BASIC OBESITY MANAGEMENT ACCREDITATION 3
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Unit No. 8

OBESITY IN MASLD AND PCOS

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ABSTRACT

Obesity is on the rise and is fast becoming a major modifiable risk factor responsible for leading non-communicable diseases and deaths. Increasingly, primary care physicians will be exposed to patients with obesity-related diseases. Beyond type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD) and polycystic ovarian syndrome (PCOS) are two other conditions that are common. In this article, we explore the underlying associations of MASLD and PCOS with insulin resistance and offer some practical advice on screening and management of both conditions.

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Keywords: Obesity, MASLD, PCOS, Insulin resistance

INTRODUCTION

Obesity is on the rise and fast becoming a major modifiable risk factor responsible for leading non-communicable diseases and deaths. The World Health Organisation (WHO) estimated that almost 1 billion adults were living with obesity in 2020. These numbers are predicted to double by 2035.[1] In Singapore, based on the 2019/2020 National Population Health Survey, the crude prevalence of overweight was 28.8 percent, and that of obesity was 10.5 percent amongst adult residents aged 18 to 74.[2] As a result, obesity-associated complications are also on the rise.

In this article, we will explore two common obesity associated conditions – metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), and polycystic ovarian syndrome (PCOS). We will focus on the association of obesity with these conditions, as well as the treatment of obesity in relation to them. For specific management of other aspects of PCOS, readers will be directed to the recommended reading list found at the end of the article.

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OVERVIEW OF MASLD

The nomenclature of non-alcoholic fatty liver disease (NAFLD) underwent a consensus change in 2023.[3] Steatotic liver disease (SLD) is the new over-arching term that includes the various aetiologies of steatosis. SLD in the presence of at least 1 of 5 cardiometabolic criteria and without significant levels of average daily alcohol consumption (defined as <30 g for males and <20 g for females), is now termed as metabolic dysfunction-associated steatotic liver disease (MASLD) (refer to **Table 1**). The new terminology was chosen to reflect a better understanding of the disease and to remove stigmatisation present in the old terminology. Histologically, steatotic liver disease is defined by the presence of hepatic steatosis in more than 5 percent of hepatocytes.[4] MASLD is estimated to affect 25 percent of adults, with an even higher prevalence of about 30-40 percent in South Asians. Twelve to 14 percent of persons with MASLD have a more aggressive form, known as Metabolic dysfunction-associated steatohepatitis (MASH, previously NASH), of which 20 percent can progress to advanced liver fibrosis, cirrhosis, or liver cancer.[5] MASH is now the most rapidly increasing cause of hepatocellular carcinoma.[6]

Table 1 Cardiometabolic criteria used in the diagnosis of MASLD[3]

At least 1 out of 5
BMI >/=25 kg/m^2 **OR** Waist circumference >94 cm (male), >80 cm (female) **OR** Ethnicity adjusted cut-offs
Fasting serum glucose >/=5.6 mmol/L **OR** 2-hour post-load glucose >/=7.8 mmol/L **OR** HbA1c >/=5.7% **OR** Type 2 diabetes **OR** Treatment for type 2 diabetes
Blood pressure >/=130/85 mmHg **OR** Antihypertensive drug treatment
Plasma triglycerides >/=1.7 mmol/L **OR** Lipid lowering treatment
Plasma HDL-cholesterol </=1.0 mmol/L (males), </=1.3 mmol/L (females) **OR** Lipid lowering treatment

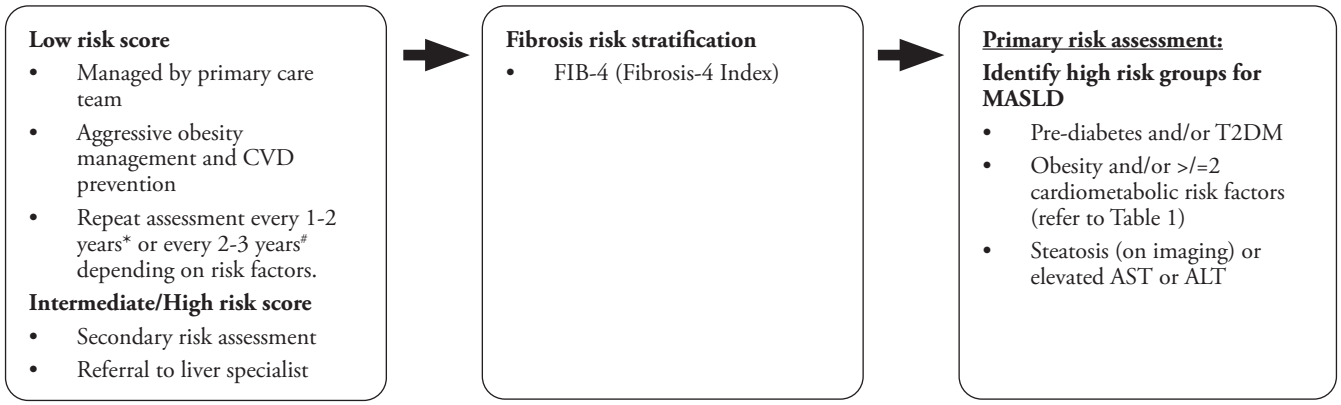
The key disease driver in MASLD is insulin resistance. As such, the prevalence of MASLD is increased two- to threefold in conditions such as obesity, T2DM, obstructive sleep apnea, and PCOS, with prevalence reaching as high as

