

## **TYPE 2 DIABETES MELLITUS: ANOTHER ONGOING SILENT PANDEMIC**

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder, with an increasing prevalence in the past two decades being associated with impaired insulin secretion, resistance to peripheral actions of insulin, or both which cause persistent hyperglycemia (1). In patients with T2DM, persistent hyperglycemia can damage different organ systems in combination with other metabolic abnormalities, which can result in life-threatening and disabling health complications. The most common of these complications are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular ones, which increase cardiovascular disease risk by two to four times (2). According to the World Health Organization (WHO), approximately 422 million adults between the ages of 20 to 79 years had T2DM in 2022 affecting 6% of the global population (3). In Romania, the prevalence rates are similar, approximately 5% of the population had this metabolic disorder. Moreover, 7 out of 10 patients with T2DM in our country, had been diagnosed with long-term complications of diabetes (e.g., peripheral arterial disease, chronic kidney disease, retinopathy or blindness) (4).

Obesity, metabolic syndrome (MetS), and non-alcoholic fatty liver disease have all become more common in recent years, along with T2DM prevalence. Type 2 diabetes (T2DM) and non-alcoholic fatty liver disease (NAFLD) are linked in both directions; NAFLD causes insulin resistance (IR) and T2DM through several pathways,

but T2DM also promotes liver disease as a separate risk factor (5). Although NAFLD was first considered to be the hepatic manifestation of MetS, there is now convincing evidence that NAFLD is a major contributor to MetS, and that hepatic involvement is one of the components of multisystemic organ involvement (6). NAFLD is now considered a global epidemic that affects 1 in 4 persons worldwide, with a prevalence estimated to range between 25% and 30%. The fact that the prevalence of NASH is rising along with the rates of MetS and its components is even more concerning with the main risk factors for NASH being obesity, T2DM, and MetS (7). Moreover, NAFLD is more common in people with T2DM-roughly 75% more common than it is in people without diabetes. Patients with severe steatosis had a higher chance of acquiring T2DM, and those with NAFLD had a risk of developing it that was at least twice as high as that of subjects without NAFLD. Also, patients with NAFLD with T2DM had a 2.2-fold greater risk of all-cause mortality (8).

The guidelines recommendations are in conflict when it comes to screen T2DM patients for liver steatosis and fibrosis. Therefore, according to European Guidelines, patients with NAFLD can be screened for T2DM by measuring their fasting blood sugar or hemoglobin A1C (9). In addition, diabetic patients with increased ALT or hepatic steatosis should be screened for NAFLD, according to the American Diabetes Association (10). In-

stead, the American Association Society of Liver Disease disagrees with the routine screening of T2DM patients (11). Due to its simplicity and low cost, abdominal ultrasonography (US) is one of the screening methods that is most frequently used. According to a meta-analysis, this approach had a specificity around 80% compared with liver biopsy for detecting mild and severe steatosis. The US has the drawback of relying on the operator to determine the degree of steatosis in obese individuals or those with moderate steatosis (12). On the other hand, vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) is a quantitative method that has a higher sensitivity and specificity for assessing hepatic steatosis. Additionally, assessments of the CAP numerical values correlate with the histological degree of steatosis (13).

Weight gain and obesity are the most important predictors factors for developing T2DM. These relationships most likely originate from inflammatory stimulation of adipose tissue, which causes insulin resistance (14). Recently, WHO estimated that 650 million people globally are obese and 2 billion adults worldwide are overweight (15). By 2025, it is anticipated that 2.7 billion adults would be overweight, nearly 1 billion individuals will be obese, and 177 million persons will be extremely obese if current trends continue. According to predictions, 1 in 5 women and 1 in 7 men would have obesity by the year 2030 (16). Obesity is defined by the WHO as an excessive buildup of body fat that is clearly related with health concerns; because of its ease of use, the body mass index (BMI) is most frequently used to measure obesity. By dividing the body weight in kilograms by the square of the height in meters, the

BMI is determined. Grade 1 obesity is defined as having a BMI  $\geq 30$  kg/m<sup>2</sup>, grade 2 obesity as having a BMI  $\geq 35$  to 40 kg/m<sup>2</sup>, and grade 3 obesity as having a BMI  $\geq 40$  kg/m<sup>2</sup> (17). There is a widespread understanding that obesity, whether it be a condition that predisposes to disease or a disease in and of itself, needs to be treated and, more importantly, prevented (particularly in children), given its serious comorbidities, mortality, and financial implications (18). The prevalence of NAFLD and T2DM, two chronic disorders linked to obesity, has increased as this silent pandemic has spread around the world. NAFLD is the obesity-related non-communicable illness with the greatest rate of growth, and it is a reliable indicator of liver and cardiovascular mortality (19). The global food system has seen significant changes over the last few decades, and billions of people are now daily exposed to processed foods and beverages high in energy that multinational firms have increasingly sophisticatedly marketed (20). As a result, it is challenging to imagine how individual-focused initiatives, like weight-loss programs or healthy eating campaigns, can be successful without laws that change the underlying environmental factors (19).

