香港糖尿科護士協會
Association of Hong Kong Diabetes Nurses

AHKDN Newsletter

Issue 18
Feb. 2023

AHKDN web-site: http//www.ahkdn.com
Email address: newsletter.ahkdn@hotmail.com

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Editorial

Fatty liver disease is one of the most common chronic liver conditions in Hong Kong. Non-alcoholic fatty liver disease (NAFLD) is liver disease affecting people who are drinkers or non-drinkers. The main characteristics of it is too much fat in liver cells. It may cause liver inflammation, liver cirrhosis and even liver failure. Recently, some experts proposed the metabolic-associated fatty liver disease (MAFLD), defined as fatty liver disease with the presence of overweight or obesity and/or T2DM. In this issue, we are pleased to invite endocrinologist, expert in Chinese medicine, dietitian and DM nurse to share their expertise and experience in caring patients with NAFLD or MAFLD.

President of AHKDN 2022-2023

Loo Kit Man

I am pleased to announce that AHKDN' s new term of office was renewed in Aug 2022. This year, we are so grateful that a lot of new faces joined our AHKDN' s big family and became our Council members or active members of the three subcommittees namely AHKDN Newsletter Committee, Clinical Work Group on Diabetes Nursing Accreditation, and Evidence-based Practice Committee. I would like to thank all the new and current council and subcommittee members for their continuous support and contributions to our Association.

Both the problems from the shortage of healthcare workers and the pandemic of COVID-19 are remaining a huge challenge to our healthcare system. COVID-19 has changed the world, our lives, and a lot of our health practices. However, on the positive side, it speeds up our health technology to develop telecare and hence it increases the convenience for some patients to access healthcare services more easily and reduces the infection risks during hospital visits. It also changes the mode of teaching and learning; we are no longer being restricted by time and place to attend lectures in person or even give up lectures due to inaccessibility.

The theme of the newsletter is diabetes and fatty liver disease. This is one of the themes of our latest AGM lecture that was conducted via ZOOM. We are so delighted to have experts from different disciplines to enlighten us on this with a wider perspective. Hope you enjoy it.

Metabolic Dysfunction-Associated Fatty Liver Disease as a Diabetic Complication

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State Key Laboratory of Pharmaceutical Biotechnology, University of Hong Kong, Hong Kong SAR

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a relatively new entity proposed by an international expert panel in 2020 in order to more precisely define fatty liver disease. It is defined as the presence of hepatic steatosis co-existing with any one of following criteria namely overweight or obesity, type 2 diabetes, or in normal weight or lean individuals, the presence of at least two metabolic dysfunction including central obesity, elevated blood pressure, dyslipidaemia, prediabetes, as well as elevated homeostasis model assessment of insulin resistance (HOMA-IR) and circulating high-sensitivity C-reactive protein (hsCRP) levels.[1] In contrast to non-alcoholic fatty liver disease (NAFLD) (Figure 1) which is a diagnosis of exclusion, MAFLD does not require the exclusion of excessive alcohol consumption, viral hepatitis and other chronic liver diseases, as well as the use of steatogenic medications. In both MAFLD and NAFLD, the detection of hepatic steatosis can be based on imaging findings, liver histology, or even blood biomarkers and predictive scores such as the fatty liver index (FLI) if imaging tools are not readily available. [1] [2]