50 percent in T2DM.[7] In addition, the risk of progression to advanced fibrosis is also higher in patients with T2DM. As the relationship between MASLD and T2DM is bidirectional, the presence of MASLD is also associated with at least a twofold increase in incident diabetes.[8]

MASLD is associated with an increased risk of cardiovascular disease, including atherosclerotic heart disease, heart failure, and arrhythmias. After advanced liver disease and hepatocellular carcinoma, cardiovascular events contribute significantly to associated morbidity. In an 18-year follow-up of MASLD patients, the hazard ratio of CVD event is 1.54 compared to controls.[9]

Development of fibrosis is a key predictor of liver-related outcomes. Screening high risk groups to identify early fibrosis and intervening early is crucial in preventing poor liver outcomes (refer to **Figure 1**).[10,11]

Figure 1: Management of MASLD in primary care



**Patients with >/=2 metabolic risk factors, presence of pre-DM/DM*
#Patients with <2 metabolic risk factors, absence of pre-DM/DM

OVERVIEW OF PCOS

PCOS is typically characterised by reproductive dysfunction (oligo-amenorrhea, subfertility) and hyperandrogenism (acne, hirsutism, male pattern alopecia, and biochemical hyperandrogenism). Although not a diagnostic criteria, metabolic dysfunction forms an important phenotype in this condition. For the diagnosis of PCOS, most local specialists would use the Rotterdam criteria, of which two out of three criteria of oligo-amenorrhea, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology must be met (refer to **Table 2**).[12]

Table 2: Rotterdam criteria, 2003 for diagnosis of PCOS

1. Clinical or biochemical evidence of excess androgen
   - Hirsutism, acne, androgenic alopecia
   - Elevated serum androgen level
2. Oligomenorrhea
   - Frequent bleeding at intervals <21 days, or infrequent bleeding >35 days
3. 3. Polycystic ovaries
   - Ovary containing 12 or more follicles measuring 2-9 mm, or an ovary with volume >10 ml on US

*Exclude thyroid disease, prolactin excess, and nonclassical congenital adrenal hyperplasia before making the diagnosis

The close link between PCOS and obesity is supported by epidemiological data, where up to 88 percent of women with PCOS are either overweight or obese, and further corroborated by genome-wide studies, that showed evidence for shared genetic variants between the two conditions. While PCOS is independently associated with insulin resistance, the co-occurrence of PCOS and obesity greatly increases the severity. PCOS also confers an increased risk for T2DM, OSA, dyslipidaemia, and MASLD. Even after adjusting for age and BMI, PCOS is associated with increased risk of steatohepatitis and fibrosis.[10,11]

There is improved understanding of this heterogenous condition, and PCOS is now understood to be a complex polygenic condition, with distinct phenotypes (reproductive or metabolic) being explained by cumulative effects of different variant genes. As such, the terminology "polycystic" may soon be a misnomer for this condition, since it is not a requirement for diagnosis, nor does it explain the pathophysiology of the condition.

Case Study 1

Miss A is a 38-year-old female who was recently diagnosed with type 2 diabetes. Her other medical history includes asthma, obesity, and irregular menstruation. Both her parents had type 2 diabetes diagnosed in their late 50s. Her mother had breast cancer and her maternal grandmother had stage 3 colon cancer. She worked as a freelance photographer and was married without children for the last eight years. She neither smoked nor took alcohol.

On examination, Miss A weighed 88 kg and was 1.58 m tall, with a BMI of 32.8kg/m^2. Her blood pressure was 138/100 mmHg. Her waist circumference was 92 cm. She had scanty fine upper lip hair. She did not appear cushingoid and there was no acanthosis nigricans. Other examination was normal.

