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Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), An Underappreciated Threat.

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Letter to editor

Dear editor

A 56-year-old woman was presented to the outpatient clinic with a dull aching pain in the right upper abdominal quadrant. She was diagnosed with type 2 diabetes mellitus (T2DM) three years ago, and she is taking Metformin tablets as the sole medication. Her body mass index (BMI) was 32 kg/m^2. An abdominal ultrasound scan revealed a single gall bladder stone and fatty liver. The platelets count was 150x10^3/ml; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 50 U/L and 40 U/L, respectively. Serological testing for viral hepatitis was negative. Other metabolic and autoimmune causes of liver disease were excluded.

What would be the most appropriate next step in management?

A.Reassurance and no further treatment is needed.

B.Liver elastography is indicated.

C.Liver biopsy is indicated urgently.

Metabolic dysfunction associated steatotic liver disease (MASLD)- previously known as non-alcoholic fatty liver disease (NAFLD)- is a common health problem with an increasing prevalence globally. Its more severe

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form, metabolic dysfunction associated hepatitis (MASH)- previously known as a non-alcoholic steatohepatitis (NASH)- is characterized by hepatic inflammation secondary to fat accumulation. MASLD was first reported in 1980s, and was described as a liver disease resembling alcoholic fatty liver among persons who were drinking little or no alcohol. The estimated global prevalence of MASLD is 38%. [1]

Importantly, MASLD and MASH are not merely hepatic conditions; they are strongly associated with metabolic syndrome and are recognized as a single risk factor for atherosclerotic cardiovascular disease. They are reported in many studies to be associated with chronic kidney disease. Nevertheless, about 5% of MASLD cases have hepatic steatosis without traditional cardiovascular risk factors. [2]

Several factors contribute to the development of MASH, including obesity, insulin resistance, obstructive sleep apnea, gut microbiota dysbiosis and genetic factors.

The initial pathological process is the accumulation of fat in the liver, where fat accumulation leads to mitochondrial dysfunction, oxidative stress and inflammation. Changes in gut microbiota increase free fatty acid release, which leads to activation of cytokines, interleukins and induces inflammation. [4]

MASH can progress to more serious complications such as; hepatic fibrosis, liver cirrhosis and hepato-cellular carcinoma. [3] It has been linked to a higher rate of uterine, renal and other gastrointestinal malignancies. [3,5]

The nomenclature shift from NAFLED/NASH to MASLD/MASH, was aimed to eliminate

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the stigma linked to the term 'alcoholic', emphasizing the underawareness of the cardio-metabolic risk of these conditions. (6)

MASLD is closely related to obesity, insulin resistance, pre-diabetes and T2DM. The presence of T2DM, abdominal obesity and age over 50 years, all increase the progression of MASLD to more serious complications. The estimated prevalence of MASLD in the Middle East and North Africa (MENA) region is 39.43% among people without T2DM and 68.71% among those with T2DM. (7) The growing prevalence of T2DM in the MENA region explains the high prevalence of MASLD in this region as both are a risk factor for each other. MASLD is also prevalent among children aged 18 years or less and it was estimated to reach 13%. (8) In a survey for cardio-metabolic risk factors in Libya, the percentage of those with overweight and obesity reached 56.8% and 28.9% respectively. (9) This might predict an expected high risk of MASLD and MASH among Libyan population, although local prevalence data are lacking.

MASLD is a diagnosis of exclusion. Other conditions such as viral hepatitis, drug- induced or autoimmune hepatitis, metabolic diseases including Wilson's disease and hemochromatosis must be ruled out.

In clinical practice, particularly in Libya, physicians tend to assure individuals with diabetes mellitus and MASLD. Some physicians may advise patients with fatty liver to lose weight and may test them for hepatitis viral serology and autoimmune hepatitis screening if they have raised liver enzymes. However; such an approach will overlook the seriousness of this condition.

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In order to prevent the progression of MASLD to more serious complications, it is of great importance to stage the disease and to manage it accordingly. Liver biopsy is the gold standard for staging and determining the severity of MASLD, however it is an invasive method and carries the risk of bleeding and infection. In order to minimize the risk of exposure to invasive methods, there are many non-invasive methods to determine fibrosis risk and in order to guide further investigations and management. Some of these tools are Fibrosis-4 (FIB-4), Steatosis-Associated Fibrosis Estimator (SAFE) and Enhanced Liver Fibrosis (ELF) scores.

One of the widely used tools is the FIB-4 score. The FIB-4 score elements include: age, BMI, AST, ALT and platelet count. It can be used easily at the out-patient's clinic. A calculated FIB-4 score of < 1.3 is considered as low risk for fibrosis, while a score of >2.67 indicates the need for direct referral to hepatologist, and a score between 1.3 and 2.67 indicates the need for the measurement of liver stiffness and referral to a specialist in liver disease. FIB-4 score is a good predictor of liver fibrosis but needs confirmation with further test. The FIB-4 score had a high negative predictive value for advanced hepatic fibrosis and it is recommended for patients with cardio-metabolic risk such as people with T2DM. [10, 11]

SAFE score is composed of age, BMI, diabetes status, platelet count, AST, ALT and globulin levels. While ELF measures hyaluronic acid, procollagen III amino-terminal peptide and tissue inhibitor of metalloproteinases-1 which are markers of fibrosis.

Liver stiffness is measured by Fibroscan, or vibration-con-

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trolled transient elastography. It is a non-invasive imaging that is used to assess liver stiffness, which determines the degree of fibrosis. The Fibroscan-AST (FAST) score is composed of liver stiffness measurements and AST level, and it is useful for individuals with MASH and who are likely to have more advanced fibrosis and may need more aggressive management.

There are several interventions to prevent the progression of MASLD to advanced liver disease, including lifestyle measures as well as pharmacological therapy. Assessment of cardio-metabolic risk factors, renal function and screening for extra-hepatic malignancies is also crucial. The Mediterranean diet and exercise for 150 minutes per week are recommended to improve liver injury. [12] Exercise is an independent factor for improving steatosis regardless of weight loss. [13] Bariatric surgery can improve the outcome of obese individuals.

Thyromimetic (Resmetirom), Ursodeoxycholic acid, Omega-3 polyunsaturated fatty acids, incretin mimetics and sodium glucose co- transporter-2 inhibitors (SGLT2i), all have beneficial effects in MASH. SGLT2i and incretin mimetics are recommended only for patients with T2DM, the latter is also recommended in obese individuals. Statins, metformin and glitazones have shown some beneficial effects on MASH.

Management of MASLD is a multidisciplinary team approach. An endocrinologist, a nutritionist and a hepatologist are the main members of the team. It is of great importance to appreciate the threat of MASLD and MASH. It is recommended to screen those at risk, like T2DM patients, and to raise the awareness

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of healthcare providers regarding case detection and the noninvasive staging of the disease. Implementation of a referral pathway is mandatory.

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