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Letter to the editor:

DO ARTIFICIAL SWEETENERS INCREASE THE RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

Tahany Abbas*, Walaa Murad

Histology Department, Faculty of Medicine, South Valley University, Qena 83523, Egypt

* **Corresponding author:** Tahany Abbas, Histology Department, Faculty of Medicine, South Valley University, Qena 83523, Egypt; E-mail: tahany_abbass@yahoo.com

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Dear Editor,

Recently, Emamat and colleagues published a review about NAFLD and a possible role of artificial sweeteners as a risk factor (Emamat et al., 2020). NAFLD is the most frequent liver disorder in industrialized countries, which affects ~25 % of the population (Younossi et al., 2018; Friedman et al., 2018). In the past years, the prevalence of NAFLD increased in adults and in children and is also present in ~7 % of lean persons (Romero-Gómez et al., 2017; Younossi et al., 2018). Moreover, NAFLD represents a risk factor of primary liver cancer (AISF, 2017; Trépo and Valenti, 2020). In their review, Emamat et al. discuss the hypothesis that artificial sweeteners increase the risk of NAFLD (Emamat et al., 2020). Artificial sweeteners or sugar substitutes are increasingly consumed to reduce caloric intake (Kakleas et al., 2020; Suez et al., 2015; Ruiz-Ojeda et al., 2019; Uebanso et al., 2017). The authors discuss the currently available evidence that artificial sweeteners alter the gut microbiota, which may increase the prevalence of NAFLD.

Currently, much experimental effort is invested to gain a deeper understanding of liver disease (Jansen et al., 2017; Godoy et al., 2013, 2015, 2016; Ghallab et al., 2016, 2019a, b; Vartak et al., 2016) and to identify compounds that cause an increased risk of hepatotoxicity (Grinberg et al., 2014, 2018; Albrecht et al., 2019; Kim et al., 2015). Research in this field is often hampered by difficulties to extrapolate data from animal or *in vitro* experiments to the *in vivo* situation (Schenk et al., 2017; Leist et al., 2017). The review of Emamat et al. clearly shows that there is strong evidence that artificial sweeteners influence the composition of gut microbiota. However, further work including prospective and intervention studies are required to clarify if this mechanism really causes an increased risk of liver disease.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

AISF, Italian Association for the Study of the Liver. AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions. Dig Liver Dis. 2017;49:471-83. doi: 10.1016/j.dld.2017.01.147.

Albrecht W, Kappenberg F, Brecklinghaus T, Stoeber R, Marchan R, Zhang M, et al. Prediction of human drug-induced liver injury (DILI) in relation to oral doses and blood concentrations. Arch Toxicol. 2019;93:1609-37. doi: 10.1007/s00204-019-02492-9.

Emamat H, Ghalandari H, Tangestani H, Abdollahi A, Hekmatdoost A. Artificial sweeteners are related to non-alcoholic fatty liver disease: Microbiota dysbiosis as a novel potential mechanism. EXCLI J. 2020;19: 620-6. doi: 10.17179/excli2020-1226.

Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24:908-22. doi: 10.1038/s41591-018-0104-9.

Ghallab A, Cellière G, Henkel SG, Driesch D, Hoehme S, Hofmann U, et al. Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases. J Hepatol. 2016;64:860-71. doi: 10.1016/j.jhep.2015.11.018.

Ghallab A, Myllys M, Holland CH, Zaza A, Murad W, Hassan R, et al. Influence of liver fibrosis on lobular zonation. Cells. 2019a;8(12):1556. doi: 10.3390/cells8121556.

Ghallab A, Hofmann U, Sezgin S, Vartak N, Hassan R, Zaza A, et al. Bile microinfarcts in cholestasis are initiated by rupture of the apical hepatocyte membrane and cause shunting of bile to sinusoidal blood. Hepatology. 2019b;69:666-83.

Godoy P, Hewitt NJ, Albrecht U, Andersen ME, Ansari N, Bhattacharya S, et al. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. Arch Toxicol. 2013;87:1315-530. doi: 10.1007/s00204-013-1078-5.