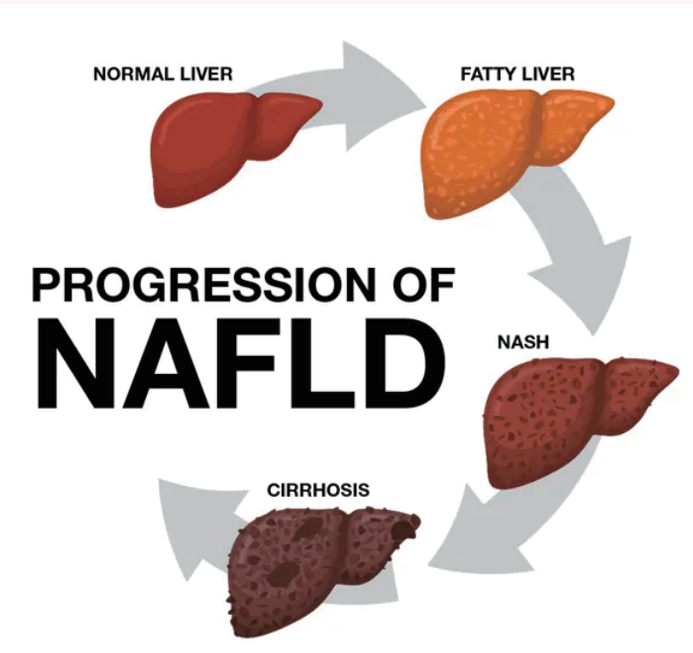


Figure 1

About a quarter of the world adult population has NAFLD,[3] whereas for MAFLD, in view of the high global prevalence of diabesity and its more inclusionary diagnostic criteria, a recent meta-analysis reported a global prevalence of 39%.[4] More alarmingly, among overweight and obese adults from the general population, the prevalence of MAFLD can be as high as over 50%.[5] On the other hand, 10.5% of the current world adult population have diabetes. The International Diabetes Federation (IDF) projected that 1 in 8 adults will be living with diabetes by year 2045 (Figure 2).[6] Notably, hepatic steatosis is found in more than 70% of patients with type 2 diabetes attending primary care and diabetes clinics. [7, 8] [9] Theoretically, all patients with co-existing type 2 diabetes and fatty liver are classified as having MAFLD. Therefore, the prevalence of MAFLD in the diabetic population is strikingly high.

It is well established that the co-existence of type 2 diabetes and fatty liver disease is mutually detrimental. Indeed, a recent meta-analysis involving over 24 million individuals globally demonstrated that type 2 diabetes was associated

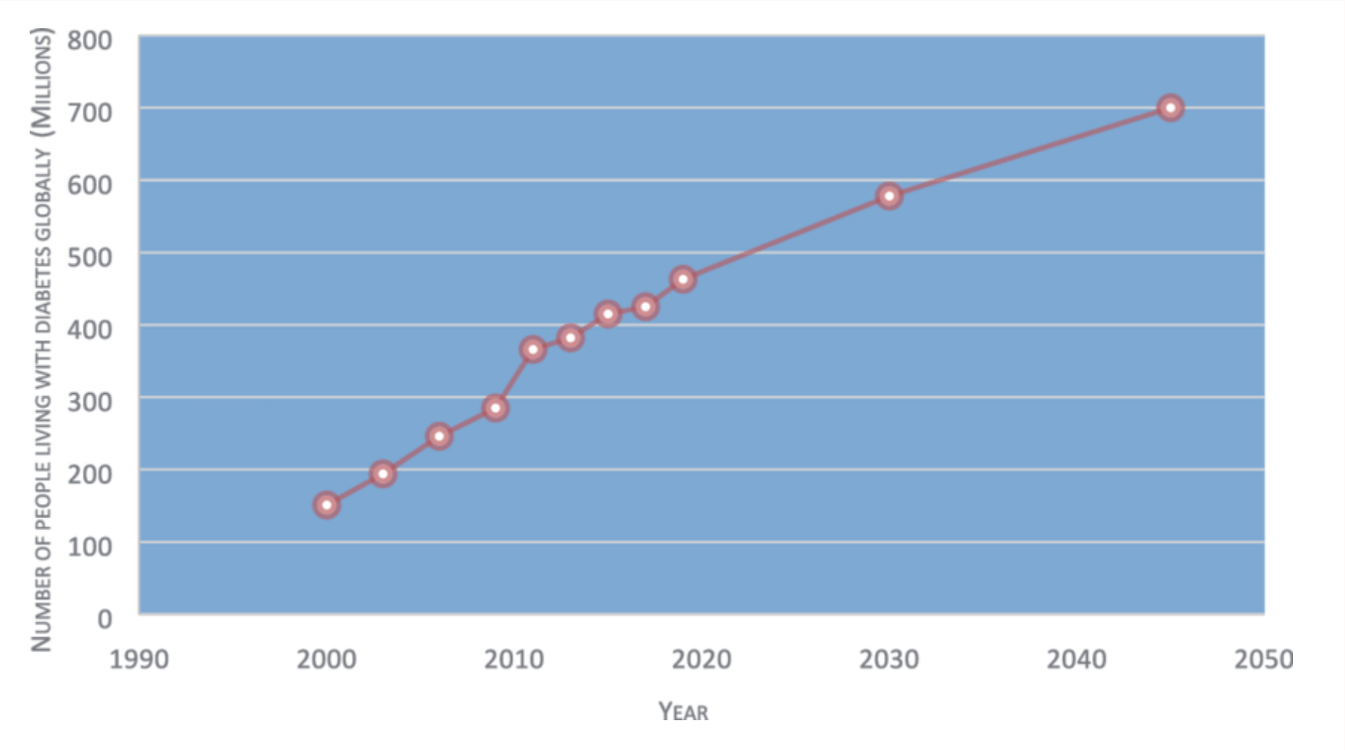


Figure 2:
A graphical description of the IDF-estimated number of adults living with diabetes globally since the year 2000 which is projected to rise to 700 million by 2045.

