., Polotsky, V.Y. and Lorenzi-Filho, G. (2011) Obstructive Sleep Apnea: An Emerging Risk Factor for Atherosclerosis. *Chest*, **140**, 534-542. https://doi.org/10.1378/chest.10-2223

[17] Eisele, H., Markart, P. and Schulz, R. (2015) Obstructive Sleep Apnea, Oxidative Stress, and Cardiovascular Disease: Evidence from Human Studies. *Oxidative Medicine and Cellular Longevity*, **2015**, Article ID: 608438.

[18] Rice, T.B., Foster, G.D., Sanders, M.H., *et al*. (2012) The Relationship between Obstructive Sleep Apnea and Self-Reported Stroke or Coronary Heart Disease in Overweight and Obese Adults with Type 2 Diabetes Mellitus. *Sleep*, **35**, 1293-1298. https://doi.org/10.5665/sleep.2090

[19] Leong, W.B., Nolen, M., Thomas, G.N., Adab, P., Banerjee, D. and Taheri, S. (2014) The Impact of Hypoxemia on Nephropathy in Extremely Obese Patients with Type 2 Diabetes Mellitus. *Journal of Clinical Sleep Medicine*, **10**, 773-778.

[20] Ozkok, A., Kanbay, A., Odabas, A.R., Covic, A. and Kanbay, M. (2014) Obstructive Sleep Apnea Syndrome and Chronic Kidney Disease: A New Cardiorenal Risk Factor. *Clinical and Experimental Hypertension*, **36**, 211-216. https://doi.org/10.3109/10641963.2013.804546

[21] Leong, W.B., Jadhakhan, F., Taheri, S., Thomas, G.N. and Adab, P. (2016) The Association between Obstructive Sleep Apnea on Diabetic Kidney Disease: A Systematic Review and Meta-Analysis. *Sleep*, **39**, 301-308. https://doi.org/10.5665/sleep.5432

[22] Tahrani, A.A., Ali, A., Raymond, N.T., *et al*. (2012) Obstructive Sleep Apnea and Diabetic Neuropathy: A Novel Association in Patients with Type 2 Diabetes. *American Journal of Respiratory and Critical Care Medicine*, **186**, 434-441. https://doi.org/10.1164/rccm.201112-2135OC

[23] Tahrani, A.A., Ali, A., Raymond, N.T., *et al*. (2013) Obstructive Sleep Apnea and Diabetic Nephropathy: A Cohort Study. *Diabetes Care*, **36**, 3718-3725. https://doi.org/10.2337/dc13-0450

[24] Baba, A., Zbiba, W., Bouayed, E., Korbi, M. and Ghrairi, H. (2016) Obstructive Sleep Apnea Syndrome. Is It a Risk Factor for Diabetic Retinopathy? *Journal Francais D Ophtalmologie*, **39**, 139-142.

[25] Louis, M. and Punjabi, N.M. (2009) Effects of Acute Intermittent Hypoxia on Glucose Metabolism in Awake Healthy Volunteers. *Journal of Applied Physiology*, **106**, 1538-1544.

[26] Polak, J., Shimoda, L.A., Drager, L.F., *et al*. (2013) Intermittent Hypoxia Impairs Glucose Homeostasis in C57BL6/J Mice: Partial Improvement with Cessation of the Exposure. *Sleep*, **36**, 1483-1490. https://doi.org/10.5665/sleep.3040

[27] Lesser, D.J., Bhatia, R., Tran, W.H., *et al*. (2012) Sleep Fragmentation and Intermittent Hypoxemia Are Associated with Decreased Insulin Sensitivity in Obese Adolescent Latino Males. *Pediatric Research*, **72**, 293-298. https://doi.org/10.1038/pr.2012.73

[28] Cakmak, E., Duksal, F., Altinkaya, E., *et al*. (2015) Association between the Severity of Nocturnal Hypoxia in Obstructive Sleep Apnea and Non-Alcoholic Fatty Liver Damage. *Hepatitis Monthly*, **15**, e32655. https://doi.org/10.5812/hepatmon.32655

[29] Stamatakis, K.A. and Punjabi, N.M. (2010) Effects of Sleep Fragmentation on Glucose Metabolism in Normal Subjects. *Chest*, **137**, 95-101. https://doi.org/10.1378/chest.09-0791

[30] Tasali, E., Leproult, R., Ehrmann, D.A. and Van Cauter, E. (2008) Slow-Wave Sleep and the Risk of Type 2 Diabetes in Humans. *Proceedings of the National Academy of Sciences*, **105**, 1044-1049. https://doi.org/10.1073/pnas.0706446105

