ESCOLA SUPERIOR DE TECNOLOGIA DA SAÚDE DE LISBOA
INSTITUTO POLITÉCNICO DE LISBOA

XV Seminário Temático
em Fisiologia Clínica
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Fisiologia Clínica

Biomarcadores na Síndrome de Apneia Obstrutiva do Sono

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SEMINÁRIO Temático

Síndrome de Apneia Obstrutiva do Sono

Caracteriza-se por obstruções parciais ou completas das vias aéreas superiores durante o sono[1].

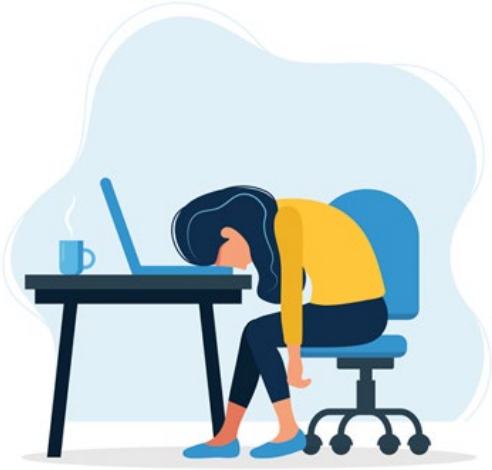
Sintomas [2]:

Diurnos:

- Sonolência diurna excessiva
- Fragmentação do sono
- Défice cognitivo e de atenção
- Fadiga
- Cefaleias matinais

Noturnos:

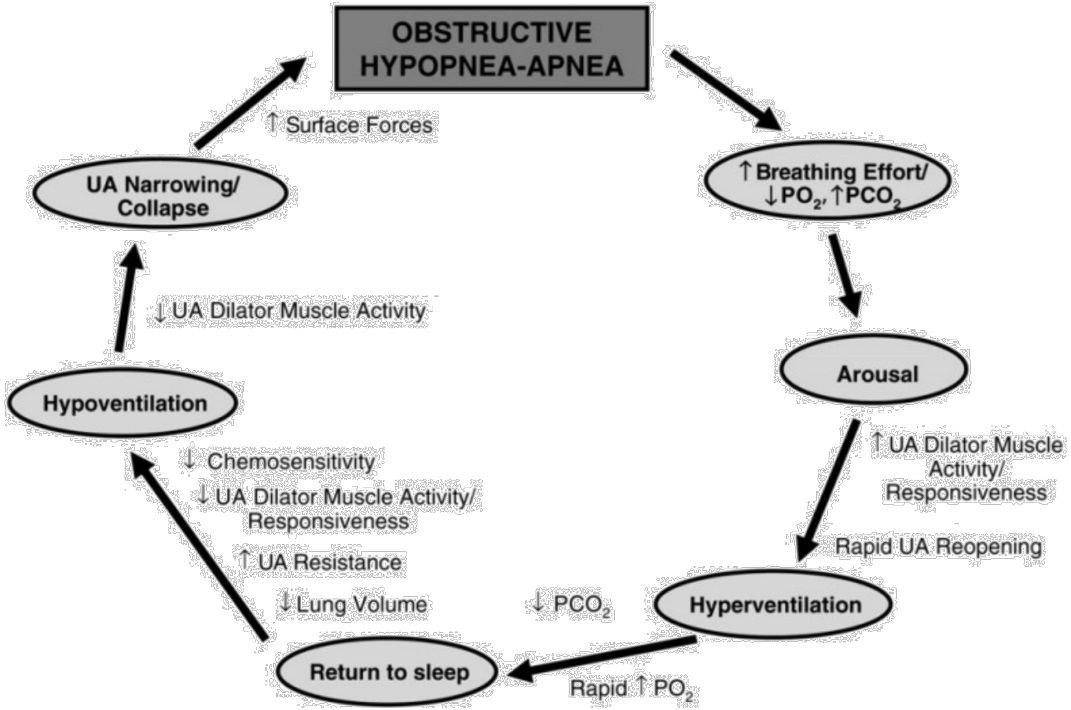
- Ronco
- Diaforese na zona do pescoço
- Refluxo gastroesofágico
- Noctúria



1. Foroughi M. et al. Diagnosis of Obstructive Sleep Apnea Syndrome in Adults: A Brief Review of Existing Data for Practice in Iran. Tanaffos. 2016.
2. Tingting X. et al. Non-surgical treatment of obstructive sleep apnea syndrome. European Archives of Oto-Rhino-Laryngology 2018.

Fisiopatologia

Colapso da via aérea → Mecanismos complexos e multifatoriais[3,4].



3. Arnaud C. et al. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. 2020

4. Eckert DJ. et al. Pathophysiology of adult obstructive sleep apnea. Proceedings of the American Thoracic Society. 2008.