Metabolic tests showed fasting blood glucose was 7.8 mmol/L, HbA1c 7.8 percent, total cholesterol 5.2 mmol/L, LDL-C 3.2 mmol/L, HDL-C 1.0 mmol/L, triglyceride 1.6 mmol/L. Liver function test showed ALT 99 IU/L, AST 88 IU/L. Creatinine was 42 umol/L. Thyroid function was normal.

Miss A was referred to the gastroenterologist in view of persistently elevated liver transaminases. A Fibroscan done revealed a fibrosis score of F2. She was then referred to the obesity clinic for further management.

Miss A was informed by her family physician that treating obesity is key to improving many aspects of her medical conditions. She shared that she had always been struggling with her weight since secondary school. In Secondary 1, she was already 60 kg. She gained more weight when she started working and was 85 kg at her peak. In her early twenties, she had taken Phentermine from her GP and lost 8 kg. She stopped it soon as she experienced insomnia and headaches while on the medication. Three years ago, upon diagnosis of T2DM, she signed up with a commercial package that included meal replacements and abdominal fat binder. She lost 4 kg over three months, which was about 5 percent of her usual weight.

She finds it increasingly difficult to juggle her busy work schedule and being conscious of her diet, and she also has no time for physical activities. While she is willing to consider medications, she is wary of their side effects. She considers surgery too "drastic" and will not consider it as well.

EVALUATION OF MASLD IN PRIMARY CARE CLINIC

In the primary care clinic, patients are often suspected to have MASLD due to presence of cardio-metabolic risk factors (refer to **Figure 1**), or incidentally identified as having fatty liver on imaging, or found to have elevated transaminitis on routine laboratory testing, and in the absence of other obvious aetiologies of steatotic liver disease. Unlike in a gastroenterology clinic, the prevalence of advanced liver disease is low in a primary care clinic. Hence, the primary objective of evaluation is to identify patients who remain at low risk of advanced fibrosis.

Liver transaminases alone are not accurate in identifying those at risk of fibrosis and MASH, since about a quarter of patients with MASLD and MASH have normal levels. Recently, the American College of Gastroenterology has considered lowering the true normal ALT range to 29 to 33 U/L for males, and 19 to 25 U/L for females.[13] Both these values are below the usual lab upper limits of normal. Liver ultrasound, though easily available, is not sensitive in picking up liver fat content below 12.5 percent.[14]

For primary risk assessment in the primary care setting, non-invasive testing such as FIB-4 is recommended due to its excellent negative predictive value. The fibrosis-4 index (FIB-4) has strong validation and is simple to apply in primary care clinics. It uses age, AST, ALT, and platelet count levels to calculate a score, where FIB-4 <1.3 denotes low risk. In patients above the age of 65, a cut-off of 2.0 should be used instead. FIB-4 should not be used in patients who are acutely ill, and it is less reliable in those below 35 years of age. Patients should be re-assessed periodically – every 1-2 years in those with pre-diabetes/diabetes or >/=2 metabolic risk factors, and every 2-3 years without the above features.[11,12]

Those with intermediate FIB-4 (1.3 to 2.67) should undergo secondary risk assessment. This may include vibration-controlled transient elastography (Fibroscan) or magnetic resonance elastography (MRE). If these are not available, the Enhanced Liver Fibrosis (ELF) test is approved for prognostication when advanced fibrosis is suspected. If secondary risks assessment still indicates intermediate to high risk of fibrosis, patients should be referred to specialty care.[11,12]

EVALUATION OF PCOS IN PRIMARY CARE CLINIC

PCOS is a heterogenous condition and patients may present to the clinic for various reasons, such as reproductive symptoms, hyperandrogenic concerns, or metabolic syndrome. The diagnosis can usually be accomplished with a thorough history and physical examination, with or without ultrasonography. Look out for clinical features of hirsutism, acne, and male pattern hair loss. Take note to exclude virilisation, and other disorders, such as thyroid dysfunction, prolactin excess, and rare causes such as androgen-secreting tumours, non-classical congenital adrenal hyperplasia, and Cushing's syndrome. Basic blood tests should include a baseline metabolic screen for diabetes and hyperlipidaemia. A biochemical test for hyperandrogenism may be obtained through the measurement of total testosterone levels and sex hormone binding globulin (SHBG) to calculate the free androgen index.

In PCOS, the goals of care would differ depending on each individual's symptoms and priorities. These could include ensuring regular periods, relieving symptoms of hyperandrogenism, or addressing fertility concerns. Early detection and treatment of metabolic syndrome is an important management point in all patients with PCOS. Readers are directed to the reading list on further details on management of PCOS.