with a higher risk of developing advanced liver disease in NAFLD to a much larger extent than that brought by other metabolic risk factors such as obesity, dyslipidaemia and hypertension.[11] In 2020, the Asian Pacific Association for the Study of the Liver (APASL) issued clinical practice guidelines that provide recommendations specifically for the diagnosis and management of MAFLD. [10] Since the diagnostic criteria of MAFLD allows the presence of dual or multiple etiologies such as alcohol and viral hepatitis[12] [13], in all MAFLD patients, it remains essential to screen for other common causes of chronic liver diseases including excessive alcohol intake, viral hepatitis (B and C). This is especially important as viral hepatitis B remains relatively common in Asia, and chronic viral hepatitis is more readily treatable nowadays. Moreover, clinicians should consider other tests including anti-nuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), etc. in patients with fatty liver disease especially if there is clinical suspicion. [14]

Liver fibrosis is a major determinant of liver-related morbidity and mortality.[15] [16] Furthermore, there has been increasing evidence that demonstrated the close associations of liver fibrosis with the development of cardiovascular disease (CVD) and chronic kidney disease (CKD)[8, 17] [18] [19] , further reinforcing the importance of fibrosis assessment in the management of MAFLD. Accordingly, the APASL guidelines recommend fibrosis assessments in all MAFLD patients to rule out significant or advanced liver fibrosis using non-invasive fibrosis scores such as Fibrosis-4 index (Fib-4), blood biomarkers such as the enhanced liver fibrosis (ELF) test, or liver stiffness (LS) measurements with vibration controlled transient elastography (VCTE), shear wave elastography (SWE) or magnetic resonance elastography (MRE) depending on the availability. Similarly, the American Diabetes Association (ADA) also recommends screening for steatohepatitis and advanced liver fibrosis in patients with prediabetes or type 2 diabetes who had elevated alanine aminotransferase (ALT) levels or fatty liver detected

on USG.[20] Notably, while some studies proposed a two-tier screening algorithm involving the sequential use of Fib-4 followed by VCTE assessments[21, 22], there have also been concerns over the performance of these conventional serum-based fibrosis scores in excluding significant or advanced liver fibrosis among patients with type 2 diabetes.[23, 24] Indeed, in a recent cross-sectional study involving 162 patients with type 2 diabetes who had liver-biopsy proven NAFLD, plasma aspartate aminotransferase (AST) alone outperformed the conventional non-invasive fibrosis scores including NAFLD fibrosis scores (NFS) and Fib-4.[24]

Lifestyle modification, in particular weight reduction, is the cornerstone management in all MAFLD patients regardless of their baseline body mass index.[10] Previous studies in NAFLD patients reported a dose-response relationship between weight loss percentage and the overall liver histological improvements, with resolution of steatohepatitis and improvement in hepatic fibrosis if 7-10% weight reduction is achieved.[25] Dietary recommendations combined with exercise strategies are more effective, and studies showed that a Mediterranean type of diet pattern is beneficial in terms of liver fibrosis development in patients with type 2 diabetes.[26] Glycaemia also influences fibrosis progression. It has been demonstrated that each 1% increase in the mean glycated haemoglobin (HbA1c) within the year preceding liver biopsy was independently associated with a 15% higher risk of having more severe stages of liver fibrosis.[27] To date, no pharmacological agents have been approved specifically for treating MAFLD. Nonetheless, according to the latest ADA guidelines in 2022 (Figure 3)[20] , pioglitazone and glucagon-like peptide 1 receptor agonists (GLP1rA), both of which are anti-diabetic agents, can be considered for use especially among patients with type 2 diabetes who show evidence of steatohepatitis and significant liver fibrosis. Peroxisome proliferator-activated receptor gamma (PPARγ) maintains hepatic stellate cells in a quiescent state and its overexpression could reduce collagen production and fibrogenesis.[28] Pioglitazone is a PPARγ agonist which has been shown to improve liver histology including fibrosis in patients with non-alcoholic steatohepatitis, and the benefits in liver fibrosis seemed to be more readily observed among patients with type 2 diabetes. [29] [30] On the other hand, both liraglutide and semaglutide have been shown to improve liver histology in two phase 2 randomized controlled trials (RCTs) that involved participants with and without type 2 diabetes. [31] [32] The hepatic benefits brought by GLP1rA are likely contributed by weight loss with indirect effects on improvements in adipose tissue dysfunction.[33] Sodium glucose co-transporter 2 inhibitor (SGLT2i) is a class of medications with great potentials to be developed for treatment of MAFLD [34] [35, 36], especially given the elevated risks of CVD and CKD in MAFLD patients with type 2 diabetes who are heavily burdened by other metabolic comorbidities including hypertension, dyslipidaemia and obesity. However, RCTs that involves participants with biopsy-proven steatohepatitis is currently lacking. The two ongoing RCTs, the Dapagliflozin Efficacy and Action in NASH (DEAN) and the Combined Active Treatment in Type 2 Diabetes with NASH (COMBAT_T2_NASH) studies, will hopefully provide more insights to clarify the role of SGLT2i in patients with co-existing type 2 diabetes and MAFLD.