[31] Pogach, M.S., Punjabi, N.M., Thomas, N. and Thomas, R.J. (2012) Electrocardiogram-Based Sleep Spectrogram Measures of Sleep Stability and Glucose Disposal in Sleep Disordered Breathing. *Sleep*, **35**, 139-148. https://doi.org/10.5665/sleep.1604

[32] Knutson, K.L., Van Cauter, E., Zee, P., Liu, K. and Lauderdale, D.S. (2011) Cross-Sectional Associations between Measures of Sleep and Markers of Glucose Metabolism among Subjects with and without Diabetes: The Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study. *Diabetes Care*, **34**, 1171-1176. https://doi.org/10.2337/dc10-1962

[33] Fang, Y., Zhang, Q., Tan, J., Li, L., An, X. and Lei, P. (2014) Intermittent Hypoxia-Induced Rat Pancreatic *β*-Cell Apoptosis and Protective Effects of Antioxidant Intervention. *Nutrition & Diabetes*, **4**, e131. https://doi.org/10.1038/nutd.2014.28

[34] Xu, J., Long, Y., Gozal, D. and Epstein, P.N. (2009) Beta-Cell Death and Proliferation after Intermittent Hypoxia: Role of Oxidative Stress. *Free Radical Biology & Medicine*, **46**, 783-790.

[35] Ota, H., Itaya-Hironaka, A., Yamauchi, A., *et al*. (2013) Pancreatic *β* Cell Proliferation by Intermittent Hypoxia via Up-Regulation of Reg Family Genes and HGF Gene. *Life Sciences*, **93**, 664-672.

[36] Wang, N., Khan, S.A., Prabhakar, N.R. and Nanduri, J. (2013) Impaired Pancreatic Beta Cell Function by Chronic Intermittent Hypoxia. *Experimental Physiology*, **98**, 1376-1385. https://doi.org/10.1113/expphysiol.2013.072454

[37] Sherwani, S.I., Aldana, C., Usmani, S., *et al*. (2013) Intermittent Hypoxia Exacerbates Pancreatic *β*-Cell Dysfunction in a Mouse Model of Diabetes Mellitus. *Sleep*, **36**, 1849-1858.

[38] Gu, C., Li, M., Li, Q. and Li, N. (2013) Chronic Intermittent Hypoxia Increases β Cell Mass and Activates the Mammalian Target of Rapamycin/Hypoxia Inducible Factor 1/Vascular Endothelial Growth Factor a Pathway in Mice Pancreatic Islet. *Chinese Medical Journal*, **126**, 2368-2373.

[39] Wang, B., Yan, B., Song, D., Ye, X. and Liu, S.F. (2013) Chronic Intermittent Hypoxia Down-Regulates Endothelial Nitric Oxide Synthase Expression by an NF-*κ*B-Dependent Mechanism. *Sleep Medicine*, **14**, 165-171.

[40] Hirotsu, C., Albuquerque, R.G., Nogueira, H., *et al*. (2017) The Relationship between Sleep Apnea, Metabolic Dysfunction and Inflammation: The Gender Influence. *Brain, Behavior, and Immunity*, **59**, 211-218.

[41] Archontogeorgis, K., Nena, E., Papanas, N. and Steiropoulos, P. (2014) Biomarkers to Improve Diagnosis and Monitoring of Obstructive Sleep Apnea Syndrome: Current Status and Future Perspectives. *Pulmonary Medicine*, **2014**, Article ID: 930535.

[42] He, Q., Yang, Q.C., Zhou, Q., *et al*. (2014) Effects of Varying Degrees of Intermittent Hypoxia on Proinflammatory

Cytokines and Adipokines in Rats and 3T3-L1 Adipocytes. *PLoS ONE*, **9**, e86326. https://doi.org/10.1371/journal.pone.0086326

[43] Vgontzas, A.N., Papanicolaou, D.A., Bixler, E.O., *et al*. (2000) Sleep Apnea and Daytime Sleepiness and Fatigue: Relation to Visceral Obesity, Insulin Resistance, and Hypercytokinemia. *The Journal of Clinical Endocrinology & Metabolism*, **85**, 1151-1158. https://doi.org/10.1210/jcem.85.3.6484

[44] Cheung, A.T., Ree, D., Kolls, J.K., Fuselier, J., Coy, D.H. and Bryer-Ash, M. (1998) An *in Vivo* Model for Elucidation of the Mechanism of Tumor Necrosis Factor-Alpha (TNF-Alpha)-Induced Insulin Resistance: Evidence for Differential Regulation of Insulin Signaling by TNF-Alpha. *Endocrinology*, **139**, 4928-4935.

