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REVIEW ARTICLE

To do one and to get more: Part II. Diabetes and metabolic dysfunction-associated fatty liver diseases

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Abstract

Type 2 diabetes mellitus (DM) is characterized by inability of faulty pancreatic β-cells to secret a normal amount of insulin to maintain normal body consumption, and/or peripheral tissue has a decreased susceptibility to insulin, resulting in hyperglycemia and insulin resistance. Similar to other chronic systemic inflammatory diseases, DM is a result from dysregulated interactions between ethnic, genetic, epigenetic, immunoregulatory, hormonal, and environmental factors. Therefore, it is rational to suppose the concept as "To do one and to get more", while using antidiabetic agents (ADA), a main pharmacologic agent for the treatment of DM, can provide an extraglycemia effect on comorbidities or concomittent comorbidities to DM. In this review, based on the much strong correlation between DM and metabolic dysfunction-associated fatty liver diseases (MAFLD) shown by similar pathophysiological mechanisms and a high prevalence of DM in MAFLD and its vice versa (a high prevalence of MAFLD in DM), it is possible to use the strategy to target both diseases simultaneously. We focus on a new classification of ADA, such as glucagon-like peptide-1 receptor (GLP1R) agonist and sodium-glucose cotransporter-2 (SGLT-2) inhibitors to show the potential benefits of extraglycemic effect on MAFLD. We conclude that the management of DM patients, especially for those who need ADA as adjuvant therapy should include healthy lifestyle modification to overcome the metabolic syndrome, contributing to the urgent need of an effective weight-reduction strategy. GLP1R agonist is one of effective body weight-lowering medications, which may be a better choice for DM complicated with MAFLD or its-associated severe form as metabolic associated steatohepatitis (MASH), although the role of SGLT-2 inhibitors is also impressive. The prescription of these two classes of ADA may satisfy the concept "To do one and to get more", based on successful sugar-lowering effect for controlling DM and extraglycemia benefits of hepatoprotective activity in DM patients.

Keywords: Anidiabetic agents; Diabetes mellitus (DM); Extraglycemic effects; Fatty liver

1. INTRODUCTION

Diabetes mellitus (DM), a complex chronic systemic inflammatory disease, is a heavy socio-economic burden resulting from the severe morbidity and mortality imposed by direct DM-associated diseases and indirect DM accompanied with disorders,[1] secondary to the micro- and macrovascular damage and dysfunction, resulting in hypertension,[2] ischemic stroke,[3] ophthalmic problems (macular edema[4,5] and neovascularization[6]), kidney-associated diseases[7] and their related complications,[8] sexual dysfunction,[9] neurological disorders,[10] peripheral neuropathy,[11] diabetic foot or other chronic subcutaneous ulcer problems,[12] metabolic associated fatty liver disease (MAFLD, also called as metabolic dysfunction-associated fatty liver disease [FLD], nonalcoholic FLD [NAFLD] or metabolic associated steatohepatitis [MASH]),[13] atherosclerosis[14] and atherosclerotic cardiovascular disease,[15] osteoporosis,[16,17] and fracture.[18] DM is also complicated by acute life-threatening diseases,[19] such as hyperglycemia (hyperglycemia hyperosmolar nonketotic coma and diabetic ketoacidosis) or hypoglycemia (syncope and sudden death)[20,21] as well as exacerbation of many chronic illnesses-related mortality (cancer as an example).[22–24] Therefore, it is a long-term effort to achieve the aim as the normalized sugar levels and maintenance of sugar homeostasis to delay or stop hyperglycemia-related organ damages.[25,26] There

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are many strategies applicable to DM control, such as lifestyle modification, routine and continuous blood glucose monitoring, and pharmacological therapy (antidiabetic agents [ADA] and sugar-lowering drugs),[27–30] and all of them attempt to minimize DM-related adverse events (AEs) and maintain the quality of life, similar to the therapy for other troublesome diseases by multiple modality strategy.[31–33]

In fact, all aforementioned strategies are essential and critical, although some recommendations favoring strategies step by step are proposed.[34,35] However, sometimes, to obtain the optimal sugar control, monotherapy or in a combination of others is needed. The similar proposal is also suitable for many chronic illnesses, including cancer, hypertension, autoimmune diseases, chronic inflammatory diseases, etc.[36–38] In part I, we try to demonstrate the policy as "To do one and to get more" in the management of complicated diseases, such as DM, and hope that one therapeutic approach can provide more benefits beyond the sugar-lowering effect,[1] but unfortunately, evidence about the impact of ADA on DM and bone health (prevention of osteoporosis and reduction of fracture) seemed to be relatively disappointing, based on failure to show that the use of ADA can satisfy this proposal as "To do one and to get more" concept.[1,39–41] Uncertain conclusions are made after reviewing recent publications from the systemic review and meta-analyses to address the effect of ADA on both DM and bone health.[1,42–44] We still optimized the unlimited potential ability of ADA on ameliorating bone loss (osteoporosis) and preventing fracture, because advance of biomedical technology for ADA can be continuously and uninterruptedly progressed and this dream may come true.[1]

Without evidence support to the "To do one and to get more" concept by ADA, it is not disappointing since another therapeutic strategy for DM–lifestyle modification to reach a healthy lifestyle seems to work well. Lifestyle modification is always considered as the front-line and best choice for all pre-DM and DM populations.[45–50] The critical and essential components of lifestyle medication include balanced food intake and caloric restriction with adequate nutrition support (grains, fruits, vegetables, proteins, seeds, nuts, and dairy), and an ideal body weight maintenance made by regular, appropriate, and tensely exercise.[51–55]

A healthy lifestyle modification takes many advantages, not only for its safety and effectiveness for both pre-DM and DM, but also directly strengthening viability of all structures and organs in human beings, contributing to significant benefits.[1] However, the poorer adherence to healthy eating patterns or poorer consumption of major food groups are common in these pre-DM and DM populations,[56–58] contributing to the extra need of application of the other one strategy as prescription of ADA for these pre-DM and DM populations.[59–63]

Since DM is frequently associated with major morbidities or concomitant comorbidities, extraglycemic effect of ADA is still highly expected. Liver is one of the most vital organs involving in many detoxication and metabolism functions, and also a significant target of metabolic syndrome (MeS), based on the observation that FLD occurs very commonly in DM,[64–69] contributing to an establishment of a new term to describe this metabolic dysfunction-related chronic disease as metabolic dysfunction-associated FLDs (MAFLD, also called as metabolic associated FLDs, and previously named NAFLD), which are based on evidence of hepatic steatosis, in addition to one of the following three criteria, namely overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation (lean/normal-weight subjects with the coexistence of two other risk factors that are related to metabolic dysregulation, including central obesity, hypertension, prediabetes, hypertriglyceridemia, low levels of high-density lipoprotein [HDL] cholesterol, insulin resistance (IR), and high-sensitivity-C-reactive protein [HS-CRP] levels).[70] Moreover, there are many systemic reviews and meta-analyses supporting the potential role of ADA in the effectiveness to restore the normal function of liver or decrease the severity of disease pattern in patients with FLD.[70–83] Therefore, it is supposed that these ADA may play a protective role in the occurrence or development of MAFLD in DM patients.

2. METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASES (ALSO CALLED AS METABOLIC ASSOCIATED FATTY LIVER DISEASES OR PREVIOUSLY NAMED NONALCOHOLIC FATTY LIVER DISEASES)

The literature involving in MAFLD can be found everywhere.[13,65–89] In brief, MAFLD, characterized by the fat accumulation >5% (by histological examination) or >5.6% (by magnetic resonance imaging (MRI)-derived proton density fat fraction [MRI-PDFF]) of hepatocytes (presence of steatosis) without excessive alcohol consumption or secondary causes of hepatic steatosis, presents a biggest health hazard globally, based on its potential continuous progression to advanced liver fibrosis (liver cirrhosis) and finally the development of hepatocellular carcinoma (HCC), contributing to the heavy economic and social burdens worldwide.[65–67,88,90–100]