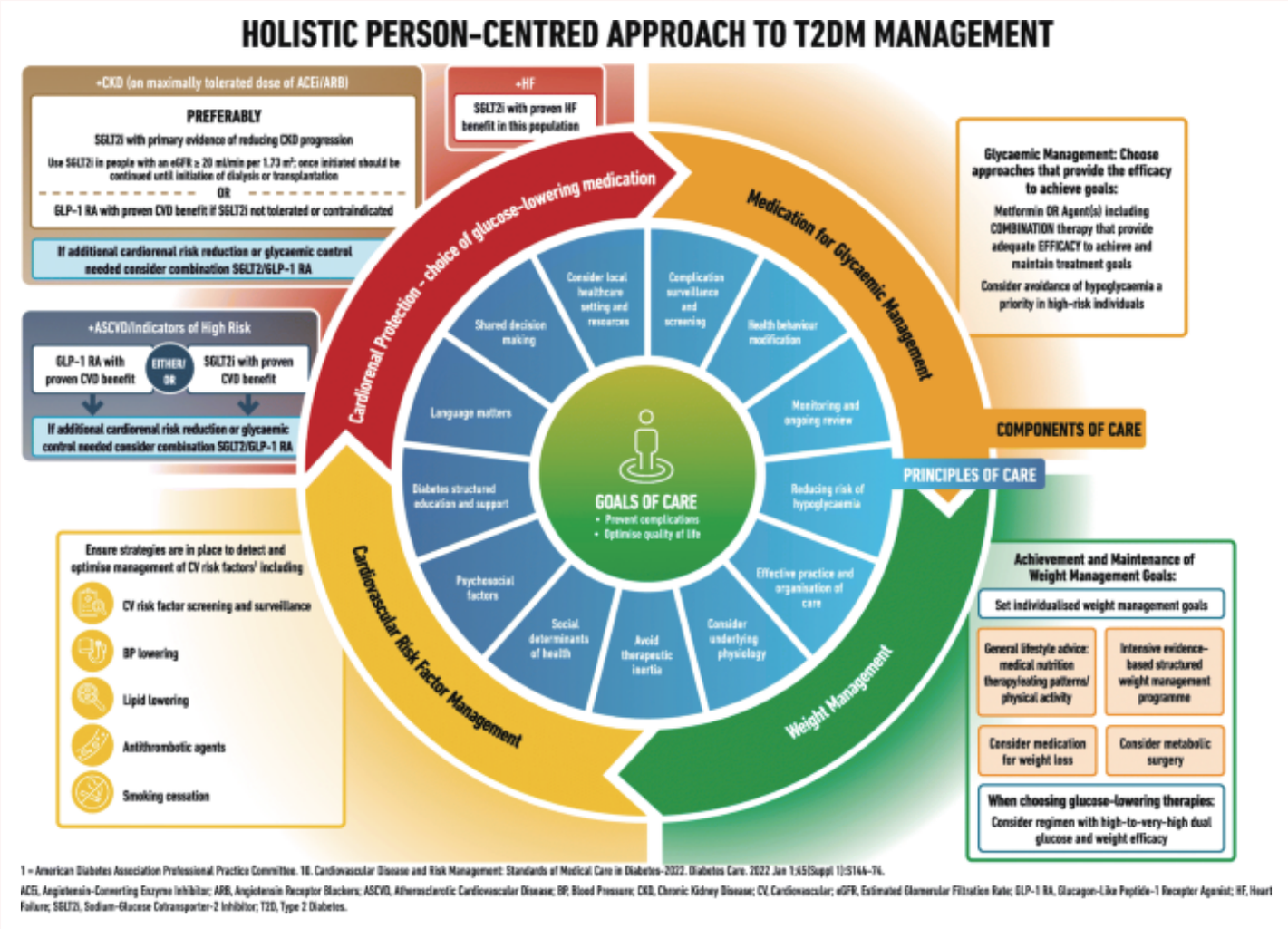


Figure 3

With regard to monitoring and follow-up, it is recommended that MAFLD patients should be monitored at regular intervals based on their baseline fibrosis assessment.[10] Patients with fibrosis at baseline should be evaluated at least annually, while those without fibrosis at baseline can be reassessed every 2-3 years as long as their concomitant metabolic risk factors do not worsen. Therefore, optimization and maintaining good control of metabolic comorbidities is important. MAFLD patients who are at intermediate to high risk of advanced liver fibrosis from non-invasive assessments should be referred to hepatologists for further evaluation including consideration of liver biopsy and eligibility for clinical trials.[10] Lastly, those with established cirrhosis should be offered regular varices screening and surveillance for hepatocellular carcinoma, as type 2 diabetes is one of the major independent predictors of incident HCC.[37]