TREATING OBESITY TO MANAGE MASLD AND PCOS

Insulin resistance is a strong pathophysiological driver in both MASLD and PCOS. As such, treatment should be aimed at improving insulin resistance and metabolic risks. There is evidence that varying amounts of weight loss are

necessary to improve different obesity-related comorbidities. Steatosis can improve with 5 percent weight loss, but weight loss of more than 10 percent is required for improvement in MASH or fibrosis score. In PCOS, as little as 2-5 percent of weight loss may already result in improvement of symptoms.[15]

Lifestyle habits form the foundation of obesity treatment. This includes medical nutritional therapy, physical activity and exercise, sleep hygiene, and stress management. Medical nutrition therapy is central to obesity treatment. There are numerous dietary strategies available – calorie-restricted diet, specific macronutrient restriction, and Mediterranean diet, to name a few. The ones that have recently garnered a lot of interest lately are intermittent fasting and ketogenic diet. Intermittent fasting is performed in a wide variety of methods. Some practise restriction in the number of hours of eating (e.g., 16:8), some restrict the number of days that they comply with a meal plan (e.g., 5:2), and some practise intermittent fasting with a combination of both.

In terms of showing improvement in metabolic markers and insulin sensitivity, early time-restricted feeding (eTRF), by restricting eating times to the early part of the day to follow our body's circadian rhythm, and to limit eating times to not more than 10 hours in the day, has been shown to be beneficial.[16,17] Distributing the calories such that most calories are consumed during breakfast, and least during dinner, has been shown to improve weight loss and glucose levels, lead to lower overall ghrelin levels, and better satiety.[18] Very low calorie ketogenic diet, usually achieved with meal replacements, have been shown to be effective in the short term, with the accumulation of low levels of ketone bodies being responsible for the suppression of hunger via lowering ghrelin levels.[19]

Specific to MASLD, high fructose cane syrup (HFCS), refined carbohydrates and saturated fat have been identified as the main culprits. It is crucial to limit the intake of these foods. A useful acronym practised by the authors is the 3 "F"s and 3 "G"s diet – to avoid **f**ructose (sugared or flavoured drinks, fruit juices), **f**uss-free food (referring to instant food – frozen, canned, or highly processed food generally packed with saturated fats), **f**ast "junk" food; and to encourage good quality **g**rains, **g**reens, **g**ood (lean) meat or protein.

Ultimately, long-term adherence to a healthy eating plan that can fulfil an individual's values and preferences, while at the same time resulting in caloric deficit and meeting their nutritional needs, is key.

Physical activity is positively related to insulin sensitivity. Regular exercises have been shown to improve insulin resistance, even in the absence of weight loss. For weight loss, the exercise volume recommended is 250 to 300 minutes of moderate exercise weekly, while for weight maintenance, the volume recommended is 150 minutes weekly. These benefits are linked to adherence and intensity.

PHARMACOTHERAPY FOR MASLD AND PCOS

Similar to managing any chronic disease, pharmacotherapy plays a role in obesity management. Most of the approved medications for obesity target the hormonal adaptation that occurs with weight changes. GLP1 agonism, dual agonism (GLP and GIP), and now triple agonism (GLP, GIP and glucagon) take centre-stage in the rapidly developing pharmacotherapy scene.

Although there are no drugs currently approved for use in MASLD and MASH, some medications, including those approved for obesity and type 2 diabetes, have shown benefits in improving liver biomarkers, MASH resolution, and fibrosis staging, and may be considered in specific situations. A meta-analysis that included only randomised controlled trials of histologically proven MASLD was conducted to evaluate the efficacy of different pharmacological approaches found semaglutide, liraglutide, pioglitazone plus vitamin E, and pioglitazone alone to be superior to placebo at MASH reolution.[20] In achieving one or more stages of fibrosis improvement, only pioglitazone and vitamin E were significantly better than placebo. The above-mentioned pharmacotherapies and relevant evidence are summarised in **Table 3** below.

In patients with PCOS, metformin has been shown to improve menstrual regularity, although the weight loss effects are often modest. Metformin should not replace intensive lifestyle modification in treating obesity and metabolic derangements.