Pathogenesis of MAFLD, similar to DM, is a result of multiple interactions and/or cross-talks among genetic, epigenetic, environmental and micro-organisms (Fig. 1), including genetic and epigenetic factors (acetyl-CoA carboxylase, adipophilin [adipose differentiation-related protein], apolipoprotein C3, adenosine triphosphate citrate lyase [Acly], calpain 10, carbohydrate response element-binding protein, catalase, ectoenzyme nucleotide pyrophosphate phosphodiesterase 1, Forkhead box protein O1, free fatty acid [FFA] oxidation-related genes such as branched-chain acyl-CoA oxidase, carnitine palmitoyltransferase 1a, cytochrome P450 2E1, cytochrome P4A11, long-chain acyl-CoA dehydrogenase, long-chain L-3-hydroxyacylcoensyme A dehydrogenase alpha, uncoupling protein 2, FFA synthase, glutathione peroxidase [GPX], insulin receptor substrate, patatin like phospholipase domain-containing protein-3, peroxisome proliferator-activated receptor-γ [PPAR-γ], sterol regulatory element-binding protein, and superoxide dismutase 2 [SOD2]) to result in malfunction of metabolism and dysregulation of immunological system, hormone system and other homeostasis status in human body; gut metabolome and environmental factors, such as drugs, heavy mental, toxins, infection to further augment oxidative stress secondary to unbalance input and output-metabolic dysregulation mediated by production of oxidative stress factors (fibroblast growth factor 21 [FGF 21], thioredoxin, copper-to-zinc SOD2, GPX, Mac-2 binding protein: M2BP, and others) as well as inflammatory factors (CC-chemokine ligand 2, c-Jun-N-terminal kinase, CRP, glycogen synthase kinase 3, interleukin 1-beta, 2, 6 and 8, and tumor necrosis factor-alpha), and formatting reactive oxygen species-reactive oxygen species leading to the increase of superoxide anion radicals to form adducts with cellular nucleophiles, cellular damage, and inflammatory responses as well as the release of a lots of amount of cytokine, adipocytokines (adipokines, adiponectin, apelin, hepcidin leptin, resistin, vaspin, and visfatin), and therefore, IR and MeS develop with subsequently progression to more specific diseases, such as DM, MAFLD, etc.[15,65,86,96–99] All, augmented by each other for figuring out a vicious cycle play a critical pathogenesis of MAFLD.[15,65,86,96–99]

The clinical course of FLD is slowly progressed, and initiated from MAFLD, nonalcoholic steatosis (metabolic dysfunction-associated liver steatosis), MASH, hepatic fibrosis to hepatic cirrhosis (Fig. 2), although some arguments are present to show a

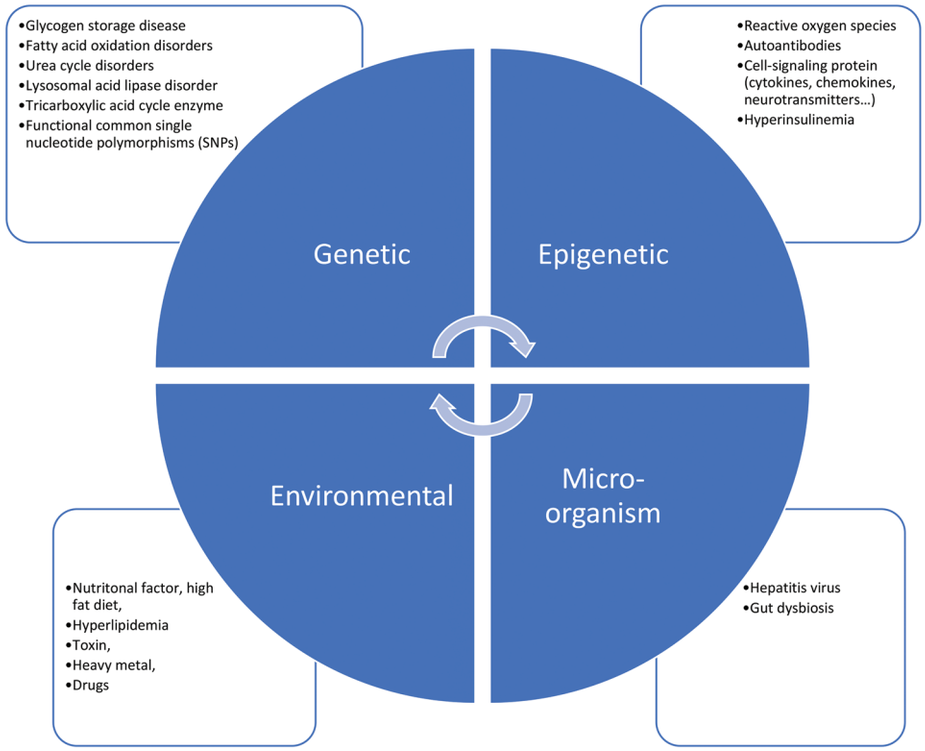

Fig. 1 Pathogenesis of metabolic dysfunction-associated fatty liver diseases is a result of multiple interactions and/or cross-talks among genetic, epigenetic, environmental, and micro-organisms.

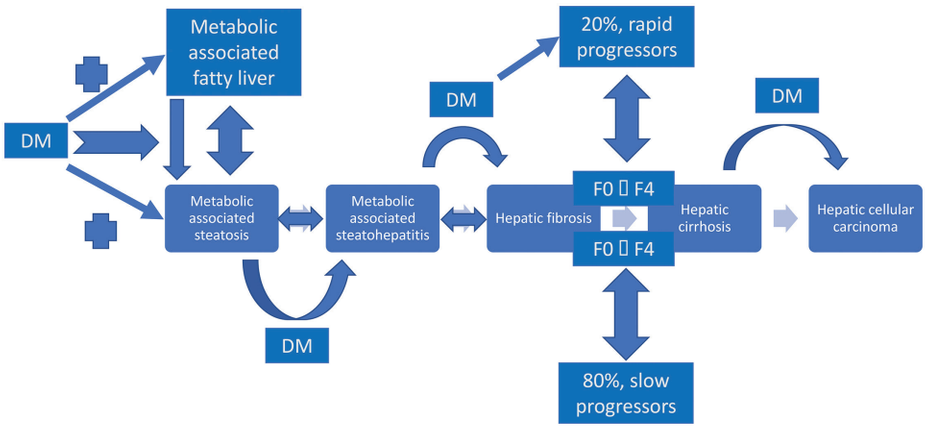

Fig. 2 The clinical course of fatty liver diseases is slowly progressed and initiated from metabolic dysfunction-associated fatty liver diseases (MAFLD), metabolic dysfunction-associated liver steatosis (MAS), metabolic dysfunction-associated steatohepatitis (MASH), and hepatic fibrosis to hepatic cirrhosis.

significantly different prognosis between uncomplicated MAFLD and MASH.[96–98] A normal healthy hepatocyte plays a major role in the maintenance of general homeostasis, including nutrition, energy, metabolism and detoxication or clearance of debris, and removal of wastes in human body. Hepatocyte also possesses the capacity to store fat in the form of lipids as energy storage.[98] However, excessive accumulation of fat (hepatic steatosis) due to disruption of liver capacity to balance between lipid acquisition (FFA derived from two major sources as lipolysis of triglycerides [TG] in adipose tissue or FFA synthesis from glucose and fructose by de-novo lipogenesis) and discharge mediated by the processes of mitochondrial FFA oxidation or the production of very low-density lipoproteins (V-LDLs) to form hepatocyte ballooning and following lipotoxicity, and all attempt to disrupt the cellular integrity, and in the un-compensatory status, it may lead hepatocyte to die to secret several kinds of chemical mediators and adipocytokines, which activates the stellate cells to procedure connective tissue growth factor and collagen and cause an accumulation in the extracellular matrix, and the parenchyma of liver may be is subsequently replaced by fibroblast, and its-associated fibrotic tissue and collagen deposits.[65,86,98]

Recently, Allen et al[100] attempted to evaluate the clinical course of MAFLD with a 23-year longitudinal population-based cohort study, and identified that 3% of the MAFLD adults

without cirrhosis will progress to cirrhosis and associated complications over 15 years, but it is surprising to find that 14% of patients will die from nonliver related cause; and additionally, MAFLD spend approximately 4 years to reach the compensated cirrhosis stage, and the risk of further progression to liver-related AEs is higher, and furthermore, MAFLD patients progressed to decompensation during this timeframe, having a risk of death up to 8% per year.[100] Review also showed the mortality rate ratio of patients with liver fibrosis increased exponentially with an increase in the stage of fibrosis (F0→F4), from 1.41 (95% CI, 0.17-11.95) in stage 1, 9.57 (95% CI, 1.67-54.93) in stage 2, 16.69 (95% CI, 2.92-95.26) in stage 3, to 42.3 (95% CI, 3.51-510.34) in stage 4.[101] It is relatively difficult to determine to whom will develop to compensated cirrhosis or decompensated cirrhosis among these MAFLD, because of absence of universal systematic screening for cirrhosis in MAFLD as well as absence of effective treatment for liver cirrhosis in the guidelines, indicating the biggest challenges between both real-world scenarios and clinical trials.[100,102] Therefore, the following section attempts to explore the screening tools in DM patients with high risk to develop MAFLD.