[45] Svedberg, J., Björntorp, P., Smith, U. and Lönnroth, P. (1992) Effect of Free Fatty Acids on Insulin Receptor Binding and Tyrosine Kinase Activity in Hepatocytes Isolated from Lean and Obese Rats. *Diabetes*, **41**, 294-298. https://doi.org/10.2337/diab.41.3.294

[46] Hennes, M.M., Shrago, E. and Kissebah, A.H. (1990) Receptor and Postreceptor Effects of Free Fatty Acids (FFA) on Hepatocyte Insulin Dynamics. *International Journal of Obesity*, **14**, 831-841.

[47] Agarwal, A., Hegde, A., Yadav, C., Ahmad, A., Manjrekar, P.A. and Srikantiah, R.M. (2017) Association of Interleukin-6 and Myeloperoxidase with Insulin Resistance in Impaired Fasting Glucose Subjects. *Indian Journal of Clinical Biochemistry*, **32**, 33-38. https://doi.org/10.1007/s12291-016-0567-8

[48] Kim, J.H., Bachmann, R.A. and Chen, J. (2009) Interleukin-6 and Insuanlin Resistence. *Vitamins & Hormones*, **80**, 613-633.

[49] Pallayova, M., Steele, K.E., Magnuson, T.H., *et al*. (2010) Sleep Apnea Predicts Distinct Alterations in Glucose Homeostasis and Biomarkers in Obese Adults with Normal and Impaired Glucose Metabolism. *Cardiovascular Diabetology*, **9**, 83. https://doi.org/10.1186/1475-2840-9-83

[50] Pallayova, M., Lazurova, I. and Donic, V. (2011) Hypoxic Damage to Pancreatic Beta Cells—The Hidden Link between Sleep Apnea and Diabetes. *Medical Hypotheses*, **77**, 930-934.

[51] Yang, J., Park, Y., Zhang, H., *et al*. (2009) Feed-Forward Signaling of TNF-Alpha and NF-Kappa B via IKK-Beta Pathway Contributes to Insulin Resistance and Coronary Arteriolar Dysfunction in Type 2 Diabetic Mice. *American Journal of Physiology. Heart and Circulatory Physiology*, **296**, H1850-H1858. https://doi.org/10.1152/ajpheart.01199.2008

[52] Gao, Z., Hwang, D., Bataille, F., *et al*. (2002) Serine Phosphorylation of Insulin Receptor Substrate 1 by Inhibitor Kappa B Kinase Complex. *The Journal of Biological Chemistry*, **277**, 48115-48121. https://doi.org/10.1074/jbc.M209459200

[53] Wu, X., Gu, W., Lu, H., *et al*. (2016) Soluble Receptor for Advanced Glycation End Product Ameliorates Chronic Intermittent Hypoxia Induced Renal Injury, Inflammation, and Apoptosis via P38/JNK Signaling Pathways. *Oxidative Medicine and Cellular Longevity*, **2016**, Article ID: 1015390.

[54] Wang, Y., Hai, B., Niu, X., *et al*. (2016) Chronic Intermittent Hypoxia Disturbs Insulin Secretion and Causes Pancreatic Injury via MAPK Signaling Pathway. *Biochemistry and Cell Biology*.

[55] Rosen, E.D. and Spiegelman, B.M. (2006) Adipocytes as Regulators of Energy Balance and Glucose Homeostasis. *Nature*, **444**, 847-853. https://doi.org/10.1038/nature05483

[56] Bonsignore, M.R. and Eckel, J. (2009) ERS Meeting Report. Metabolic Aspects of Obstructive Sleep Apnoea Syndrome. *European Respiratory Review*, **18**, 113-124. https://doi.org/10.1183/09059180.00000109

[57] Kanbay, A., Kokturk, O., Ciftci, T.U., Tavil, Y. and Bukan, N. (2008) Comparison of Serum Adiponectin and Tumor Necrosis Factor-Alpha Levels between Patients with and without Obstructive Sleep Apnea Syndrome. *Respiration*, **76**, 324-330. https://doi.org/10.1159/000134010

[58] Ryan, S. (2016) Adipose Tissue Inflammation by Intermittent Hypoxia: Mechanistic Link between Obstructive Sleep Apnoea and Metabolic Dysfunction. *The Journal of Physiology*.