Fatty liver disease, be it NAFLD or MAFLD, has been regarded as a multisystem disease that requires multidisciplinary approach with comprehensive evaluation. Moreover, it has been suggested that MAFLD should be recognized as an important diabetic complication and therefore systematically evaluated as in other conventional diabetic complications. Treating physicians of patients with type 2 diabetes play pivotal roles in MAFLD by identifying those who are at a higher risk of progression and refer them to hepatologists for further care, while at the same time managing their metabolic co-morbidities and monitor for the development of cardio-renal complications.

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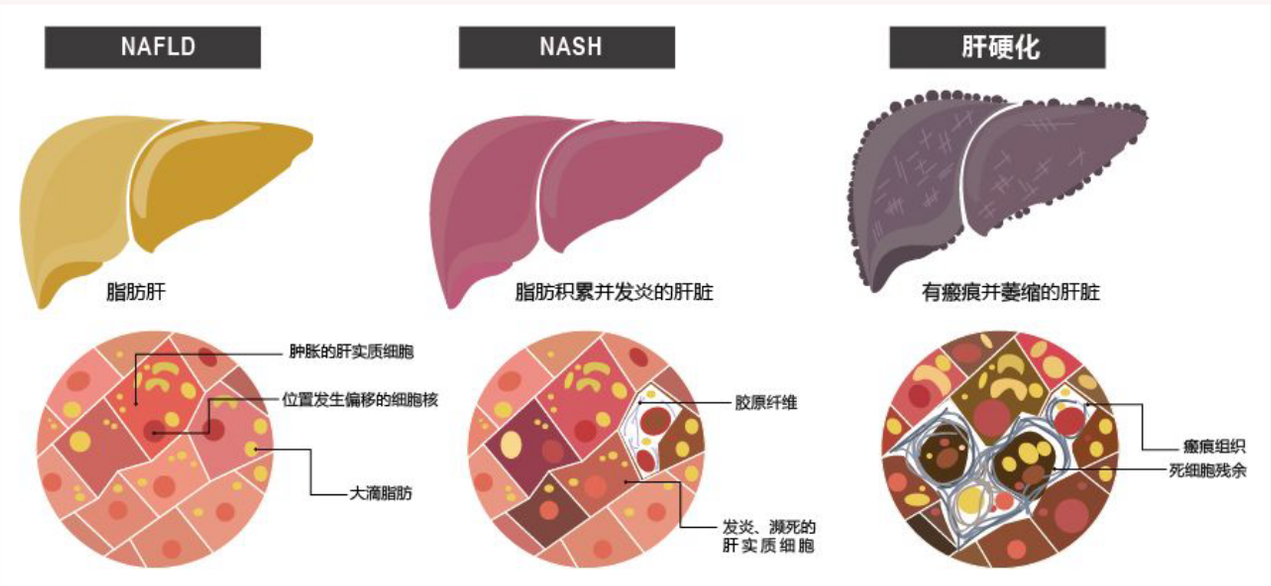
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脂肪肝的中醫治療
(Management of Fatty Liver with Chinese Medicine)