3. SCREENING OF MAFLD

The American Association of the Study of Liver Disease (AASLD) recommends using the noninvasive tests, such as biochemistry and image, or an invasive procedure, suchas liver biopsy, to evaluate the NAFLD.[96–98,101,103–105] Blood test for biochemistry evaluation is the most convenient and frequently used tool to evaluate the severity of MAFLD, but the abnormality is seldom found at the initial stage of MAFLD or mild MAFLD. These blood tests include basic liver function test, serum iron contents (ferritin, iron, and iron saturation), infection (hepatitis B or hepatitis C), and certain-type of autoimmune antibodies (antinuclear antibody [ANA], antimitochondrial antibody, and antismooth muscular atrophy) and others by indication.[98] Among the blood tests, the most common detectable abnormalities are an elevated liver functional enzyme, such as elevated serum levels of alanine transaminase (ALT) and/or aspartate transaminase (AST), and γ-glutamyl transferase (GGT).[101] Other serum markers, such as elevated ferritin levels (40%-58%), positive ANA (33%), and isolated alkaline phosphatase (10%), are also found in NAFLD with varied percentages.[98]

Image evaluation is made by ultrasound, and ultrasound is always considered as the first-line examination based on Hamaguchi score and the utrasonographic FLD indicator) and because of its low cost, making it suitable for screening routine.[13,65,66,104,106] A meta-analysis about the role of ultrasound on the diagnosis of MAFLD showed 84.8% sensibility (95% CI, 79.0%-88.9%) and 93.6% specificity (95% CI, 87.2%-97.0%) for moderate-severe NAFLD.[66,103] Unfortunately, the predictive performance for FLD detection is insufficient based on lost ability to discriminate mild steatosis, and the reliability and sensitivity are more defective in those obese individuals or those with either mild steatosis or preexisting chronic liver diseases, contributing to the urgent need of artificial intelligence (AI) assistance with deep learning on a medical image to offer more accurate, reproducible, and reliable diagnosis.[107] Additionally, it can allow medical units to finish ultrasound assisted by AI with the aid of a deep learning-based strategy to further classify the degree of FLD and give a precise diagnosis.[107] Furthermore, advanced technology of ultrasound, such as vibration-controlled transient elastography, measuring the shear wave velocity (the time interval it takes for a sound wave to flow through the liver) to predict liver parenchymal stiffness (liver stiffness measurement [LSM] in kilopascals [kPa] for possible cutoff value of 12 kPa) or controlled attenuation parameter, further provides an additional value in diagnosis of FLD (with more accuracy and quantifiability), although there is presence of many factors, including marked steatosis, cellular inflammation, cholestasis, increased central venous pressure, overweight, preexamination food intake, ascites, and inter- and intraoperator's experience and all of them may result in measurement failure and the diagnostic accuracy.[98,101]

With combination of blood tests and/or image evaluations, the scoring systems according to anthropometric and biological parameters, such as fatty liver index (including body mass index [BMI], waist circumference, plasma TG level, and GGT), MAFLD fibrosis score, Fibrosis-4 score (including age, AST, ALT, and platelet count for possible cutoff value of 1.3), BARD score, NAFIC score based on clinical parameters, including hematological examination, such as ALT, AST, albumin, platelet counts, and physical examination, such as age, BMI, and medical history, can be applied for those patients at risk to be associated with FLD.[65,66,98] However, the aforementioned scoring system is easily confounded by liver function test and age, and additionally, the cutoff values are also easily changed based on the different studies, leaving an uncertain diagnosis.[104] Many novel biomarkers (serum cytokeratin-18 [CK-18] fragment as an example) and surrogate scores have been reported to target the following components, such as a presence of severity of NAFLD, a prognostic value, and a predictive value not only to stratify the progression and/or treatment response, but these biomarkers may be of high cost, not popular, and need a validation about their reliability and feasibility,[104,105] contributing to uncertainty of the diagnosing MAFLD. Therefore, MRI-PDFF or high-resolution magnetic resonance spectroscopy (H-MRS), another choice of noninvasive tool may be needed based on its potential surrogate for histologic improvement,[107] although it may be still underestimated in patients with advanced fibrosis, and defect by high cost and limited availability leading to limit the routine clinic use of MRI-PDFF.[104,105]

Although these noninvasive diagnostic tools have received increasing attention, based on the absence of consensus scoring system,[101,102] the definite diagnostic procedure, such as an invasive procedure, may be needed. That is why the AASLD still recommends high-risk patients, such as patients with MeS (of course, DM is included) should be considered for liver biopsy for the identification of severity of MAFLD and offering the better chance to slow or cease the progression of MAFLD. Liver biopsy is the most effective and reliable diagnostic tool to identify MAFLD, and is needed to distinguish uncomplicated MAFLD from MASH, according to the fact that the latter is associated with more severe and possible life-threatened clinical situations, such as the developing liver cirrhosis, HCC, and requiring a liver transplantation.[98] However, there is no doubt that liver biopsy is a highly invasive testing tool, not only accompanied with a high cost, but also associated with high risk of procedure-related AEs.[98]

Taken together, an early and accurate diagnosis of MAFLD is needed for general population because of its high prevalence as well as its related life-threatened sequelae, such as cirrhosis and HCC if prompt and appropriate intervention is not initiated. According to the statement of the AASLD, it is essentially important and critical for DM patients, suggesting the DM and MAFLD may be twins and live together.

4. DIABETES MELLITUS AND METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Globally, it is estimated that 25% to 30% of the general adult population may have MAFLD, and 3% to 6% may have MASH.[106] MAFLD is a reflective of hepatic manifestation of the MeS or a spectrum of metabolic dysfunction,[65] which contains

hyperglycemia, IR, dyslipidemia, hypertriglyceridemia, and obesity,[65,106,108] and it is further supported by those patients with MAFLD have high rates of MeS (43%), hyperlipidemia (69%), obesity (51%), and DM (23%).[84] Furthermore, the exacerbation or severe forms of FLD are apparently accompanied with metabolic dysfunction, and it is reported that up to 81% of MASH patients were obese.[87]

Vice versa, the high prevalence of MAFLD in those DM, dyslipidemia, IR, hypertriglyceridemia, and obesity populations is also noted.[108,109] One meta-analysis tried to summarize the prevalence of MAFLD in DM population and found among 49 419 DM patients (mean age: 58.5 years; mean BMI: 27.9 kg/m^2; males: 52.9%), the prevalence of MAFLD was 55.5% (95% CI, 47.3-63.7), and it was apparent in Europe (68.0%; 95% CI, 62.1%-73.0%).[109] Besides strong association between DM and MAFLD, DM patients are at higher risk to have much severe FLD. For example, 37.3% (95% CI, 24.7%-50.0%) of DM patients were associated with NASH and 17.0% (95% CI, 7.2%-34.8%) were complicated with advanced fibrosis.[109] This is highly alarming, reflecting the high rates of severe liver disease in DM patients.[87]

In fact, DM and MAFLD frequently coexist, acting synergistically to increase the adverse hepatic and extrahepatic outcomes in MAFLD population as well as to increase the worse DM and extra-DM outcomes in DM patients. For example, the faster progression of MAFLD to MASH, liver cirrhosis, or HCC occurred in DM patients compared with that in general population.[71] Furthermore, DM patients have an increase in the likelihood of developing MASH, cirrhosis, and HCC, and this risk has been positively correlated with the duration of DM, and, moreover, DM patients have a dramatically reduced disease-free survival and overall survival when they are complicated with HCC.[71,88–90]

Dr. Allen found DM patients have an extremely high risk to develop decompensation in MASH cirrhosis with an odds ratio of 3.4 (95% CI, 1.06-9.60) compared with all covariate parameters.[100] Taken together, all support a bilateral pathogenic relationship between DM and MAFLD and the interaction between each other may exert significant impact on their mortality.[71,100] Additionally, FLD tends to be more common in DM and these patients usually have severer form of FLD, and prevalence of DM is high in FLD and severe form of FLD, suggesting that screening of DM in FLD patients and FLD in DM patients is critical for both.[98,106]

5. STRATEGY FOR TARGETING DM AND NAFLD SIMULTANEOUSLY: HEALTHY LIFESTYLE

As shown above, DM and MAFLD share the similar pathophysiological process (one of the MeS or a spectrum of metabolic dysfunction), contributing to the rationale to use the same strategy for the treatment of DM to MAFLD patients or both. In part I, we found that establishment of the healthy lifestyle may be one of the best strategies in the management of DM patients with a high risk of concomittent with osteoporosis and fracture, because it improves the status of IR and subsequently helps sugar control to delay and possibly avoid the DM-related micro- and macrovascular injuries damaging to bony and muscular structure, and additionally strengths the general performance of musculoskeletal system and further decrease the risk of fall and fall-related fracture.[1] Since the relationship between DM and MAFLD is more apparent than that between DM and osteoporosis, the effectiveness of using the same therapeutic strategy as shown by DM and bone health may be more attractive in DM patients with coconcomitant MAFLD, based on strong linkage between MAFLD and obesity with high prevalence of MAFLD in obese patients undergoing weight-reduction surgery (95%), and in Chinese obese general patients (66.2%) compared with only 11.7% in those of normal BMI or less,[105] contributing to the recognition of a critical role about the weight-reduction as a cornerstone of lowering the DM-MAFLD–related disability and mortality.[27,110,111] It is reported that 3% to 5% weight loss can significantly decrease the transformation rate from MAFLD to MASH, and ~7% reduction of weight reduce inflammation and at least 10% body loss can initiate regression of liver fibrosis.[110] Healthy eating pattern, such as a Mediterranean eating pattern may effectively reduce IR independent of weight loss and NASH.[110,112,113] Furthermore, weight-reduction surgery, such as bariatric surgery was shown to reduce body weight, HbA1c, IR, and even led to partial or complete remission of DM as well as MAFLD or MASH or more severe form FLD in some cases.[112] In summary, there is significant overlap in several aspects of using lifestyle modification for the treatment of MAFLD and DM. Dietary can be emphasized on consumption of vegetables, fruits, legumes, nuts, whole grains, and fish, as well as on reducing intake of cholesterol and sodium, limitation of processed meats, refined carbohydrates, and sweetened beverages.[101,112] Of most importance, calorie restriction is always encouraged and recommended for MASH management.[98,108] Finally, moderate-intensity and vigorous-intensive exercise may reduce IR and ameliorate metabolic overload to effectively treat both DM and MAFLD.[101,112]