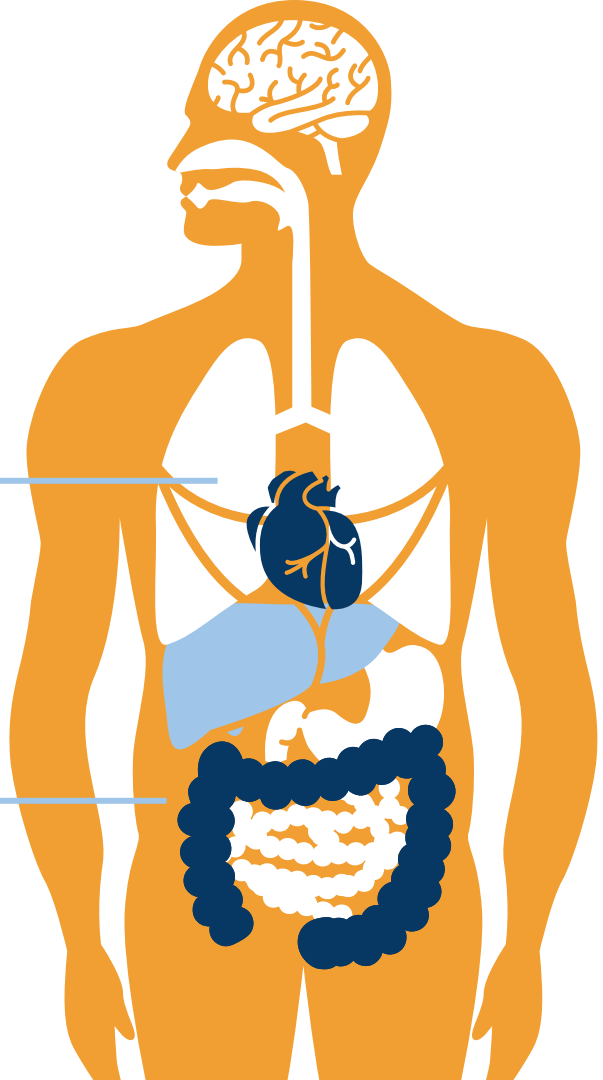
Consequências da SAOS

Doenças cardiovasculares

Alterações vasculares, doença arterial coronária, arritmias, HTA e insuficiência cardíaca[5,6].

Síndrome metabólica

Aumento dos níveis glicose e triglicéridos, marcadores inflamatórios, rigidez arterial e aterosclerose[7].



5. Jordan AS., et al. Airway Dilator Muscle Activity and Lung Volume During Stable Breathing in Obstructive Sleep Apnea. 2009.
6. Borel AL, et al. The severity of nocturnal hypoxia but not abdominal adiposity is associated with insulin resistance in non-obese men with sleep apnea.2013.
7. Kline LR. Clinical presentation and diagnosis of obstructive sleep apnea in adults. 2021.

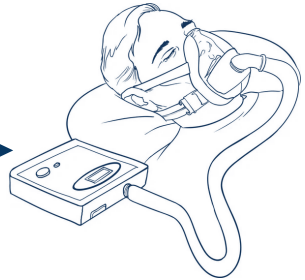
Diagnóstico

Polissonografia em laboratório (nível I) ou ambulatório (nível II e III)[7-9].

- Sintomas específicos
- Eventos respiratórios durante o sono

Tratamento

Cirúrgico ou não cirúrgico [2] + Estratégias de perda de peso[3]



2. Tingting X, et al. Non-surgical treatment of obstructive sleep apnea syndrome. 2018.
3. Arnaud C., et al. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. 2020
7. Kline LR. Clinical presentation and diagnosis of obstructive sleep apnea in adults. 2021.
8. Kapur VK., et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. 2017
9. Collop N. Home sleep apnea testing for obstructive sleep apnea in adults. 2021.

Em Portugal, estima-se que mais de 1 milhão de indivíduos tenha SAOS[10].

10. Associação Portuguesa de Sono. 2022.

Biomarcadores

Marcador para processos biológicos normais, patogénicos e de respostas farmacológicas[11].

SAOS → variações moleculares, oxidativas e inflamatórias[12]

Objetivos [12-15]:

- Sensível e específico
- Identificação precoce
- Grau de gravidade
- Bom custo-benefício
- Monitorização da terapêutica

11. Strimbu K, Tavel J A. What are Biomarkers? 2010.
12. Archontogeorgis K. et al. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. 2014.
13. Luca Canto G. et al. Biomarkers associated with obstructive sleep apnea: A scoping review. 2015.
14. Mullington J M, et al. Developing Biomarker Arrays Predicting Sleep and Circadian-Coupled Risks to Health. Sleep. 2016.
15. Mehra R. Building Evidence Implicating Novel Cardiovascular Biomarkers in Obstructive Sleep Apnea. 2017.