劉昭勁博士 香港中文大學香港中西醫結合醫學研究所專業顧問，註冊中醫師

非酒精性脂肪性肝病（簡稱脂肪肝）是現時香港最常見的慢性肝病，約四分之一的成年人患有脂肪肝。單純脂肪肝的初期常沒有明顯症狀，超過一半患者的肝酵素正常，病情容易被忽視。脂肪肝同時與胰島素抵抗、2 型糖尿病、代謝綜合徵等密切相關。長期脂肪肝有機會形成脂肪性肝炎，容易進一步發展成肝纖維化、肝硬化及肝癌。

中醫角度認為，肝主疏泄，即負責調節全身氣的運動，須保持舒暢條達；脾主升清、運化，即脾負責將飲食的精微、津液上輸，轉化為氣血，繼而營養全身。脂肪肝的發病多因為肝失疏泄，脾失健運，痰、濁、瘀積於肝而引起。中醫診斷稱為「肝癖」，又名「肝痞」。



根據國內擬定的《肝癖（非酒精性脂肪性肝炎）診療方案》，可分為以下常見的辨證分型：

	常見症狀	治法
1. 肝鬱脾虛、痰濕阻滯	肝區不適，易疲倦，頭身困重，嗜臥乏力，胸脘痞悶，厭食油膩，口黏不渴，便稀不爽，尿黃。舌苔白膩，脈滑有力	疏肝健脾，化濕活血
2. 肝膽濕熱、痰阻血瘀	肝脅脹痛，觸痛明顯而拒按，或牽引肩背，伴納呆噁心，厭食油膩，口乾口苦，腹脹少尿，或有黃疸。舌苔黃膩，脈弦滑	化痰活血，祛濕清熱
3. 肝陰不足、濕鬱血瘀	肝區不適，脅肋隱痛，甚至脅下腫塊，綿綿不已，遇勞加重，口乾咽燥，心中煩熱，兩目乾澀，頭暈目眩，易疲倦。舌質紫暗有瘀斑瘀點，脈弦細數	祛濕化瘀，滋補肝陰

中醫進行臨床診治時會透過望聞問切了解個別患者病情，參考西醫檢查結果，針對患者肝氣鬱滯、肝膽濕熱、肝陰不足、脾胃虛弱、痰濕阻滯、氣滯血瘀等不同的情況，設計合適的個體化治療方案。

研究顯示，連續中醫治療可有助改善患者脅肋脹痛、腹脹、胃脘脹悶、疲倦乏力、食慾不振、噁心、口乾口苦、大便異常等各種臨床症狀，並可改善肝功能，調節血糖、血脂水平，預防及改善早期肝纖維化及肝硬化。

治療以外，患者日常須注意改變不良生活方式，調整飲食結構，堅持足夠帶氧運動。研究顯示，持續以上生活方式的改變，已經可以一定程度上改善肝功能和血糖、血脂水平，如同時配合中醫治療，效果更為明顯。

為預防肝病進一步發展的可能，脂肪肝患者應該重視日常的病情監控並配合針對性的中西醫治療。針對脂肪肝的理想中西醫配合治療，應該一方面有西醫的診治及定期檢查，另一方面給予合適的中醫治療，調整臟腑功能，保護肝功能，避免慢性脂肪性肝炎引起的肝臟損傷，預防肝纖維化、肝硬化及肝癌的發生和發展。

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Nutritional therapy for nonalcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is a metabolic stress-related liver disease, characterized by excess fat in the liver in the absence of substantial alcohol consumption. Dietary modification, which is a key modifiable risk factor, and increase in physical activity to achieve gradual weight reduction are the mainstay of the treatment of NAFLD.

Weight management

The American Association for the Study of Liver Diseases (AASLD) recommends weight loss of at least 3-5% of body weight to ameliorate steatosis. A greater weight loss of 7-10% is required in order to lead to significant improvement in liver histology in patients with non-alcoholic steatohepatitis (NASH).

In order to achieve gradual and sustained weight loss, a caloric-restricted diet is recommended. There is no robust evidence supporting a particular composition of weight reduction diet unique for NAFLD patients. A meta-analysis found that neither the low carbohydrate nor low fat diet is superior on ameliorating liver fat or transaminases levels in NAFLD [9]. Very low calories diets are generally not recommended as they may be associated with adverse side-effects related to nutrients deficiency. On the other hand, the ketogenic diet, characterized by very low carbohydrate intake (5 to 10% of daily energy intake or 20 to 50g/day in a 2000 kcal per day diet) [10], may have favorable effects on body weight and intrahepatic triglycerides in individuals with obesity and NAFLD. Nevertheless, this high fat dietary regimen may increase LDL-cholesterol levels, and thus, large-scale, long-term intervention trials are needed to prove safety and efficacy of the ketogenic diet in NAFLD.