Taken together, modification of lifestyle should include the followings, including caloricity-limitation of diet and weight-reduction goals but avoidance of very low-calorie diets (<500 Kcal per day); reduction of saturated fats consumption to less than 7% as well as increased polyunsaturated fatty acids (omega-3 group) and monounsaturated fatty acids; a decrease in the consumption of simple carbohydrates and complete exclusion of added sugar or fructose and sucrose; rich protein diet (40% of energy resource) but avoidance of AEs for renal function or bone health; the use of anthocyanins, resveratrol, cinnamon, turmeric and adequate amount of antioxidant-rich food (vitamin C, E, etc.); supplementation with probiotics, prebiotics, and oligofructose to correct intestinal dysbiosis, which is associated with MAFLD by: (1) increasing energy absorption from food due to the altered capacity to digest and ferment complex polysaccharides; (2) increasing intestinal epithelial damage by ethanol produced by bacteria; (3) increasing transmission or transportation of endotoxins produced by bacteria to the portal circulation and activation of proinflammatory signaling of liver; (4) modifications of bile acid synthesis; (5) a decrease in choline metabolism, resulting in reduced liver export of VLDL; reduction of alcohol consumption; and aerobic exercise >150 min/week and preferably 30 min/day with moderate-to-high–intensity aerobic training, since nonpharmacological treatment remains a first-line strategy in MAFLD and DM management.[112,113]

6. STRATEGY FOR TARGETING DM AND MAFLD SIMULTANEOUSLY: ADA

The close and dynamic association between MAFLD and MeS (IR as one of major components) suggests the ADA may play a role for the prevention and/or treatment of MAFLD, and it is especially important that there are no approved drugs, which are recommended for the treatment of MAFLD.[112–114] Additionally, many preclinical data also supported the potential role of ADA in the management of MAFLD and/or its severe form, such as cirrhosis.[115] So far, evidence, including randomized controlled trials (RCTs), review, and meta-analyses shows at least three classes of ADA, such as insulin sensitizers (metformin and thiazolidinediones), sodium-glucose cotransporter-2 inhibitors (SGLT-2i),

glucagon-like peptide-1 receptor agonist (GLP-1R agonist), and so on that may have favorable effects on the spectrum of MAFLD (Table 1).[27,28,30,63,65,67,69,71–84,87,96–98,101,102,108–110,112–114,116,117]

The first class of ADA is an insulin sensitizer, including an adenosine monophosphate (AMP)-activated protein kinase (AMPK) activator and a thiazolidinedione, which have been evaluated for the treatment of MAFLD. Metformin, an AMPK activator, is considered the first-line agent for pre-DM and DM, except for those patients with poor estimated glomerular filtration rate (<30 mL/min).[30,33,36,60,112,117–120] Unfortunately, there are several RCTs that failed to support the effectiveness of metformin in the prevention and treatment of MAFLD, suggesting no improvement in MASH stages in patients treated with metformin.[101,112,116,117] By contrast, reports suggested that the use of metformin may decrease the risk of developing HCC (hazard ratio [HR], 0.25) in MAFLD as well as decrease the overall mortality of patients with liver cirrhosis and DM (HR, 0.42).[112] Of course, metformin successfully reduced glycosylated hemoglobin (HbA_{1C}) and fasting plasma glucose and led to significant weight reduction and subsequent reduction of IR.[116,117]

Pioglitazone (a thiazolidinedione), works as insulin sensitizer to decrease IR through binding PPAR-γ (also called glitazone receptor, nuclear receptor subfamily I, group C, member 3) to enhance white adipocyte differentiation and lipid storage and subsequently increase sequestration of lipids and further lower serum levels of FFA, contributing to totally decrease FFA delivery to the target organs, such as liver and skeletal muscular system, with resulting in amelioration of lipotoxicity of the liver and skeletal muscular system to improve insulin sensitivity and reduce glucose output (suppression of glucogenesis process).[101,115] A meta-analysis enrolling 10 RCTs and 887 subjects found pioglitazone consistently improved histological features of MAFLD (to decrease the severity of steatosis, hepatocyte injury, lobular inflammation, Mallory bodies, and fibrosis), and normalized liver function test, and also significantly decrease insulin concentration, serum FFA levels and signaling a marked increment in insulin sensitivity.[116] Furthermore, the effectiveness of pioglitazone is more apparent in DM and MASH populations.[116] Tang et al[119] (eight RCTs, 412 participants, 60% male) found that pioglitazone significantly decreased liver functional enzymes compared with placebo (weighted mean difference [WMD]: −22.27%) and the aforementioned benefits are also reflective by improved liver histology of steatosis, such as decreased ballooning necrosis, and inflammation compared with placebo. Luo et al[114] (20 RCTs, 1506 subjects) found pioglitazone significantly decreased the ALT or AST levels with MD (mean difference) of −14.94 or −7.96. Additionally, the authors also found that pioglitazone may be the most effective intervention to reduce the liver fat contents of patients using MRI-PDFF or H-MRS.[110] Unfortunately, AEs are significant, including weight gain, exacerbation of heart failure, osteoporosis, and possibly increased risk of fracture, limiting widespread use of a thiazolidinedione as a purpose in the management of DM and MAFLD patients,

Table 1

Sodium-glucose cotransporter-2 inhibitors and nonalcoholic fatty liver diseases

	Authors (y)	General data	Liver function	Imaging
SGLT-2i	wk/mg	WMD	WMD	WMD
Nonspecific	Mantovani (2020)	BW: −3.74 kg HbA_{1C}: −0.19 FIB-4: −0.21	ALT/AST/GGT: −10.0/−1.9/−14.5	MRI: −2.05 LSM: −0.65
For the total Nonspecific	Zafar[a](2022)		AST/ALT/GGT: −2.31/−5.53/−6.49	
For the total Canagliflozin	Li[b] (2018)		ALT/AST/GGT: −11.68/−7.5/−15.17	
For the total Canagliflozin	Li[b] (2018) (a) 26/100 (b) 26/300 (c) 52/100 (d) 52/300		ALT/AST/GGT: (a) −7.39/-/−16.00 (b) −10.30/-/−12.60 (c) −11.05/−9.85/−13.99 (d) −14.95/−11.35/−16.50	
Canagliflozin	Lee (2021)		GGT: −5.47 AST: −4.07 ALT: −5.94	
Dapagliflozin	Lee (2021)	HbA_{1C}: −0.73 HOMA-IA: −0.80		
Dapagliflozin	Luo[c] (2022)		AST: −7.49	
Dapagliflozin	He[d] (2022)	BMI: −1.20 BW: −3.60 kg HbA_{1C}: −0.28 FIB-4: −0.19	ALT/AST/GGT: −5.58/−6.17/−4.87	
Dapagliflozin	Sun[e] (2022)	BMI: −1.33 BW: −3.79 kg HOMA-IR: −0.88	ALT/AST/GGT: −6.62/−4.20/−7.28 LDL-C: −2.66 TG: −16.77	
Empagliflozin	Zhang (2022)	BMI: −0.98 HOMA-IR: −0.45	AST: −3.10	LSM: −0.49
Ipragliflozin	Luo (2022)		ALT: −17.41	

95% CI = 95% confidence interval; AST = aspartate aminotransferase; BMI = body mass index; FIB-4 = Fibrosis-4 score; GGT = gamma-glutamyl transferase; HBA_{1C} = glycated hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance; LSM = liver stiffness measurement; MD = mean difference; MRI-PDFF = magnetic resonance image-proton density fat fraction; SGLT-2i = sodium-glucose cotransporter-2 inhibitors; WMD = weighted mean difference.

[a]Zafar: for a total, including 40 eligible studies containing 13134 subjects, but for each item of specific interest, eligible studies and subjects were varied.

[b]Li: for a total, including 11 eligible studies containing 6745 subjects, but for each item of specific interest, eligible studies and subjects were varied.

[c]Luo: for a total, including 27 eligible studies containing 3416 subjects, but for each item of specific interest, eligible studies and subjects were varied.

[d]He: for a total as 11 eligible studies, but for each item of specific interest, eligible studies and subjects were varied.