BARIATRIC SURGERY

Bariatric surgery can be considered as a treatment option for patients with BMI >32.5 kg/m^2 in the presence of obesity-associated complications. It is well established that bariatric surgery induces sustained weight loss for up to 20 years, reduces mortality rates, and increases life expectancy compared to usual obesity management.[31,32] Bariatric surgery is 3.6 times more likely to result in MASH resolution and 1.7 times more likely to result in improvement of at least one stage of liver fibrosis compared to usual care.[33] Caution against surgery is necessary in those with advanced fibrosis or cirrhosis, as liver decompensation can occur. In patients desiring fertility, bariatric surgery is associated with improved rates of fertility, gestational diabetes, hypertensive disorders, and obstetric related complications.[34,35] However, there is a small increased risk of small-for-gestation age babies.[36] Other benefits of bariatric surgery include improved diabetes remission rates, reduction in micro- and macrovascular complications of diabetes, sleep apnea improvement, and physical, social, and emotional quotients.[37]

Bariatric surgery is permanent and the decision to undergo it should involve a multi-disciplinary team consisting of a bariatric surgeon, an endocrinologist, dietitians, a psychologist, and a physiotherapist.

Table 3: Summary of pharmacotherapies that can be considered in the management of MASLD

	MOA	Dose	Evidence	Side effects	CVD benefit	Ref
Liraglutide	97% structural homology with endogenous GLP1. Incretin effect. Slows gastric emptying. Acts on GLP1 receptors in hypothalamus to promote satiety	SC injection (DM) 0.6 to 1.8 mg daily (Obesity) 0.6 to 3.0 mg daily	+ALT, AST, steatosis (dose dependent) +FBG, HBA1c, TG, TC, LDL-C, BMI	GI side effects, pancreatitis, cholecystitis	Yes	21, 22, 23
Semaglutide		SC injection (Liver trials) 0.1-0.4 mg daily (DM) 0.5 – 1.0 mg weekly (Obesity) – 2.4 mg weekly	+NASH resolution ? Fibrosis		Yes	21, 24
Tirzepetide	GLP-GIP dual agonism	SC injection 5-15mg weekly	+ALT/AST/Procollagen-III/Adiponectin Lack of histological evidence	GI side effects, cholecystitis	Awaiting results	25
Pioglitazone	PPAR-gamma receptor	Oral 30-45 mg daily	+ALT/AST, steatosis, lobular inflammation, ballooning necrosis, NASH resolution, fibrosis -BMI	Weight gain, edema, bone loss, bladder cancer	Yes	21, 26
Vitamin E	Antioxidant properties	Oral 400 iu daily	+ALT/AST, steatosis, ballooning necrosis ? Fibrosis ? BMI	Increased risk of bleeding, prostate cancer	No	21, 27
SGLT2-inhibitors	Reduces renal tubular glucose reabsorption	Based on individual dosing	+ALT/AST/Non-invasive markers of liver fibrosis and liver fat	Urinary frequency, UTI	Yes	28, 29, 30

+: positive evidence

-: negative evidence

?: inconclusive evidence

Case Study 2

Patient A was under the care of a multi-disciplinary team. She had cut out sweetened beverages as well as snacking on biscuits. She adhered to an early time-restricted feeding between 10 am and 6 pm. Her diet was based on a Mediterranean concept with a focus on whole grains and vegetables, good fat such as nuts, and avoiding red meat. She joined a neighbourhood running club and, on most weeks, was able to clock 150 minutes weekly. She stopped going out for supper and ensured that she got about seven hours of sleep daily. After counselling by the doctor, she was also started on subcutaneous injection of Semaglutide 0.5 mg weekly. In four months, she lost 10 percent of her weight. She felt more energetic and confident about herself. Her periods have become regular. Her husband commented that she is no longer snoring in her sleep. At her most recent follow-up, her BP was 118/70 mmHg, and her HbA1c and liver transaminases were all in the normal range.

CONCLUSION

MASLD and PCOS are both obesity-related diseases that have close links with insulin resistance. In the primary care clinics, one should consider MASLD in patients at high cardio-metabolic risks. Primary risk assessment using FIB-4 can identify patients who remain at low risk of advanced fibrosis and can continue to be managed in primary care clinics. In patients with PCOS, the aims of treatment must be individualised to the priorities of the patient. Obesity treatment is central to managing these two conditions. A multi-disciplinary approach should be utilised, with good foundational lifestyle habits taking centre stage. In recognition that obesity is a chronic and relapsing condition, pharmacotherapy should be prescribed along with medical nutrition therapy. Bariatric surgery can be recommended appropriately.

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LEARNING POINTS

- **Persons with T2DM have a higher prevalence of MASLD, as well as a higher likelihood of progression to liver fibrosis.**
- **PCOS is associated with metabolic complications as well as higher risks of endometrium cancer.**
- **Limiting refined/highly processed carbohydrates and trans/saturated fat intake is crucial in the management of MASLD.**
- **Consider the use of pharmacotherapy and surgery appropriately in the management of MASLD, PCOS, and T2DM.**