Non-alcoholic fatty pancreatic disease and insulin resistance: overlooked complication of obstructive sleep apnea and hypopnea syndrome - signaling pathway diagram

Doença pancreática gordurosa não alcoólica e resistência insulínica: complicação negligenciada da síndrome de apneia e hipopneia obstrutiva do sono

Gustavo Magno Baptista[1], Rosangela Carvalho de Melo[1], Gabriela Correia Matos de Oliveira[2], Luís Jesuíno de Oliveira Andrade[1]

ABSTRACT

Objective: To demonstrate the interaction between obstructive sleep apnea/hypopnea syndrome, insulin resistance, and non-alcoholic fatty pancreatic disease through the signaling pathway diagram. **Methods:** To investigate the involvement of metabolic signaling pathway, a search was performed using the Kyoto Encyclopedia of Genes and Genomes. The signaling pathway mapping was performed using the automatic annotation server of this encyclopedia. The Modeller 9.19 package was used to predict 3-dimensional structures based on the homology modeling protocol. The signaling pathway map was performed using PathVisio software, which is a free available signaling pathway drawing software. Based on the 3-dimensional structures, we have designed several peptide activators of the signaling pathway of non-alcoholic fatty pancreatic disease. **Results:** The contigs were taken from the Kyoto Encyclopedia of Genes and Genomes database and their mapped transcription represented the signaling pathway of the main biomolecules that triggered non-alcoholic fatty pancreatic disease. The interaction between obstructive sleep apnea/hypopnea syndrome, insulin resistance, and inflammatory factors contributes to the possible development of fatty infiltration of pancreas, leading to the loss of function of the pancreatic β-cells, and even to the development of other metabolic diseases. **Conclusion:** The interaction between obstructive sleep apnea/hypopnea syndrome and insulin resistance demonstrated through the signaling pathway contributes to the possible development of non-alcoholic fatty pancreatic disease.

Keywords: Sleep apnea, obstructive; Insulin resistance; Non-alcoholic fatty liver disease.

RESUMO

Objetivo: Demonstrar a interação entre a síndrome de apneia/hipopneia obstrutiva do sono, a resistência à insulina e a doença pancreática gordurosa não alcoólica considerando o desenho de uma via de sinalização. **Métodos:** Para avaliar o envolvimento da via de sinalização metabólica, realizou-se uma pesquisa usando a Enciclopédia de Genes e Genomas de Kyoto. O mapeamento da via de sinalização foi realizado com o servidor de anotação automático desta enciclopédia. O *software* MODELLER 9.19 foi usado para prever estruturas tridimensionais, com base no protocolo de modelagem por homologia. O desenho da via de sinalização foi realizado por meio do programa PathVisio, um *software* de domínio público para desenho de via de sinalização. Com base nas estruturas tridimensionais, desenhamos os vários ativadores peptídicos da via de sinalização da esteatose pancreática. **Resultados:** Os *contigs* foram retirados do banco de dados da Enciclopédia de Genes e Genomas de Kyoto, e sua transcrição mapeada representou a via de sinalização das principais biomoléculas que desencadearam doença pancreática gordurosa não alcoólica. A interação entre síndrome de apneia/hipopneia obstrutiva do sono, resistência à insulina e fatores inflamatórios contribuiu para o possível desenvolvimento de infiltração gordurosa do pâncreas, levando à perda de função das células beta pancreáticas e até mesmo ao desenvolvimento de outras doenças metabólicas. **Conclusão:** A interação entre síndrome de apneia/hipopneia obstrutiva do sono e resistência à insulina demonstrada pela via de sinalização contribui para o possível desenvolvimento de doença pancreática gordurosa não alcoólica.

Descritores: Apneia obstrutiva do sono; Resistência à insulina; Hepatopatia gordurosa não alcoólica.

[1] Departamento de Saúde - Universidade Estadual de Santa Cruz, Ilhéus, BA, Brazil.
[2] Faculdade de Medicina, Salvador, BA, Brazil.
Received on: 26/11/2017. **Accepted on**: 05/02/2018.
Conflict interest: none.
Corresponding author: Luís Jesuíno de Oliveira Andrade. Departamento de Saúde da Universidade Estadual de Santa Cruz – *Campus* Soane Nazaré de Andrade – Rodovia Jorge Amado, km 16 – Salobrinho – Zip code: 45662-900 – Ilhéus, BA, Brasil – Phone: 55 (73) 3212-2928 – E-mail: luis_jesuino@yahoo.com.br