[59] Fouillioux, C., Contreras, F., Lares, M., *et al*. (2008) Metabolic and Hemodynamic Markers of Endothelial Dysfunction in Patients with Hypertension and Patients with Type 2 Diabetes during the Cold Pressor Test. *American Journal of Therapeutics*, **15**, 389-396. https://doi.org/10.1097/MJT.0b013e318169bca8

[60] Hargens, T.A., Guill, S.G., Kaleth, A.S., *et al*. (2013) Insulin Resistance and Adipose-Derived Hormones in Young Men with Untreated Obstructive Sleep Apnea. *Sleep Breath*, **17**, 403-409. https://doi.org/10.1007/s11325-012-0708-0

[61] Arnardottir, E.S., Mackiewicz, M., Gislason, T., Teff, K.L. and Pack, A.I. (2009) Molecular Signatures of Obstructive Sleep Apnea in Adults: A Review and Perspective. *Sleep*, **32**, 447-470.

[62] De Santis, S., Cambi, J., Tatti, P., Bellussi, L. and Passali, D. (2015) Changes in Ghrelin, Leptin and Pro-Inflammatory Cytokines after Therapy in Obstructive Sleep Apnea Syndrome (OSAS) Patients. *Polish Journal of Otolaryngology*, **69**, 1-8. https://doi.org/10.5604/00306657.1147029

[63] Lam, J.C.M., Mak, J.C.W. and Ip, M.S.M. (2012) Obesity, Obstructive Sleep Apnoea and Metabolic Syndrome. *Respirology*, **17**, 223-236. https://doi.org/10.1111/j.1440-1843.2011.02081.x

[64] Reinke, C., Bevans-Fonti, S., Drager, L.F., Shin, M. and Polotsky, V.Y. (2011) Effects of Different Acute Hypoxic Regimens on Tissue Oxygen Profiles and Metabolic Outcomes. *Journal of Applied Physiology*, **111**, 881-890.

[65] Yang, R., Sikka, G., Larson, J., *et al*. (2011) Restoring Leptin Signaling Reduces Hyperlipidemia and Improves Vascular Stiffness Induced by Chronic Intermittent Hypoxia. *American Journal of Physiology. Heart and Circulatory Physiology*, **300**, H1467-H1476. https://doi.org/10.1152/ajpheart.00604.2009

[66] Li, J., Bosch-Marce, M., Nanayakkara, A., *et al*. (2006) Altered Metabolic Responses to Intermittent Hypoxia in Mice with Partial Deficiency of Hypoxia-Inducible Factor-Lalpha. *Physiological Genomics*, **25**, 450-457. https://doi.org/10.1152/physiolgenomics.00293.2005

[67] Zhang, X., Wang, Y., Li, Q., *et al*. (2010) Changes in Genioglossus and Their Association with Serum Adiponectin Levels in Rats Subjected to Chronic Intermittent Hypoxia. *Chinese Medical Journal*, **123**, 2249-2253.

[68] Lam, D.C.L., Lam, K.S.L. and Ip, M.S.M. (2015) Obstructive Sleep Apnoea, Insulin Resistance and Adipocytokines. *Clinical Endocrinology*, **82**, 165-177. https://doi.org/10.1111/cen.12597

[69] Lam, J.C.M., Xu, A., Tam, S., *et al*. (2008) Hypoadiponectinemia Is Related to Sympathetic Activation and Severity of Obstructive Sleep Apnea. *Sleep*, **31**, 1721-1727. https://doi.org/10.1093/sleep/31.12.1721

[70] De Lima, A.M.J., Franco, C.M.R., de Castro, C.M.M.B., *et al*. (2010) Effects of Nasal Continuous Positive Airway Pressure Treatment on Oxidative Stress and Adiponectin Levels in Obese Patients with Obstructive Sleep Apnea. *Respiration*, **79**, 370-376. https://doi.org/10.1159/000227800

[71] Wolk, R., Svatikova, A., Nelson, C.A., *et al*. (2005) Plasma Levels of Adiponectin, a Novel Adipocyte-Derived Hormone, in Sleep Apnea. *Obesity Research*, **13**, 186-190. https://doi.org/10.1038/oby.2005.24

[72] Gao, Z., He, Q., Peng, B., Chiao, P.J. and Ye, J. (2006) Regulation of Nuclear Translocation of HDAC3 by Ikappabalpha Is Required for Tumor Necrosis Factor Inhibition of Peroxisome Proliferator-Activated Receptor Gamma Function. *The Journal of Biological Chemistry*, **281**, 4540-4547. https://doi.org/10.1074/jbc.M507784200

[73] Yokoe, T., Alonso, L.C., Romano, L.C., *et al*. (2008) Intermittent Hypoxia Reverses the Diurnal Glucose Rhythm and Causes Pancreatic β-Cell Replication in Mice. *The Journal of Physiology*, **586**, 899-911.