Mediterranean diet

The traditional Mediterranean diet (MedDiet) is characterized by high consumption of olive oil, legumes, cereals as whole grains, fruits and vegetables, moderate to high consumption of fish, moderate consumption of dairy products and wine, low consumption of meat and meat products [9]. Numerous interventional and observational studies suggest that the MedDiet may be beneficial on body weight, insulin sensitivity and hepatic steatosis and fibrosis, although there is no clear evidence in lowering the likelihood of having NAFLD. Since the benefits of MedDiet in lowering the risk of cardiovascular disease and the development of diabetes, which are conditions that share common etiological factors with NAFLD, are well established, the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline advises the MedDiet to improve steatosis and insulin sensitivity [2].

Influence of macronutrients on NAFLD

Excessive intakes of either carbohydrate or fat may promote the development of NAFLD. It is also probable that specific carbohydrates and fatty acids are more prone to induce or improve NAFLD.

Carbohydrate

People are consuming more highly processed food such as candy, syrups and soft drinks which are rich in simple carbohydrates nowadays. Studies have shown that a high consumption of fructose (e.g. soft drinks that are sweetened with fructose and juices in high-fructose corn syrup) results in insulin resistance, stimulates lipogenesis and triglycerides synthesis, which may lead to the development of NAFLD. Hence, these processed foods, which are of little nutritional benefits and may also lead to weight gain, should be avoided.

Fat

Saturated fatty acids (SFAs) have adverse effects on lipid and glucose homeostasis, which in turn worsen the progression of metabolic syndrome and possibly NAFLD. On the contrary, a positive correlation between monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) with NAFLD is found. Thus, it is advised to replace SFAs with PUFAs, especially long-chain omega-3, and MUFAs, and use them moderately. Major food sources of MUFAs include olive oil, canola oil, peanut oil, avocado and nuts whereas food sources of PUFAs, omega 3 fatty acids in particular, include salmon, mackerel, cod, halibut, oyster, mussels, walnuts and flaxseed oil. Until further data regarding the efficacy are available, omega-3 fatty acids supplementation is not recommended to treat NAFLD.

Influence of micronutrients on NAFLD

Vitamin E

Vitamin E is an anti-oxidant present in a variety of food such as vegetable oil and nuts. The results in the efficacy of vitamin E to ameliorate biochemical and/or histological abnormalities of NASH are heterogeneous. The AASLD recommends vitamin E (800 IU/day) to be prescribed to non-diabetic NASH adults for the improvement of liver enzymes and histology. Until further data supporting its efficacy is available, vitamin E is not recommended to treat NASH in patients with diabetes, NAFLD without liver biopsy, NASH cirrhosis or cyptogenic cirrhosis. It should also be noted that in a large RCT published in 2011, vitamin E administered at a dose of 400 IU/day was associated with a modest increase in the risk of prostate cancer. Risks and benefits should be discussed with each patient before starting supplementation.

Coffee

A systemic review reported that coffee consumption was inversely related to the severity of steatohepatitis in patients with NAFLD. These data suggested a potential protective effect of coffee on NAFLD, yet cause and effect could not be determined. As such, routine prescription of coffee is not recommended, but consumption within doses of ≤400mg /day (up to ~ 4 cups) may be allowed.

In conclusion, diet and nutrients can affect the pathophysiology of NAFLD. Achieving weight loss for overweight / obese NAFLD patients via dietary and lifestyle modifications, replacing SFAs with MUFAs and omega-3 fatty acids, and reducing intakes of soft drinks are the recommended treatments for NAFLD.

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沿途有你

林綺清 聖母醫院 糖尿科護士

眼前的陳先生，腹部腫脹，四肢纖細，皮膚黃疸，行動緩慢。他因肝癌引致腹水，不時需要進行抽腹水。現在定期回到糖尿中心接受糖尿控制教育。

回想大約 4 年前，陳先生因為肝硬化及肝功能轉差，原本用口服降糖藥物控制糖尿病，因而轉用胰島素。我們第一次見面就是教他學習胰島素注射。初期的方案是減少口服糖尿藥物，如容易引致血糖過低等的磺胺尿素劑等，並逐漸用胰島素取代口服藥物。