INTRODUCTION

The non-alcoholic fatty pancreatic disease (NAFPD) is defined as a lesion that varies from the excessive fatty infiltration of the pancreas without fat replacement to pancreatic inflammation, pancreatitis which may progress to pancreatic fibrosis.[1] NAFPD may occur due to the replacement by adipocytes of dead pancreatic acinar cells, or accumulation of fat associated with metabolic disease. Several words of similar meaning for the increase of fat in the pancreas have been used in the literature; however, the NAFPD term shall mean fat accumulation in the pancreas associated with obesity and metabolic syndrome.[2] Few studies have evaluated the prevalence of NAFPD, which was estimated between 16% and 35% in the adult population, and 10% in a pediatric population.[3,4]

The obstructive sleep apnea hypopnea syndrome (OSAHS) is due to usual absence or reduction in breathing in the course of sleep regardless of a regular effort to breathe normally. It is characterized by an Apnea-Hypopnea Index (AHI) of 15 or greater or an AHI of 5 or greater with frequent arousals during sleep, in addition to disruptive snoring and excessive daytime sleepiness, and has been associated with several adverse health outcomes, including insulin resistance (IR).[5] The prevalence of OSAHS is 3% to 7% in men and 2% to 5% in women.[6]

IR is a metabolic disorder defined clinically as low capability of insulin to increase glucose uptake and utilization in target tissues, which may be due to several mechanisms, among which the genetic changes of proteins of the insulin action cascade, fetal malnutrition, and increases in visceral adiposity.[7]

OSAHS has been associated with the level of IR which in turn would lead to pancreatic adipocyte infiltration, with consequent NAFPD.[8,9]

We focus on OSAHS and the roles of transcription factors in inflammation-induced IR, and their involvement in the pathogenesis of NAFPD, with the objective of demonstrating the interaction between OSAHS and NAFPD through signaling pathway diagrams.

INTERACTION BETWEEN OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME AND NON-ALCOHOLIC FATTY PANCREATIC DISEASE

OSAHS seems to be one of the key factors in the development of NAFPD, and this was suggested in a recent study.[10]

There is data suggesting that OSAHS is a risk factor for dyslipidemia because it is independently associated with metabolic syndrome, with increased levels of triglycerides and reduced levels of high-density lipoproteins.[11] This association would be mediated by lipid clearance reduction, increased lipolysis, and regulation of lipid synthesis in the liver. Moreover, OSAHS can influence the development of type 2 diabetes mellitus (DM2) in predisposed individuals due to hypoxic damage to pancreatic β-cells, because intermittent hypoxia leads to hormonal derangements, inducing enhanced lipid synthesis and inflammation, contributing for pancreatic fatty infiltration.[12]

A relation between metabolic alterations and fatty infiltration of the pancreas was showed in various studies with animals, and it considered the hypothesis that fatty infiltration of the endocrine pancreas would lead to a change in insulin secretion and the development of DM2.[13-15]

The prevalence of OSAHS is directly proportional to increases in body weight gain and, consequently, to an increase in body mass index (BMI).[16] Likewise, studies show that NAFPD is closely associated with BMI.[17]

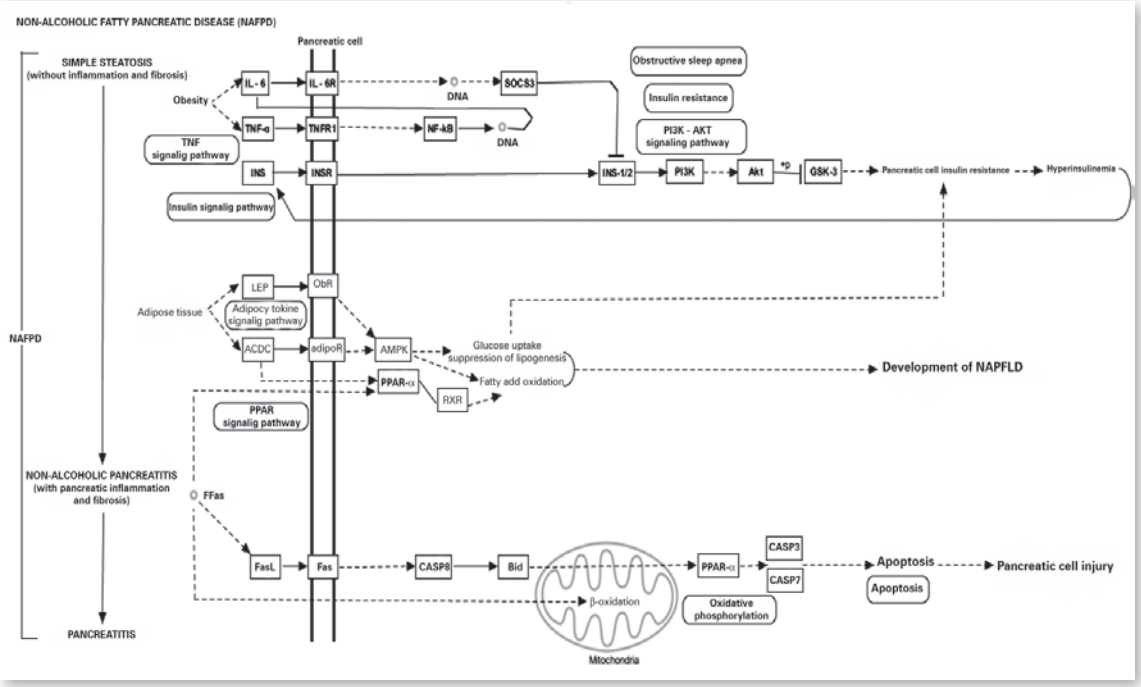
Therefore, factors such as increase in BMI, IR, damage to pancreatic β-cells leading to DM2, dyslipidemia, and metabolic syndrome common to OSA and NAFPD could explain the interaction between both of them.