[74] Morton, N.M. (2010) Obesity and Corticosteroids: 11 Beta-Hydroxysteroid Type 1 as a Cause and Therapeutic Target in Metabolic Disease. *Molecular and Cellular Endocrinology*, **316**, 154-164.

[75] Tamisier, R., Pépin, J.L., Rémy, J., *et al*. (2011) 14 Nights of Intermittent Hypoxia Elevate Daytime Blood Pressure and Sympathetic Activity in Healthy Humans. *European Respiratory Journal*, **37**, 119-128. https://doi.org/10.1183/09031936.00204209

[76] Prabhakar, N.R., Kumar, G.K. and Peng, Y. (2012) Sympatho-Adrenal Activation by Chronic Intermittent Hypoxia. *Journal of Applied Physiology*, **113**, 1304-1310.

[77] Kline, C.E., Reboussin, D.M., Foster, G.D., *et al*. (2016) The Effect of Changes in Cardiorespiratory Fitness and Weight on Obstructive Sleep Apnea Severity in Overweight Adults with Type 2 Diabetes. *Sleep*, **39**, 317-325. https://doi.org/10.5665/sleep.5436

[78] Kuna, S.T., Reboussin, D.M., Borradaile, K.E., *et al*. (2013) Long-Term Effect of Weight Loss on Obstructive Sleep Apnea Severity in Obese Patients with Type 2 Diabetes. *Sleep*, **36**, 641-649. https://doi.org/10.5665/sleep.2618

[79] Pamidi, S., Wroblewski, K., Stepien, M., *et al*. (2015) Eight Hours of Nightly Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea Improves Glucose Metabolism in Patients with Prediabetes. A Randomized Controlled Trial. *American Journal of Respiratory and Critical Care Medicine*, **192**, 96-105. https://doi.org/10.1164/rccm.201408-1564OC

[80] Weinstock, T.G., Wang, X., Rueschman, M., *et al*. (2012) A Controlled Trial of CPAP Therapy on Metabolic Control in Individuals with Impaired Glucose Tolerance and Sleep Apnea. *Sleep*, **35**, 617-625. https://doi.org/10.5665/sleep.1816

[81] Guo, L., Zhao, X., Pan, Q., *et al*. (2015) Effect of Continuous Positive Airway Pressure Therapy on Glycemic Excursions and Insulin Sensitivity in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome and Type 2 Diabetes. *Chinese Medical Journal*, **128**, 2301-2306. https://doi.org/10.4103/0366-6999.163382

[82] Salord, N., Fortuna, A.M., Monasterio, C., *et al*. (2016) A Randomized Controlled Trial of Continuous Positive Airway Pressure on Glucose Tolerance in Obese Patients with Obstructive Sleep Apnea. *Sleep*, **39**, 35-41. https://doi.org/10.5665/sleep.5312

[83] Iftikhar, I.H., Khan,M.F., Das, A. and Magalang, U.J. (2013) Meta-Analysis: Continuous Positive Airway Pressure Improves Insulin Resistance in Patients with Sleep Apnea without Diabetes. *Annals of the American Thoracic Society*, **10**, 115-120. https://doi.org/10.1513/AnnalsATS.201209-081OC

[84] Guest, J.F., Panca, M., Sladkevicius, E., Taheri, S. and Stradling, J. (2014) Clinical Outcomes and Cost-Effectiveness of Continuous Positive Airway Pressure to Manage Obstructive Sleep Apnea in Patients with Type 2 Diabetes in the U.K. *Diabetes Care*, **37**, 1263-1271. https://doi.org/10.2337/dc13-2539

[85] Prasad, B., Carley, D.W., Krishnan, J.A., Weaver, T.E. and Weaver, F.M. (2012) Effects of Positive Airway Pressure Treatment on Clinical Measures of Hypertension and Type 2 Diabetes. *Journal of Clinical Sleep Medicine*, **8**, 481-487. https://doi.org/10.5664/jcsm.2136

[86] Plíhalová, A., Westlake, K. and Polák, J. (2016) Obstructive Sleep Apnoea and Type 2 Diabetes Mellitus. *Vnitrní Lékarství*, **62**, 79-84.