尤記得陳先生當時大約 50 多歲，仍需要上班，雖然只是文職工作，但是十分担心每日一次注射會影響工作及未能順利做到 60 歲退休之齡而影響退休福利。

經過糖尿科護士詳盡解釋低血糖狀況，教導處理低血糖及預防，當時病情及治療方法，演練打針程序，經過他本人親身試練，順利開始使用胰島素生涯。

陳先生媽媽都有糖尿病，她過世前都曾經打過胰島素，技巧各方面都好快「上手」，但是他的血糖卻時高時低，據了解他用藥準成，但另一方面他的飲食習慣亦是危險因素，他喜愛食即食麵及薯片等高脂食物。雖然轉介營養師提供營養計劃及營養知識，以及糖尿科護士不厭其煩解釋高脂，除咗令體重增加脂肪飆升，更會引致代謝功能障碍相關的代謝性脂肪肝病（MAFLD，metabolic dysfunction-associated fatty liver disease），並將其定義為伴有超重、糖尿病和 / 或其他代謝危險因素的肝臟脂肪變化。

他本身並無飲酒或者胡亂服藥習慣，飲食習慣有可能是他最大危險因素。經過一輪不同專業人士講解教育後，他已經減少進食高脂食物，同時已經純熟地運用胰島素注射技巧，及有定期血糖監察。糖尿科護士教育亦暫告一段落。

陳先生肝臟隨著歲月流逝亦逐漸變差，需要逐漸減少口服降糖藥物，增加胰島素劑量，原本一針長效胰島素，變成一針長效再加速效。隨着肝癌情況轉壞，體力下降，腹水嚴重，陳先生現在已經提早退休。家中經濟負擔，現由妻子及已成年兒子維持。

他經常進出醫院，通常入院就為了「抽取腹水」，因為肝硬化後，血流進入門脈的阻力增大，造成肝門脈高壓，全身性的血管擴張物質會增加，使得腎臟末端微小動脈擴張，「腎素─血管收縮素─醛固酮系統」被活化後，強化了腎小管的留鹽、留水功能，造成全身水份過多；另一方面，門脈高壓也會造成腹腔內的小血管壓力增加，造成水份容易外滲，進而形成腹水。

陳先生開始會覺得腹脹，隨著水量的增加壓迫到腹腔內的器官，會產生食慾下降、胃口不好等情形，有時會因為惡性腹水造成腸子蠕動變差，出現麻痺性腸阻塞，繼而產生嘔吐症狀。當腫瘤壓迫血管，因而影響全身性血管循環，便會導致下肢的水腫。

胃口不佳，亦影響血糖穩定，若未能如常進食，便要教導病人停用速效胰島素，若情況嚴重時，長效胰島素劑量都要減少，避免血糖過低。由於陳先生早已喪失低血糖警兆，當發現暈倒或者胡言亂語時，便可能已經是很危險低糖狀況。陳先生都表示太太及兒子對其身體狀況表示担心。

糖尿科護士亦再三提醒他們不要輕視處理低血糖外，依時用餐、進食足夠碳水化合物以及定時監察血糖情況，都是非常重要。當然若有水腫情況出現，盡快求醫，一旦胃口減少，減用速效胰島素，有需要時，可致電糖尿科中心，與護士商討胰島素劑量的改變。

Upcoming Professional Meetings

Course / Conference	Date / Duration	Venue
The 2023 American Diabetes Association (ADA) Clinical Update Conference https://professional.diabetes.org/meeting/local-continuing-education-activities/2023-clinical-update-conference	10 - 12th February, 2023	the Westin Tampa Waterside Hotel and virtually
13th Emirates Diabetes & Endocrine Congress 2023 https://www.edec-uae.com	11 - 13th February, 2023	Dubai International Convention & Exhibition Center
Detection and Prevention of Insulin-induced Lipohypertrophy Part 3: Application of Pointof Care Ultrasound to Detect Insulin-induced Lipohypertrophy On-site Workshop	25th March, 2023	DM centre, 4/F, Ambulatory Centre Block, Tseung Kwan O Hospital
The 15th AHKDN Annual General Meeting & Symposium	24th June, 2023	Crystal Ballroom 2/F, CityView Hostel
the American Diabetes Association' s 83rd Scientific Sessions	23-26th June, 2023	San Diego Convention Center
59th Annual Meeting of European Association for The Study of Diabetes (EASD) https://www.easd.org/annual-meeting/easd-2023.htmlhttps://www.easd.org/annual-meeting/easd-2023.html	3-6th October, 2023	Hamburg Exhibition and Congress