MODEL

Signaling pathways regulate cellular decisions, and mathematical models have been used in the elaboration of biological signaling pathways. To investigate the involvement of metabolic signaling pathway, a search was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG), a database containing biological information about signaling pathway maps, extraction of biological processes networks, molecular interaction, as well as protein domains data. We investigated a total of 46 signaling pathways in the KEGG databases, and for each pathway we identify all the proteins related to obesity, IR, DM2, dyslipidemia, and metabolic syndrome common to OSA and NAFPD, and we compared the proteins and interactions of ten pathways. The MODELLER 9.19 package was used to predict 3D structure based on the homology modeling protocol. The signaling pathway map design was done with PathVisio software, a free available signaling pathway drawing software. Based on the 3-dimensional (3D) structure, we have designed several peptide activators of signaling pathway of NAFPD.

Signaling pathway design

As shown in Figure 1, multiple mechanisms underlying NAFPD are shown, and its interaction with OSAHS.



NAFDP: non-alcoholic fatty pancreatic disease; TNF-α: tumor necrosis factor alpha; IL: interleukin; INS: insulin; TNFR: tumor necrosis factor receptor; INSR: beta-subunit of insulin receptor; NF-κB: factor nuclear kappa B; Pt3K-AKT: phosphatidylinositol 3-kinase - protein kinase B; AKT: protein kinase B; GSK-3: glycogen synthase kinase 3; LEP: leptin; ObT: octanoate breath test; ACDC: adiponectin; AMPK: AMP-activated protein kinase; PPAR-α: peroxisome proliferator-activated receptor alpha; RXR: retinoid X receptor; FFas: free fatty acids; FasL: fatty acids ligand; Fas: fatty acids; CASP: caspase; Bid: BH3 interacting domain death agonist.

Figure 1. Signaling pathway of non-alcoholic fatty pancreatic disease model.

Non-alcoholic fatty pancreatic disease signaling pathway

NAFPD represents a spectrum ranging from simple steatosis to more severe steatopancreatitis with pancreatic inflammation and fibrosis, known as non-alcoholic steatopancreatitis (NASP). NASP may further lead to pancreatic fibrosis. This diagram shows a stage-dependent progression of NAFPD. In the first phase of NAFPD, adipose tissue accumulation has been demonstrated as activators of inflammatory factors. The main cause is the induction of IR, which leads to a defect in insulin suppression of free fatty acids (FFA) disposal.[18] Moreover, transcription factor Peroxisome proliferator-activated receptor-α (PPAR-α) activates key enzymes of lipogenesis and increases the synthesis of FFA in the pancreas.[19] In the second phase, as a consequence of the progression to NASP, the production of reactive oxygen species is enhanced due to oxidation stress through mitochondrial β-oxidation of fatty acids and endoplasmic reticulum stress, leading to lipid peroxidation. The lipid peroxidation can further cause the production of cytokines, caspases, promoting cell death, inflammation and fibrosis.[20] The chronic inflammation is one of the determining causes of IR, and OSAHS also induces an inflammatory state directly due to the increase in visceral fatty that is an abundant source of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and profibrogenic adipokine leptin. In addition, the development of IR following inactivation of the phosphoinositide-3-kinase (PIK3) regulatory → serine/threonine kinase (STK) signaling pathway, leading to the progression of pancreatic cell IR and consequent NAFPD.