01. Inflamatórios

Padrão de hipoxia intermitente [17]

Lesões mecânicas [16]:

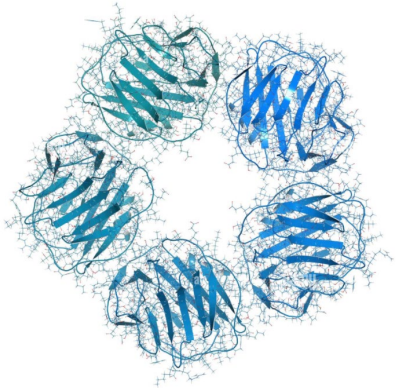
- Ronco
- Esforço respiratório
- Obstrução da via aérea

16. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: The road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep medicine reviews [Internet]. 2018 Dec 1 [cited 2021 Dec 9];42:211–9. Available from: https://pubmed.ncbi.nlm.nih.gov/30279095/

17. Ryan S, Cormac ;, Taylor T, Mcnicholas WT. Selective Activation of Inflammatory Pathways by Intermittent Hypoxia in Obstructive Sleep Apnea Syndrome. 2005;.

01. Inflamatórios

Proteína C-reativa (PCR)



Indicador para processos inflamatórios e infeciosos[16].

Aumenta com ..:[18]

- Índice de apneia e hipopneia
- Índice de microdespertares
- Dessaturação de oxigénio
- Obesidade visceral

	SIM	NÃO
DIMINUI APÓS CPAP	✓	

16 Gaines J., et al. Obstructive sleep apnea and the metabolic syndrome : The road to clinically -meaningful phenotyping , improved prognosis , and personalized treatment . 2018.
18 Bezerra C. Proteína C-reativa (PCR) o que é e porque pode estar alta . 2021.

01. Inflamatórios

Interleucina-6 (IL-6)

Responsável pela resposta aguda da inflamação[12].

Provoca **fadiga** e **sonolência diurna excessiva** em pacientes com SAOS[19].

Bom preditor da gravidade da SAOS.

12. Archontogeorgis K., et al. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. 2014.
19. Li Y, et al. Objective, but Not Subjective, Sleepiness is Associated With Inflammation in Sleep Apnea. Sleep. 2017.

01. Inflamatórios

Pentraxina-3 (PTX-3)

Glicoproteína cuja função é a regulação de reações inflamatórias[20,21].

Correlaciona -se com ..:[21]

- IMC
- Índice de dessaturação de oxigénio
- Níveis mínimos de saturação de oxigénio
- Disfunções endoteliais
- Relação entre espessura da camada íntima e média da carótida

	SIM	NÃO
DIMINUI APÓS CPAP	✓	

20. Sobrinho O. Efeito biológico da proteína pentraxina 3 sobre as características morfológicas e fisiológicas de células tumorais humanas. 2016.
21. Sozer V., et al. Changes in inflammatory mediators as a result of intermittent hypoxia in obstructive sleep apnea syndrome. 2018.

01. Inflamação

Fator de necrose tumoral alfa (FNT-α)

Citoquina pró-inflamatória produzida na fase aguda de inflamação[22].

Correlaciona -se com ..:[12,23]

- Sonolência diurna excessiva
- Índice de dessaturação de oxigénio
- Distúrbios do sono

	SIM	NÃO
DIMINUI APÓS CPAP	✓	

12. Archontogeorgis K. et al. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. 2014.
22. Idriss HT., et al. TNF and the TNF Receptor Superfamily: Structure-Function Relationship(s). 2000.
23. Kobukai Y., et al. Morning pentraxin3 levels reflect obstructive sleep apnea-related acute inflammation. 2014.

02. Metabólicos

Leptina[12]

Correlaciona -se com …

- IMC
- Índice de apneias e hipopneia
- Gravidade da SAOS

Resistina[12]

Correlaciona -se com …

- Saturação de oxiemoglobina durante o sono
- Gravidade da SAOS

	SIM	NÃO
DIMINUI APÓS CPAP	✓	

12. Archontogeorgis K, Nena E, Papanas N, Steiropoulos P. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. Pulmonary medicine.

03. Ateroscleróticos

Molécula de adesão intercelular-1 (MAIC-1) Molécula de adesão celular vascular-1 (MACV-1) L-seletina

Aterosclerose : adesão de leucócitos e células endoteliais circulantes, em resposta às citoquinas pró-inflamatórias[12].

SAOS → Hipoxia → Inflamação → Aumento níveis **MAIC-1, MACV-1, L-seletina** → Processo de adesão celular → **Pior prognóstico cardiovascular**

12. Archontogeorgis K., et al. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. 2014.

Qual é o biomarcador ideal?