[e]Sun: for a total as 7 eligible studies, containing 390 subjects, but for each item of specific interest, eligible studies and subjects were varied.

although all may be possibly complicated by a result of comorbidity cofounders of DM and/or MAFLD.[111,115,116,118]

The second important class is SGLT-2i, which has been tested for the effectiveness in treatment of patients complicated with NAFLD (Table 1). There are many products available in the market for the purpose as ADA, such as canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin.[119] All of them are also tested their effect on the reduction of NALFD or its severe forms as MASH and more.

Mantovani et al[121] in 2020 conducted a meta-analysis enrolling 12 reactive chemical species to test the efficacy of SGLT-2 inhibitors (canagliflozin [n = 1], dapagliflozin [n = 6], empagliflozin [n = 3], and ipragliflozin [n = 2]) for the treatment of MAFLD and the results show the dramatically significant effects of SGLT-2 inhibitors on reduced severity of MAFLD, including decreased serum ALT (WMD: −10), GGT (WMD: −14.5) as well as the absolute of percentage of liver fat contents on MRI-based techniques (WMD: −2.01%). Lee et al[122] in 2021 further showed canagliflozin significantly reduced the ALT, AST, and GGT levels (WMD: −5.94, −4.07, and −5.47, respectively) compared with other comparators. Zafar et al[71] (22 studies, 27 studies, 12 studies, 4 studies) also confirmed the aforementioned benefits of SGLT-2 inhibitors on the management of MAFLD, based on significant improvement of liver function test, including AST (WMD: −2.31), ALT (WMD: −5.93), GGT (WMD: −6.49), and FIB-4 (WMD: −0.21), suggesting SGLT-2 inhibitors have been proven to have hepatoprotective effects in patients with DM and MAFLD.

In terms of the impact of canagliflozin on MAFLD, Li et al[118] enrolled 11 RCT or active-controlled, parallel group trials containing 6745 subjects to perform a meta-analysis and the results showed that canagliflozin decreased serum concentrations of AST (WMD: −9.85) in 52 week/100 mg (52/100) group and WMD −11.35 in 52 week/300 mg (52/300) group. Other data all demonstrated the beneficial effects on reduced severity of MAFLD (Table 1). Lipid profiles also favored the benefits of canagliflozin treatment (a decreased LDL/HDL ratio as an example), and this benefits is positively correlated with dosage and duration of treatment.[119]

In term of empagliflozin, the meta-analyses favored the benefits of using empagliflozin in the management of patients with DM and MAFLD because of its positive impact on the improvement of MAFLD.[102,113,120,121] For example, Zhang et al[102] conducted a meta-analysis enrolling four studies including 244 participants to test the empagliflozin effect on MAFLD and found the significant improvement of BMI, LSM, liver function test, and homeostasis model assessment of IR (HOMA-IR) severity.

In term of dapagliflozin, evidence from meta-analyses favored the use of dapagliflozin for the treatment of MAFLD.[102,113,118–123] He et al[123] enrolling 11 eligible studies containing more than one thousand subjects found that dapagliflozin significantly improved metabolic syndrome, such as decreased body weight as well BMI (MD: −3.60 kg and MD: −1.20 BMI), the reduced serum levels of ALT/AST/GGT (MD: −5.58/−6.17/−4.87 U/L, respectively). Additionally, levels of TG, HbA_{1C} or fasting plasma sugar (MD: −0.16 mmol/L; MD: −0.28%; MD: −0.69 mmol/L) is also improved in dapagliflozin treatment.[123] All are reflective by improvement of FIB-4 level or HOMA-IR (MD: −0.19 or MD: −0.22, respectively).[123]

Sun et al[124] (seven RCTs) further augmented the evidence to support the effectiveness of using dapagliflozin in the management of MAFLD, which not only improved liver function test, but also improved metabolic syndrome, such as reduced levels of ALT (WMD: −6.62 U/L); AST (WMD: −4.20 U/L;); body weight (WMD: −3.79 kg); BMI (WMD: −1.33); LDL-C (WMD: −2.66 mg/dL), and TG (WMD: −16.77 mg/dL). One study also claimed that dapagliflozin is the most effective SGLT-2 inhibitor for reducing GGT level compared with other SGLT-2 inhibitors.[114]

The other SGLT-2 inhibitors, such as ipragliflozin,[114,124] luseogliflozin,[125,126] and tofogliflozin,[114] also showed the benefits on reduction of metabolic syndrome for DM patients, supporting the potential role in treatment for MAFLD.

The third class is GLP-1R agonist,[71,73,74,79,114,119,126] the effect of this class may provide a protective role in the ceased progression of MAFLD (Table 2), and it is reported that GLP-1R may have much stronger benefit on the reduction of IR in MAFLD compared with other ADA.[126] Zafar et al[71] (10 studies, 5 studies, 4 studies, 2 studies) also confirmed the aforementioned benefits of GLP-1R agonists on the management of MAFLD, based on significant improvement of liver function test, including AST (WMD: −3.29), ALT (WMD: −9.92), GGT (WMD: −12.38), and FIB-4 (WMD: −0.15), suggesting that DM patients who take GLP-1R agonists also have extraglycemic benefits on MAFLD. In theory, this class medication is linked to the suppression of dysfunctional endoplasmic reticulum stress response, sparing hepatocytes from damage by FFA; the blockage of the process of macroautophagy to injury hepatocytes, and inhibition of FGF 21 production to avoid obesity-related liver injury.[71]

Yan et al[126] (25 studies, 1595 subjects) found that GLP-1R agonists decreased the HOMA-IR (MD: −1.57), visceral fat (MD: −0.64), body weight (MD: −2.39), fasting blood sugar (MD: −0.66), and TG (MD: −0.610) during the mean treatment duration of 29 weeks. Additionally, compared with SGLT-2 inhibitors, GLP-1R agonists significantly decreased visceral fat

Table 2

Glucagon-like peptide-1 receptor agonists and nonalcoholic fatty liver diseases

	Authors (y)	General data	Liver function	Imaging
GLP-1R agonist	**Study/subject**	**WMD**	**WMD**	**WMD**
Nonspecific For the total	Yan (2022) 25/1595	BW: −2.39 kg HOMA-IA: −1.57 Fasting sugar: −0.66		Visceral fat: −0.64
Nonspecific For the total	Zafar[a](2022)	FIB-4: −0.15	AST/ALT/GGT: −3.29/−9.92/−12.38	
Semaglutide	Luo[b] (2022)		ALT/AST/GGT: −17.72/−14.88/−12.38	LSM: −0.49
Liraglutide	Luo[b] (2022)			CAP: −30.30

95% CI = 95% confidence interval; AST = aspartate aminotransferase; BW = body weight; CAP = controlled attenuation parameter; FIB-4 = Fibrosis-4 score; GGT = gamma-glutamyl transferase; GLP-1R agonist: glucagon-like peptide-1 receptor agonists; HBA_{1C} = glycated hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance; LSM = liver stiffness measurement; MD = mean difference; WMD = weighted mean difference.

[a]Zafar: for a total, including 40 eligible studies containing 13 134 subject, but for each item of specific interest, eligible studies and subjects were varied.

[b]Luo: for a total, including 27 eligible studies containing 3416 subjects, but for each item of specific interest, eligible studies and subjects were varied.

(MD: –0.56) and TG (MD: –0.61).[127] Although clinical approvement of GLP-1R agonists for MAFLD or MASH is available, GLP-1R agonist monotherapy and/or in a combination regimen is a ray of hope for successful treatment of MASH.[128]

In conclusion, with better understanding of underlying pathophysiology of MAFLD and DM, as well as the mechanisms of ADA, the management of DM patients, especially for those who need ADA as adjuvant therapy should include healthy lifestyle modification to overcome the MeS status, contributing to the urgent need of an effective weight-reduction strategy. GLP-1R agonist is one of effective body weight-lowering medications, which may be a better choice for DM complicated with MAFLD or its-associated severe form as MASH, although the role of SGLT-2 inhibitors are also impressive. Of course, all prescriptions about ADAs for the aforementioned purposes should be according to the patient's age, patient's compliance, patient's general condition, comorbidities, disease courses, drug efficacy, and drug-related side effects.[1]