Several studies that were recently published found that Romanian patients with T2DM, had a prevalence in NAFLD of approximately 73%, and the main prognostic factor of steatosis was the severity of liver fibrosis (21, 22). Using VCTE, Trifan *et al.* found that the prevalence of advanced fibrosis was 11.7%, and the prevalence of cirrhosis was 13.6%. Moreover, 40.8% of the subjects included in the study had a BMI  $\geq 30$  kg/m<sup>2</sup> and was associated with severe steatosis and fibrosis (advanced

fibrosis and cirrhosis) (21). In another study, which included medical students by Nastasa *et al.* found that half of the obese subjects had NAFLD (23).

T2DM, obesity and NAFLD are regarded as risk factors for each other. This causes us to be cautious about the potential effects of early detection of one disease in the presence of another. Additionally, the progres-

sion and consequences of each disease are influenced by the presence of NAFLD, T2DM and obesity (24). The same lifestyle adjustments, oral hypoglycemic drugs, and bariatric surgery as a last-resort therapy option are the key components of their prevention and management plans, which have been found to have an impact on the management of NAFLD, T2DM and obesity.

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## REFERENCES

1. Zheng Y, Ley SH, Hu FB. Global etiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018; 14(2): 88-98.
2. Picke AK, Campbell G, Napoli N, Hofbauer LC, Rauner M. Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties. *Endocr Connect* 2019; 8(3): R55-R70.
3. [https://www.who.int/health-topics/diabetes#tab=tab\\_1](https://www.who.int/health-topics/diabetes#tab=tab_1) (Accessed on 17 September 2022).
4. [https://insp.gov.ro/download/cnepss/stare-de\\_sanatate/boli\\_netransmisibile/diabet/Analiza-de-situatie-Diabet-2022](https://insp.gov.ro/download/cnepss/stare-de_sanatate/boli_netransmisibile/diabet/Analiza-de-situatie-Diabet-2022). (Accessed on 27 September 2022).
5. Muzica CM, Sfarti C, Trifan A, *et al.* Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: A Bidirectional Relationship. *Can J Gastroenterol Hepatol* 2020; 2020: 6638306.
6. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015; 13(4): 643-54.e1-9.
7. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64(1): 73-84.
8. Williamson RM, Price, JF, Glancy S, *et al.* Edinburgh type 2 diabetes study investigators. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetes Care* 2011; 34: 1139-1144.
9. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol* 2016; 64: 1388-1402.

10. American Diabetes Association. Improving care and promoting health in populations: Standards of medical care in Diabetes 2019. *Diabetes Care* 2019; 42: S7-S12.
11. Chalasani N, Younossi Z, Lavine JE, *et al.* The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. *Hepatology* 2012, 55, 2005-2023.
12. Hernaez R, Lazo M, Bonekamp S, *et al.* Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. *Hepatology* 2011; 54: 1082-1090.
13. Semmler G, Wöran K, Scheiner B, *et al.* Novel reliability criteria for controlled attenuation parameter assessments for non-invasive evaluation of hepatic steatosis. *United Eur. Gastroenterol. J* 2020; 8: 321-331.
14. Jaacks LM, Siegel KR, Gujral UP, Narayan KM. Type 2 diabetes: A 21<sup>st</sup> century epidemic. *Best Pract Res Clin Endocrinol Metab* 2016; 30(3): 331-343.
15. <https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity> (accessed on September 18, 2022).
16. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism* 2022; 133: 155217.
17. World Health Organization. Obesity and Overweight. Available online: <http://www.who.int/mediacentre/factsheets/fs311/en/> (Accessed on 4 October 2022)
18. Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions-but do we have the will? *Fertil Steril* 2017; 107(4): 833-839.
19. Sinn DH, Kang D, Choi SC, *et al.* Non-Alcoholic Fatty Liver Disease Without Metabolic Associated Fatty Liver Disease and the Risk of Metabolic Syndrome. *Clin Gastroenterol Hepatol.* 2022: S1542-3565(22) 00912-0.
20. The Lancet Gastroenterology Hepatology. Obesity: another ongoing pandemic. *Lancet Gastroenterol Hepatol* 2021; 6(6): 411.
21. Trifan A, Stratina E, Nastasa R, *et al.* Simultaneously Screening for Liver Steatosis and Fibrosis in Romanian Type 2 Diabetes Mellitus Patients Using Vibration-Controlled Transient Elastography with Controlled Attenuation Parameter. *Diagnostics (Basel)* 2022; 12(7): 1753.
22. Sporea I, Mare R, Popescu A, *et al.* Screening for Liver Fibrosis and Steatosis in a Large Cohort of Patients with Type 2 Diabetes Using Vibration Controlled Transient Elastography and Controlled Attenuation Parameter in a Single-Center Real-Life Experience. *J Clin Med* 2020; 9(4): 1032.
23. Nastasa R, Stanciu C, Zenovia S, *et al.* The Prevalence of Liver Steatosis and Fibrosis Assessed by Vibration-Controlled Transient Elastography and Controlled Attenuation Parameter in Apparently Healthy Romanian Medical Students. *Diagnostics (Basel)* 2021; 11(12): 2341.
24. Padda J, Khalid K, Khedr A, *et al.* Non-Alcoholic Fatty Liver Disease and Its Association With Diabetes Mellitus. *Cureus* 2021; 13(8): e17321.