Considerações finais

Sensível e específico

Identificação precoce

Custo-benefício

Tabela 1 – Resumo do desempenho dos biomarcadores quanto à predição da gravidade da SAOS e resposta à terapêutica

	PCR	IL-6	PTX-3	FTN-α	Leptina	Resistina	MAIC-1	MACV-1	L-seletina
Gravidade	✓	✓	✓	✓	?	?	✗	✗	✗
Terapêutica	✓	✗	✓	✓	✓	✓	?	?	?

Referências bibliográficas

1. Foroughi M, Razavi H, Malekmohammad M, Naghan PA, Jamaati H. Diagnosis of Obstructive Sleep Apnea Syndrome in Adults: A Brief Review of Existing Data for Practice in Iran. Tanaffos. 2016;15(2):70–4.

2. Tingting X, Danming · You, Xin · Chen. Non-surgical treatment of obstructive sleep apnea syndrome. European Archives of Oto-Rhino-Laryngology [Internet]. 2018;275(3):335–46. Available from: https:// doi.org/ 10.1007/ s00405-017-4818-y

3. Arnaud C, Bochaton T, Pépin JL, Belaidi E. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. Archives of cardiovascular diseases [Internet]. 2020 May 1 [cited 2022 Jan 2];113(5):350–8. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 32224049/

4. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proceedings of the American Thoracic Society [Internet]. 2008 Feb [cited 2022 Feb 4];5(2):144–53. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 18250206/

5. Jordan AS, Whit DP, Lo YL, Wellman A, Eckert DJ, Yim-Yeh S, et al. Airway Dilator Muscle Activity and Lung Volume During Stable Breathing in Obstructive Sleep Apnea. Sleep [Internet]. 2009 [cited 2022 Jan 2];32(3):361. Available from: / pmc/ articles/ PMC2647790/

6. Borel AL, Monneret D, Tamisier R, Baguet JP, Faure P, Levy P, et al. The severity of nocturnal hypoxia but not abdominal adiposity is associated with insulin resistance in non-obese men with sleep apnea. PloS one [Internet]. 2013 Aug 12 [cited 2022 Jan 2];8(8). Available from: https:// pubmed.ncbi.nlm.nih.gov/ 23951064/

7. Kline LR. Clinical presentation and diagnosis of obstructive sleep apnea in adults [Internet]. 2021 [cited 2021 Dec 29]. Available from: https:// www.uptodate.com/ contents/ clinical-presentation-and-diagnosis-of-obstructive-sleep-apnea-in-adults#H1422369420

8. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of clinical sleep medicine : JCSM: official publication of the American Academy of Sleep Medicine [Internet]. 2017 [cited 2021 Dec 29];13(3):479–504. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 28162150/

9. Collop N. Home sleep apnea testing for obstructive sleep apnea in adults [Internet]. 2021 [cited 2021 Dec 29]. Available from: https:// www.uptodate.com/ contents/ home-sleep-apnea-testing-for-obstructive-sleep-apnea-in-adults?sectionName=Type%203%20devices%20(portable%20devices)&topicRef=7706&anchor=H5&source=see_link#H5

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13. de Luca Canto G, Pachêco-Pereira C, Aydinoz S, Major PW, Flores-Mir C, Gozal D. Biomarkers associated with obstructive sleep apnea: A scoping review. Sleep medicine reviews [Internet]. 2015 Oct 1 [cited 2021 Dec 9];23:28–45. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 25645128/

14. Mullington JM, Abbott SM, Carroll JE, Davis CJ, Dijk DJ, Dinges DF, et al. Developing Biomarker Arrays Predicting Sleep and Circadian-Coupled Risks to Health. Sleep [Internet]. 2016 Apr 1 [cited 2022 Jan 3];39(4):727–36. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 26951388/

15. Mehra R. Building Evidence Implicating Novel Cardiovascular Biomarkers in Obstructive Sleep Apnea:393-400. Journal of Clinical Sleep Medicine [Internet]. 2017;13(3). Available from: http:// dx.doi.org/ 10.5664/ jcsm.6476

16. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: The road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep medicine reviews [Internet]. 2018 Dec 1 [cited 2021 Dec 9];42:211–9. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 30279095/

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19. Li Y, Vgontzas AN, Fernandez-Mendoza J, Kritikou I, Basta M, Pejovic S, et al. Objective, but Not Subjective, Sleepiness is Associated With Inflammation in Sleep Apnea. Sleep [Internet]. 2017 Feb 1 [cited 2022 Jan 3];40(2). Available from: https:// pubmed.ncbi.nlm.nih.gov/ 28364485/

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23. Kobukai Y, Koyama T, Watanabe H, Ito H. Morning pentraxin3 levels reflect obstructive sleep apnea-related acute inflammation. J Appl Physiol [Internet]. 2014;117:1141–8. Available from: http:// www.jappl.org

Obrigada pela atenção.

Questões?

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