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REFERENCES

1. Lee WL, Wang PH, Yang ST, Liu CH, Chang WH, Lee FK. To do one and to get more: Part I. Diabetes and bone. *J Chin Med Assoc* 2022;**85**:965–71.
2. Chi NF, Chung CP, Cheng HM, Liu CH, Lin CJ, Hsu LC, et al; Taiwan Stroke Society Guideline Consensus Group. 2021 Taiwan Stroke Society Guidelines of blood pressure control for ischemic stroke prevention. *J Chin Med Assoc* 2022;**85**:651–64.
3. Chen YL, Chi NF, Chiou HY, Hu CJ, Jeng JS, Tang SC, et al; Formosa Stroke Genetic Consortium. Application of hyperglycemia/diabetes-derived polygenic risk scores on the risk of poor outcomes after an ischemic stroke. *J Chin Med Assoc* 2022;**85**:81–7.
4. Wang JK, Huang TL, Hsu YR, Chang PY. Effect of dexamethasone intravitreal implant for refractory and treatment-naive diabetic macular edema in Taiwanese patients. *J Chin Med Assoc* 2021;**84**:326–30.
5. Sheu SJ, Yang CH, Lai CC, Wu PC, Chen SJ. One-year outcomes of the treat-and-extend regimen using aflibercept for the treatment of diabetic macular edema. *J Chin Med Assoc* 2022;**85**:246–51.
6. Lo WJ, Lin YC, Chang HY, Chen MJ. Risk factors for ocular neovascularization after central retinal artery occlusion. *J Chin Med Assoc* 2022;**85**:881–6.
7. Tang CY, Lai CC, Huang PH, Yang AH, Chiang SC, Huang PC, et al. Magnolol reduces myocardial injury induced by renal ischemia and reperfusion. *J Chin Med Assoc* 2022;**85**:584–96.
8. Hsu CY, Chen JC, Tsai YC, Chen TW. Low-dose ferrous bisglycinate chelate supplementation in chronic kidney disease and hemodialysis patients. *J Chin Med Assoc* 2022;**85**:566–70.
9. Yang CC, Liao PH, Cheng YH, Chien CY, Cheng KH, Chien CT. Diabetes associated with hypertension exacerbated oxidative stress-mediated inflammation, apoptosis and autophagy leading to erectile dysfunction in rats. *J Chin Med Assoc* 2022;**85**:346–57.
10. Hsu HM, Lu YH, Su IC, Chan L. Number of cerebral microbleeds after intracranial/extracranial stenting and dual antiplatelet therapy. *J Chin Med Assoc* 2022;**85**:704–8.
11. Huang CW, Yin CY, Huang HK, Chen TM, Hsueh KK, Yang CY, et al. Influential factors of surgical decompression for Ulnar nerve neuropathy in Guyon's canal. *J Chin Med Assoc* 2021;**84**:885–9.
12. Perng CK, Chou HY, Chiu YJ. Identifying major predictors of lower-extremity amputation in patients with diabetic foot ulcers. *J Chin Med Assoc* 2021;**84**:285–9.
13. Chen BF, Chien Y, Tsai PH, Perng PC, Yang YP, Hsueh KC, et al. A PRISMA-compliant meta-analysis of apolipoprotein C3 polymorphisms and nonalcoholic fatty liver disease. *J Chin Med Assoc* 2021;**84**:923–9.
14. Lim SS, Huang CC, Hsu PF, Lin CC, Wang YJ, Ding YZ, et al. Prolonged sitting time links to subclinical atherosclerosis. *J Chin Med Assoc* 2022;**85**:51–8.
15. Chien C, Lin CJ, Chang FC, Chung CP, Lin CJ, Liu HY, et al. Quantitative CT angiography predicts large artery occlusion types and successful thrombectomy in acute ischemic stroke. *J Chin Med Assoc* 2021;**84**:61–7.
16. Lee WL, Lee FK, Wang PH. Dipeptidyl peptidase-4 (DPP-4) inhibitors and osteoporosis. *J Chin Med Assoc* 2022;**85**:889–90.
17. Chang CH, Lu CH, Chung CH, Su SC, Kuo FC, Liu JS, et al. Dipeptidyl peptidase-4 inhibitors attenuates osteoporosis in patients with diabetes: a nationwide, retrospective, matched-cohort study in Taiwan. *J Chin Med Assoc* 2022;**85**:747–53.
18. Chang YC, Yao YC, Lin HH, Wang ST, Chang MC, Chou PH. Predictability of the preoperative lateral fulcrum radiograph of success in one-level vertebroplasty to treat painful osteoporotic vertebral fracture. *J Chin Med Assoc* 2022;**85**:129–35.
19. Lin CH, Tung YC, Chang TJ, Huang CN, Hwu CM; for Taiwan Type 1 DM Consortium. Use of expert consensus to improve the diagnosis and management of type 1 diabetes mellitus. *J Chin Med Assoc* 2022;**85**:741–6.
20. Chen CY, Lin PT, Wang YH, Syu RW, Hsu SL, Chang LH, et al. Etiology and risk factors of intracranial hemorrhage and ischemic stroke in young adults. *J Chin Med Assoc* 2021;**84**:930–6.
21. Jenkins DJA, Dehghan M, Mente A, Bangdiwala SI, Rangarajan S, Srichaikul K, et al; PURE Study Investigators. Glycemic index, glycemic load, and cardiovascular disease and mortality. *N Engl J Med* 2021;**384**:1312–22.
22. Lee WL, Lee FK, Wang PH. Glycemic control and outcome of cancer patients. *J Chin Med Assoc* 2022;**85**:265–7.
23. Hsu SJ, Huang HC. Nonalcoholic fatty liver disease and hepatocellular carcinoma: distinct links. *J Chin Med Assoc* 2021;**84**:737–8.
24. Lin CC, Wu MF, Chang YL, Sheu WH, Liou WS. Glycemic control was associated with nonprostate cancer and overall mortalities in diabetic patients with prostate cancer. *J Chin Med Assoc* 2022;**85**:331–40.
25. Jonas DE, Crotty K, Yun JDY, Middleton JC, Feltner C, Taylor-Phillips S, et al. Screening for prediabetes and type 2 diabetes: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2021;**326**:744–60.
26. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, et al; US Preventive Services Task Force. Screening for prediabetes and type 2 diabetes: US Preventive Services Task Force recommendation statement. *JAMA* 2021;**326**:736–43.
27. Kalyani RR. Glucose-lowering drugs to reduce cardiovascular risk in type 2 diabetes. *N Engl J Med* 2021;**384**:1248–60.
28. Zhu S, Bai Q, Li L, Xu T. Drug repositioning in drug discovery of T2DM and repositioning potential of antidiabetic agents. *Comput Struct Biotechnol J* 2022;**20**:2839–47.
29. Rashid R, Mir SA, Kareem O, Ali T, Ara R, Malik A, et al. Polycystic ovarian syndrome-current pharmacotherapy and clinical implications. *Taiwan J Obstet Gynecol* 2022;**61**:40–50.
30. Marx N, Davies MJ, Grant PJ, Mathieu C, Petrie JR, Cosentino F, et al. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *Lancet Diabetes Endocrinol* 2021;**9**:46–52.
31. Li YT, Chang WH, Wang PH. New strategies accelerate the path to overcome refractory interstitial cystitis. *J Chin Med Assoc* 2022;**85**:665–6.
32. Yang ST, Liu CH, Wang PH. Combination of hyaluronic acid and mesenchymal stem cells for treatment of intrauterine adhesions. *Taiwan J Obstet Gynecol* 2022;**61**:8–9.
33. Liu CH, Kung YH, Lin CJ, Chuang CM, Wu HH, Jiang LY, et al. Synergistic therapeutic effect of low-dose bevacizumab with cisplatin-based chemotherapy for advanced or recurrent cervical cancer. *J Chin Med Assoc* 2021;**84**:1139–44.
34. Wang JW, Chen PY, Huang HH, Yeh C, Chen SC, Lee WJ, et al. Change of plasma amylin after bariatric surgery challenged by oral glucose is associated with remission of type 2 diabetes mellitus. *J Chin Med Assoc* 2021;**84**:1001–6.
35. Lee WL, Lee FK, Wang PH. Amylin, bariatric surgery, and type 2 diabetes mellitus. *J Chin Med Assoc* 2021;**84**:983–4.
36. Li YT, Liu CH, Wang PH. Treatment for recurrent epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2021;**60**:803–4.