Godoy P, Schmidt-Heck W, Natarajan K, Lucendo-Villarin B, Szkolnicka D, Asplund A, et al. Gene networks and transcription factor motifs defining the differentiation of stem cells into hepatocyte-like cells. J Hepatol. 2015;63:934-42. doi: 10.1016/j.jhep.2015.05.013.

Godoy P, Widera A, Schmidt-Heck W, Campos G, Meyer C, Cadenas C, et al. Gene network activity in cultivated primary hepatocytes is highly similar to diseased mammalian liver tissue. Arch Toxicol. 2016;90:2513-29. doi: 10.1007/s00204-016-1761-4.

Grinberg M, Stöber RM, Edlund K, Rempel E, Godoy P, Reif R, et al. Toxicogenomics directory of chemically exposed human hepatocytes. Arch Toxicol. 2014;88:2261-87. doi: 10.1007/s00204-014-1400-x.

Grinberg M, Stöber RM, Albrecht W, Edlund K, Schug M, Godoy P, et al. Toxicogenomics directory of rat hepatotoxicants in vivo and in cultivated hepatocytes. Arch Toxicol. 2018;92:3517-33. doi: 10.1007/s00204-018-2352-3.

Jansen PL, Ghallab A, Vartak N, Reif R, Schaap FG, Hampe J, et al. The ascending pathophysiology of cholestatic liver disease. Hepatology. 2017;65:722-38. doi: 10.1002/hep.28965.

Kakleas K, Christodouli F, Karavanaki K. Nonalcoholic fatty liver disease, insulin resistance, and sweeteners: a literature review. Expert Rev Endocrinol Metab. 2020;15:83-93. doi: 10.1080/17446651.2020.1740588.

Kim JY, Fluri DA, Marchan R, Boonen K, Mohanty S, Singh P, et al. 3D spherical microtissues and microfluidic technology for multi-tissue experiments and analysis. J Biotechnol. 2015;205:24-35. doi: 10.1016/j.jbiotec.2015.01.003.

Leist M, Ghallab A, Graepel R, Marchan R, Hassan R, Bennekou SH, et al. Adverse outcome pathways: opportunities, limitations and open questions. Arch Toxicol. 2017;91:3477-505. doi: 10.1007/s00204-017-2045-3.

Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017;67:829-46. doi: 10.1016/j.jhep.2017.05.016.

Ruiz-Ojeda FJ, Plaza-Diaz J, Saez-Lara MJ, Gil A. Effects of sweeteners on the gut microbiota: A review of experimental studies and clinical trials. Adv Nutr. 2019;10:S31–S48. doi: 10.1093/advances/nmy037.

Schenk A, Ghallab A, Hofmann U, Hassan R, Schwarz M, Schuppert A, et al. Physiologically-based modelling in mice suggests an aggravated loss of clearance capacity after toxic liver damage. Sci Rep. 2017;7: 6224. doi: 10.1038/s41598-017-04574-z.

Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E. Non-caloric artificial sweeteners and the microbiome: findings and challenges. Gut Microb. 2015;6:149–55. doi: 10.1080/19490976.2015.1017700.

Trépo E, Valenti L. Update on NAFLD genetics: From new variants to the clinic. J Hepatol. 2020;72:1196-209. doi: 10.1016/j.jhep.2020.02.020.

Uebanso T, Ohnishi A, Kitayama R, Yoshimoto A, Nakahashi M, Shimohata T, et al. Effects of low-dose non-caloric sweetener consumption on gut microbiota in mice. Nutrients. 2017;9:560. doi: 10.3390/nu9060560.

Vartak N, Damle-Vartak A, Richter B, Dirsch O, Dahmen U, Hammad S, et al. Cholestasis-induced adaptive remodeling of interlobular bile ducts. Hepatology. 2016;63:951-64. doi: 10.1002/hep.28373.

Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15:11-20. doi: 10.1038/nrgastro.2017.109.