The development of IR involves numerous underlying mechanisms, including increment of phosphorylation of IRS (insulin receptor substrate) protein by protein kinase C, c-Jun N-terminal protein kinase 1 and inhibitor of nuclear factor kappa B kinase subunit beta.[21] It also involves increased IRS-1 proteasome damage by mammalian target of rapamycin (mTOR), besides reduction of activation of signaling molecules, including the PI3K and protein kinase B (AKT), and increased action of phosphatases encompassing protein tyrosine phosphatase (PTPs), phosphatase and tensin homolog (PTEN), and protein phosphatase 2A (PP2A).[22]

CONCLUSION

Obstructive sleep apnea/hypopnea syndrome and non-alcoholic fatty pancreatic disease have obesity, in-

sulin resistance, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome in common. The factors leading to the progression of simple steatosis to non-alcoholic steatopancreatitis are likely to be multiple and complex, and involve transcription factors in inflammation-induced insulin resistance. Thus, we proposed a model of interaction between obstructive sleep apnea hypopnea syndrome and non-alcoholic fatty pancreatic disease through signaling pathway map.

REFERENCES

1. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas. 2010; 39(8):1185-90.
2. Kono M, Tatsumi K, Saibara T, Nakamura A, Tanabe N, Takiguchi Y, et al. Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. Chest. 2007;131(5):1387-92.
3. Wu WL, Gan WH, Tong ML, Li XL, Dai JZ, Zhang CM, et al. Overexpression of NYGGF4 (PID1) inhibits glucose transport in skeletal myotubes by blocking the IRS1/PI3K/AKT insulin pathway. Mol Genet Metab. 2011;102(3):374-7.
4. Tariq H, Nayudu S, Akella S, Glandt M, Chilimuri S. Non-alcoholic fatty pancreatic disease: a review of literature. Gastroenterology Res. 2016;9(6):87-91.
5. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, et al. Screening for obstructive sleep apnea in adults: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2017;317(4):415-33.
6. Minville C, Hilleret MN, Tamisier R, Aron-Wisnewsky J, Clement K, Trocme C, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. Chest. 2014;145(3):525-33.
7. Lebovitz HE. Insulin resistance: definition and consequences. Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S135-48.
8. Pham YH, Bingham BA, Bell CS, Greenfield SA, John SD, Robinson LH, et al. Prevalence of pancreatic steatosis at a pediatric tertiary care center. South Med J. 2016;109(3):196-8.
9. Fratantonio D, Cimino F, Molonia MS, Ferrari D, Saija A, Virgili F, et al. Cyanidin-3-O-glucoside ameliorates palmitate-induced insulin resistance by modulating IRS-1 phosphorylation and release of endothelial derived vasoactive factors. Biochim Biophys Acta. 2017;1862(3):351-7.
10. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus? World J Diabetes. 2014;5(4):415-9.
11. Mathur A, Marine M, Lu D, Swartz-Basile DA, Saxena R, Zyromski NJ, et al. Nonalcoholic fatty pancreas disease. HPB (Oxford). 2007;9(4):312-8.
12. Mirrakhimov AE. Nonalcoholic fatty pancreatic disease and cardio-metabolic risk: is there is a place for obstructive sleep apnea? Cardiovasc Diabetol. 2014;13:29.
13. Lee Y, Lingvay I, Szczepaniak LS, Ravazzola M, Orci L, Unger RH. Pancreatic steatosis: harbinger of type 2 diabetes in obese rodents. Int J Obes (Lond). 2010;34(2):396-400.
14. Braganza JM, Wickens DG, Cawood P, Dormandy TL. Lipid-peroxidation (free-radical-oxidation) products in bile from patients with pancreatic disease. Lancet. 1983;2(8346):375-9.
15. Hellemans KH, Hannaert JC, Denys B, Steffensen KR, Raemdonck C, Martens GA, et al. Susceptibility of pancreatic beta cells to fatty acids is regulated by LXR/PPARalpha-dependent stearoyl-coenzyme A desaturase. PLoS One. 2009;4(9):e7266.
16. Shimabukuro M, Zhou YT, Levi M, Unger RH. Fatty acid-induced beta cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci U S A. 1998;95(5):2498-502.
17. Murphy AM, Thomas A, Crinion SJ, Kent BD, Tambuwala MM, Fabre A, et al. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. Eur Respir J. 2017;49(4):1601731.
18. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015;7(8):1311-22.
19. Lesmana CR, Pakasi LS, Inggriani S, Aidawati ML, Lesmana LA. Prevalence of Non-Alcoholic Fatty Pancreas Disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. BMC Gastroenterol. 2015;15:174.
20. Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol. 2011;8(3):169-77.
21. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230-5.
22. Sepe PS, Ohri A, Sanaka S, Berzin TM, Sekhon S, Bennett G, et al. A prospective evaluation of fatty pancreas by using EUS. Gastrointest Endosc. 2011;73(5):987-93.