37. Wang PY, Lee YC, Liu WM, Chen CH. Surgical outcome of benign cases with pelvic adhesions undergoing robotic total hysterectomy. *J Chin Med Assoc* 2022;**85**:853–8.
38. Yang ST, Liu CH, Wang PH. No impact of tumor size on oncological outcomes in cervical cancer patients after radical hysterectomy and postoperative radiotherapy: is it real? *Taiwan J Obstet Gynecol* 2022;**61**:575–7.
39. Li YT, Yang ST, Wang PH. Is it real of lower incidence of vitamin D deficiency in T2DM patients? *J Chin Med Assoc* 2022;**85**:958.
40. Chang WH, Liu CH. Different genders should be considered for the extraglycemic benefits of oral antidiabetic drugs. *J Chin Med Assoc* 2022;**85**:959.
41. Chang CH, Lu CH, Hsieh CH, Chien WC. Reply to "Is it real of lower incidence of vitamin D deficiency in T2DM patients?". *J Chin Med Assoc* 2022;**85**:960.
42. Zhang YS, Zheng YD, Yuan Y, Chen SC, Xie BC. Effects of anti-diabetic drugs on fracture risk: a systematic review and network meta-analysis. *Front Endocrinol (Lausanne)* 2021;**12**:735824.
43. Cowan A, Jeyakumar N, Kang Y, Dixon SN, Garg AX, Naylor K, et al. Fracture risk of sodium-glucose cotransporter-2 inhibitors in chronic kidney disease. *Clin J Am Soc Nephrol* 2022;**17**:835–42.
44. Doni K, Bühn S, Weise A, Mann NK, Hess S, Sönnichsen A, et al. Safety of dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Drug Saf* 2022;**13**:20420986211072383.
45. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022;**399**:394–405.
46. Kuo SC, Lee WL, Wang PH. The effects of maternal body weight and gestational diabetes mellitus on the risk of the delivery of large-for-gestational age babies: synergistic or additive? *Taiwan J Obstet Gynecol* 2022;**61**:413–4.
47. Lee WL, Lee FK, Wang PH. Pre-pregnancy body mass index is a determined risk factor for the development of gestational diabetes, regardless of singleton or twin pregnancy. *Taiwan J Obstet Gynecol* 2022;**61**:1–2.
48. Chen HM, Wu CF, Hsieh CJ, Kuo FC, Sun CW, et al. Relationship of maternal body weight and gestational diabetes mellitus with large-for-gestational-age babies at birth in Taiwan: the TMICS cohort. *Taiwan J Obstet Gynecol* 2022;**61**:234–42.
49. Chang WH, Lee WL, Wang PH. Gestational weight gain and birth weight of newborn. *Taiwan J Obstet Gynecol* 2021;**60**:979–80.
50. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. *Lancet* 2021;**396**:2019–82.
51. Chen CT, Lin MC, Lee YJ, Li LH, Chen YJ, Chuanyi Hou P, et al. Association between body mass index and clinical outcomes in out-of-hospital cardiac arrest survivors treated with targeted temperature management. *J Chin Med Assoc* 2021;**84**:504–9.
52. Hwang HJ, Hwang YJ, Kim YJ, Kim M, Hwang KA. Immature sword bean pods (Canavalia gladiata) inhibit adipogenesis in C3H10T1/2 cells and mice with high-fat diet-induced obesity. *J Chin Med Assoc* 2022;**85**:67–76.
53. Al-Adwi ME, Al-Haswsa ZM, Alhmmadi KM, Eissa YA, Hamdan A, Bawadi H, et al. Effects of different diets on glycemic control among patients with type 2 diabetes: a literature review [Epub ahead of print]. *Nutr Health* 2022:2601060221112805. doi: 10.1177/02601060221112805.
54. Jayedi A, Zeraattalab-Motlagh S, Jabbarzadeh B, Hosseini Y, Jibril AT, Shahinfar H, et al. Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2022;**116**:40–56.
55. Lee WL, Lee FK, Wang PH. Vitamin D and systemic lupus erythematous. *J Chin Med Assoc* 2022;**85**:811–2.
56. Yang YL, Leu HB, Yin WH, Tseng WK, Wu YW, Lin TH, et al. Adherence to healthy lifestyle improved clinical outcomes in coronary artery disease patients after coronary intervention. *J Chin Med Assoc* 2021;**84**:596–605.
57. Chuang WC, Chu CH, Hsu YH, Yao CS. Effect of socioeconomic status on survival in patients on the Diabetes Shared Care Program: finding from a Taiwan nationwide cohort. *J Chin Med Assoc* 2022;**85**:311–6.
58. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med* 2021;**384**:2219–28.
59. Seow KM, Chang YW, Chen KH, Juan CC, Huang CY, Lin LT, et al. Molecular mechanisms of laparoscopic ovarian drilling and its therapeutic effects in polycystic ovary syndrome. *Int J Mol Sci* 2020;**21**:8147.
60. Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. *Lancet Diabetes Endocrinol* 2022;**10**:75–84.
61. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al; SURPASS-2 Investigators. Tirzepatide versus Semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;**385**:503–15.
62. Chong WH, Yanoff LB, Andraca-Carrera E, Thanh Hai M. Assessing the safety of glucose-lowering drugs - a new focus for the FDA. *N Engl J Med* 2020;**383**:1199–202.
63. Wu TH, Lee IT, Ho LT, Sheu WH, Hwu CM. Combined lipid goal attainment in patients with type 2 diabetes and dyslipidemia: a head-to-head comparative trial of statins. *J Chin Med Assoc* 2022;**85**:832–9.
64. Bedi O, Aggarwal S, Trehanpati N, Ramakrishna G, Krishan P. Molecular and pathological events involved in the pathogenesis of diabetes-associated nonalcoholic fatty liver disease. *J Clin Exp Hepatol* 2019;**9**:607–18.
65. Bica C, Sandu C, Suceveanu AI, Sarbu E, Stoica RA, Gherghiceanu F, et al. Non-alcoholic fatty liver disease: a major challenge in type 2 diabetes mellitus (Review). *Exp Ther Med* 2020;**20**:2387–91.
66. Yamazaki H, Wang J, Tauchi S, Dohke M, Hanawa N, Katanuma A, et al. Inverse association between fatty liver at baseline ultrasonography and remission of type 2 diabetes over a 2-year follow-up period. *Clin Gastroenterol Hepatol* 2021;**19**:556–64.e5.
67. Fernandes GW, Bocco BMLC. Hepatic mediators of lipid metabolism and ketogenesis: focus on fatty liver and diabetes. *Curr Diabetes Rev* 2021;**17**:e110320187539.
68. Ilias I, Thomopoulos C. Non-alcoholic fatty liver disease, diabetes medications and blood pressure. *World J Diabetes* 2021;**12**:1809–11.
69. Shin J, Choi SJ, Lee HR, Han K, Chang J, Jeong SM, et al. Non-alcoholic fatty liver disease and the risk of diabetes mellitus by menopausal status: a nationwide cohort study. *J Pers Med* 2022;**12**:546.
70. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020;**73**:202–9.
71. Zafar Y, Rashid AM, Siddiqi AK, Ellahi A, Ahmed A, Hussain HU, et al. Effect of novel glucose lowering agents on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2022;**46**:101970.
72. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. *J Clin Endocrinol Metab* 2022;**107**:29–38.
73. Fu ZD, Cai XL, Yang WJ, Zhao MM, Li R, Li YF. Novel glucose-lowering drugs for non-alcoholic fatty liver disease. *World J Diabetes* 2021;**12**:84–97.
74. Nowrouzi-Sohrabi P, Rezaei S, Jalali M, Ashourpour M, Ahmadipour A, et al. The effects of glucagon-like peptide-1 receptor agonists on glycemic control and anthropometric profiles among diabetic patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pharmacol* 2021;**893**:173823.
75. Makri ES, Goulas A, Polyzos SA. Sodium-glucose co-transporter 2 inhibitors in nonalcoholic fatty liver disease. *Eur J Pharmacol* 2021;**907**:174272.
76. Kumar J, Memon RS, Shahid I, Rizwan T, Zaman M, Menezes RG, et al. Antidiabetic drugs and non-alcoholic fatty liver disease: a systematic review, meta-analysis and evidence map. *Dig Liver Dis* 2021;**53**:44–51.
77. Manka PP, Kaya E, Canbay A, Syn WK. A review of the epidemiology, pathophysiology, and efficacy of anti-diabetic drugs used in the treatment of nonalcoholic fatty liver disease. *Dig Dis Sci* 2021;**66**:3676–88.
78. Dougherty JA, Guirguis E, Thornby KA. A systematic review of newer antidiabetic agents in the treatment of nonalcoholic fatty liver disease. *Ann Pharmacother* 2021;**55**:65–79.
79. Wong C, Lee MH, Yaow CYL, Chin YH, Goh XL, Ng CH, et al. Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: a meta-analysis. *Front Endocrinol (Lausanne)* 2021;**12**:609110.
80. Lian J, Fu J. Efficacy of various hypoglycemic agents in the treatment of patients with nonalcoholic liver disease with or without diabetes: a network meta-analysis. *Front Endocrinol (Lausanne)* 2021;**12**:649018.

81. Kaneto H, Obata A, Kimura T, Shimoda M, Kinoshita T, Matsuoka TA, et al. Unexpected pleiotropic effects of SGLT2 inhibitors: pearls and pitfalls of this novel antidiabetic class. *Int J Mol Sci* 2021;**22**:3062.
82. Kim KS, Lee BW. Beneficial effect of anti-diabetic drugs for nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2020;**26**:430–43.
83. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. *Curr Diab Rep* 2020;**20**:59.
84. Ranjbar G, Mikhailidis DP, Sahebkar A. Effects of newer antidiabetic drugs on nonalcoholic fatty liver and steatohepatitis: think out of the box!. *Metabolism* 2019;**101**:154001.
85. McPherson S, Armstrong MJ, Cobbold JF, Corless L, Anstee QM, Aspinall RJ, et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. *Lancet Gastroenterol Hepatol* 2022;**7**:755–69.
86. Kao WY, Lin YF, Chang IW, Chen CL, Tang JH, Chang CC, et al. Interleukin-2 receptor alpha as a biomarker for nonalcoholic fatty liver disease diagnosis. *J Chin Med Assoc* 2021;**84**:261–6.
87. Polyzos SA, Kechagias S, Tsochatzis EA. Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations. *Aliment Pharmacol Ther* 2021;**54**:1013–25.
88. Lin BZ, Lin TJ, Lin CL, Liao LY, Chang TA, Lu BJ, et al. Differentiation of clinical patterns and survival outcomes of hepatocellular carcinoma on hepatitis B and nonalcoholic fatty liver disease. *J Chin Med Assoc* 2021;**84**:606–13.
89. Chhabra S, Singh SP, Singh A, Mehta V, Kaur A, Bansal N, et al. Diabetes mellitus increases the risk of significant hepatic fibrosis in patients with non-alcoholic fatty liver disease. *J Clin Exp Hepatol* 2022;**12**:409–16.
90. Nakatsuka T, Tateishi R. Development and prognosis of hepatocellular carcinoma in patients with diabetes. *Clin Mol Hepatol* 2022. doi: 10.3350/cmh.2022.0095.
91. Chen YJ, Su CW, Wei CY, Chau GY, Chen PH, Chao Y, et al. Comparison of prognoses between cirrhotic and noncirrhotic patients with hepatocellular carcinoma and esophageal varices undergoing surgical resection. *J Chin Med Assoc* 2022;**85**:679–86.
92. Liao CY, Lee CY, Wei CY, Chao Y, Huang YH, Hou MC, et al. Differential prognoses among male and female patients with hepatocellular carcinoma. *J Chin Med Assoc* 2022;**85**:554–65.
93. Wu HL, Kuo HC, Li CC, Wu YM, Lin SP, Chang KY, et al. A comparison of prognostic performance of perioperative inflammation markers in surgical resection for hepatocellular carcinoma. *J Chin Med Assoc* 2021;**84**:614–22.
94. Lei HJ, Wang SY, Chau IY, Li AF, Chau YP, Hsia CY, et al. Hepatoma upregulated protein and Ki-67 expression in resectable hepatocellular carcinoma. *J Chin Med Assoc* 2021;**84**:623–32.
95. Chang CY, Wei CY, Chen PH, Hou MC, Chao Y, Chau GY, et al. The role of albumin-bilirubin grade in determining the outcomes of patients with very early-stage hepatocellular carcinoma. *J Chin Med Assoc* 2021;**84**:136–43.
96. Teng T, Qiu S, Zhao Y, Zhao S, Sun D, Hou L, et al. Pathogenesis and therapeutic strategies related to non-alcoholic fatty liver disease. *Int J Mol Sci* 2022;**23**:7841.
97. Makri ES, Makri E, Polyzos SA. Combination therapies for nonalcoholic fatty liver disease. *J Pers Med* 2022;**12**:1166.
98. Patel M. Evidence-based management of patients with nonalcoholic fatty liver disease. *JAAPA* 2022;**35**:20–4.
99. Huang YS, Chang TE, Perng CL, Huang YH. Genetic variations of three important antioxidative enzymes SOD2, CAT, and GPX1 in nonalcoholic steatohepatitis. *J Chin Med Assoc* 2021;**84**:14–8.
100. Allen AM, Therneau TM, Ahmed OT, Gidener T, Mara KC, Larson JJ, et al. Clinical course of non-alcoholic fatty liver disease and the implications for clinical trial design. *J Hepatol* 2022; **77**:1237–45.
101. Kuchay MS, Misra A. Role of diabetologists in the management of non-alcoholic fatty liver disease: primary prevention and screening/management of fibrosis and cirrhosis. *Diabetes Metab Syndr* 2022;**16**:102446.
102. Zhang Y, Liu X, Zhang H, Wang X. Efficacy and safety of empagliflozin on nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2022;**13**:836455.
103. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 2011;**54**:1082–90.
104. Zhou YJ, Wong VW, Zheng MH. Consensus scoring systems for non-alcoholic fatty liver disease: an unmet clinical need. *Hepatobiliary Surg Nutr* 2021;**10**:388–90.
105. Li G, Zhang X, Lin H, Liang LY, Wong GL, Wong VW. Non-invasive tests of non-alcoholic fatty liver disease. *Chin Med J (Engl)* 2022;**135**:532–46.
106. Henry L, Paik J, Younossi ZM. Review article: the epidemiologic burden of non-alcoholic fatty liver disease across the world. *Aliment Pharmacol Ther* 2022;**56**:942–56.
107. Chou TH, Yeh HJ, Chang CC, Tang JH, Kao WY, Su IC, et al. Deep learning for abdominal ultrasound: a computer-aided diagnostic system for the severity of fatty liver. *J Chin Med Assoc* 2021;**84**:842–50.
108. Filipovic B, Lukic S, Mijac D, Marjanovic-Haljilji M, Vojnovic M, Bogdanovic J, et al. The new therapeutic approaches in the treatment of non-alcoholic fatty liver disease. *Int J Mol Sci* 2021;**22**:13219.
109. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;**71**:793–801.
110. Bril F. Nonalcoholic fatty liver disease in type 2 diabetes: awareness is the first step toward change. *HepatoBiliary Surg Nutri* 2020;**9**:493–6.
111. Yang ST, Liu CH, Ma SH, Chang WH, Chen YJ, Lee WL, et al. Association between pre-pregnancy overweightness/obesity and pregnancy outcomes in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;**19**:9094.
112. Tomah S, Alkhouri N, Hamdy O. Nonalcoholic fatty liver disease and type 2 diabetes: where do diabetologists stand? *Clin Diabetes Endocrinol* 2020;**6**:9.
113. Jeznach-Steinhagen A, Ostrowska J, Czerwonogrodzka-Senczyna A, Boniecka I, Shahnazaryan U, Kuryłowicz A. Dietary and pharmacological treatment of nonalcoholic fatty liver disease. *Medicina (Kaunas)* 2019;**55**:166.
114. Luo Q, Wei R, Cai Y, Zhao Q, Liu Y, Liu WJ. Efficacy of off-label therapy for non-alcoholic fatty liver disease in improving non-invasive and invasive biomarkers: a systematic review and network meta-analysis of randomized controlled trials. *Front Med (Lausanne)* 2022;**9**:793203.
115. Huang HC, Hsu SJ, Chuang CL, Hsiung SY, Chang CC, Hou MC, et al. Effects of dipeptidyl peptidase-4 inhibition on portal hypertensive and cirrhotic rats. *J Chin Med Assoc* 2021;**84**:1092–9.
116. Shyangdan D, Clar C, Ghouri N, Henderson R, Gurung T, Preiss D, et al. Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review. *Health Technol Assess* 2011;**15**:1–110.
117. Ndakotsu A, Vivekanandan G. The role of thiazolidinediones in the amelioration of nonalcoholic fatty liver disease: a systematic review. *Cureus* 2022;**14**:e25380.
118. Li YT, Liu CH, Wang PH. Serum cystatin C or cystatin C-based glomerular filtration rate may be a better choice in estimating renal function in women with preeclampsia. *Taiwan J Obstet Gynecol* 2021;**60**:801–2.
119. Tang W, Xu Q, Hong T, Tong G, Feng W, Shen S, et al. Comparative efficacy of anti-diabetic agents on nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized and non-randomized studies. *Diabetes Metab Res Rev* 2016;**32**:200–16.
120. Li B, Wang Y, Ye Z, Yang H, Cui X, Wang Z, et al. Effects of canagliflozin on fatty liver indexes in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *J Pharm Pharm Sci* 2018;**21**:222–35.
121. Mantovani A, Petracca G, Csermely A, Beatrice G, Targher G. Sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Metabolites* 2020;**11**:22.
122. Lee KW, Devaraj NK, Ching SM, Veettil SK, Hoo FK, Deuraseh I, et al. Effect of SGLT-2 inhibitors on non-alcoholic fatty liver disease among patients with type 2 diabetes mellitus: systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. *Oman Med J* 2021;**36**:e273.
123. He K, Li J, Xi W, Ge J, Sun J, Jing Z. Dapagliflozin for nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2022;**185**:109791.
124. Sun L, Deng C, Gu Y, He Y, Yang L, Shi J. Effects of dapagliflozin in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Clin Res Hepatol Gastroenterol* 2022;**46**:101876.
125. Teo YN, Ting AZH, Teo YH, Chong EY, Tan JTA, Syn NL, et al. Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors and combined SGLT1/2 inhibitors on cardiovascular, metabolic, renal, and safety

outcomes in patients with diabetes: a network meta-analysis of 111 randomized controlled trials. *Am J Cardiovasc Drugs* 2022;**22**:299–323.
126. Yan H, Huang C, Shen X, Li J, Zhou S, Li W. GLP-1 RAs and SGLT-2 inhibitors for insulin resistance in nonalcoholic fatty liver disease: systematic review and network meta-analysis. *Front Endocrinol (Lausanne)* 2022;**13**:923606.
127. Mahapatra MK, Karuppasamy M, Sahoo BM. Therapeutic potential of semaglutide, a newer GLP-1 receptor agonist, in abating obesity, non-alcoholic steatohepatitis and neurodegenerative diseases: a narrative review. *Pharm Res* 2022;**39**:1233–48.
128. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;**28**:528–62.