https://doi.org/10.33591/sfp.48.7.u8

Unit No. 8

OBESITY IN NAFLD AND PCOS

Dr Lee Yingshan, Dr Kalaiyarasi Kaliyaperumal

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, non -alcoholic fatty liver disease (NAFLD) and polycystic ovarian syndrome (PCOS) are two other conditions that are common, yet also often overlooked. In this article, we explore the underlying associations of NAFLD and PCOS with insulin resistance, and offer some practical advice on screening and management of both conditions.

SFP2022; 48(7): 48-53

Keywords: Obesity, Fatty liver, PCOS, Insulin resistance

INTRODUCTION

Obesity is on the rise and fast becoming a major modifiable risk factor responsible for leading noncommunicable diseases and deaths. The World Health Organisation (WHO) estimated that there were about 650 million adults living with obesity in 2016.[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 obesity associated conditions – 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.

Dr Lee Yingshan
Consultant
Department of Endocrinology, Tan Tock Seng Hospital

DR KALAIYARASI KALIYAPERUMAL
Consultant
Department of Gastroenterology, Tan Tock Seng Hospital

OVERVIEW OF NAFLD AND PCOS

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis in more than 5 percent of hepatocytes, in the absence of ongoing or recent alcoholic consumption and other known causes of liver disease. It is estimated to affect 25 percent of adults, with an even higher prevalence of about 30-40 percent in South Asians.[3] Twelve to 14 percent of persons with NAFLD have a more aggressive form, known as non-alcoholic steatohepatitis (NASH), of which 20 percent can progress to advanced liver fibrosis, cirrhosis, or liver cancer. Non-alcoholic steatohepatitis (NASH) is now the third most common cause of liver cirrhosis and liver cancer.

The key disease driver in NAFLD is insulin resistance. As such, the prevalence of NAFLD is increased by two- to threefold in patients with obesity, T2DM, and PCOS, with prevalence reaching as high as 50 percent in T2DM. In addition, the risk of progression to advanced fibrosis is also higher in these populations. Persons with NAFLD have increased carotid intima-media thickness compared to those without NAFLD, and hence it is not surprising that increased cardiovascular disease is a major cause of morbidity and mortality in this group of patients.

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**).[3]

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 1**).[4]

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 NAFLD. Large cohort studies demonstrated that metabolic syndrome is more prevalent in the subgroup of PCOS that displays both hyperandrogenism and reproductive features, compared to those who only display a single PCOS phenotype.[5,6]

Figure 1: Management of NAFLD in primary care

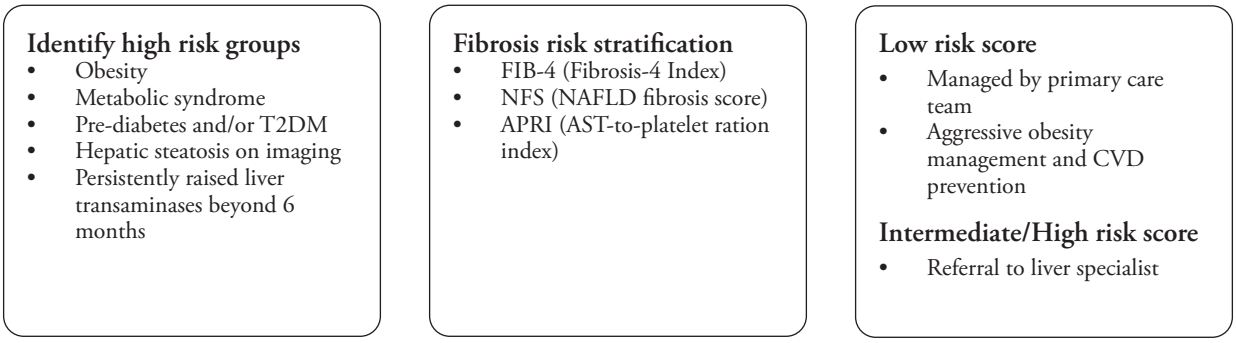

Table 1: Rotterdam criteria, 2003 for diagnosis of PCOS

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. 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*

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 conditions include 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 NAFLD IN PRIMARY CARE CLINIC

In the primary care clinic, after the initial step of identifying patients who are at "high risk" of harbouring NAFLD, the subsequent steps should be aimed at identifying a subset who may be at risk of advanced fibrosis. While liver biopsy is the "gold standard" for diagnosis of liver fibrosis, it is impractical. Other methods used for risk stratification include simple blood tests, radiological tests, and fibrosis assessment tools. Liver transaminases alone are not accurate in identifying those at risk of fibrosis and NASH, since about a quarter of patients with NAFLD and NASH 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. Both these values are below the usual lab upper limits of normal. Liver ultrasound is easily available but takes up resources and cost and is not sensitive in picking up liver fat content <20 percent.

For primary care physicians, the use of fibrosis prediction calculations is recommended. The value of fibrosis calculators is that they generally have good specificity and negative predictive value to rule out advanced fibrosis. The fibrosis-4 index (FIB-4) has been the most validated and is simple to use. Those with intermediate and high-risk FIB-4 scores should be referred to a gastroenterologist for further work-up. When referred to the specialist clinic, further lab tests such as vibration-controlled transient elastography (Fibroscan) may be performed to assess liver stiffness and identify significant fibrosis.

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 through 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 NAFLD AND PCOS

Insulin resistance is a strong pathophysiological driver in both NAFLD and PCOS. As such, treatment should be aimed at improving insulin resistance and should be metabolically beneficial. There is evidence that varying amounts of weight loss is necessary to improve different obesity related comorbidities. For NAFLD or NASH, weight loss of 5-15 percent should be targeted, whereas in PCOS, weight loss of as little as 3-5 percent may already result in improvement of symptoms.

Lifestyle and daily habits form the foundation of obesity treatment – this includes medical nutritional therapy, physical activity level, sleep, and stress management. Medical nutrition therapy is central to obesity treatment. There are numerous dietary plans available; the ones that have recently garnered a lot of interest lately are intermittent fasting and keto-diet. Intermittent fasting is performed in a wide variety of methods. Some practice restriction in the number of hours of feeding (e.g., 16:8), some restrict the number of days that they comply with a meal plan (e.g., 5:2), and some practice 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.[9,10] Distributing the calories such that most calories are consumed during breakfast, and least during dinner, has been shown to improve weight loss, glucose levels, and lead to lower overall ghrelin levels and better satiety.[11] 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.[12]

Specific to NAFLD, high fructose cane syrup (HFCS) and saturated fat have been identified as the main culprits. It is crucial to limit refined and highly processed carbohydrates, as well as saturated and trans-fat. A useful acronym practised by the authors is the 3 "F"s and 3 "G"s – 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 **g**rains, **g**reens, **g**ood (lean) meat or protein.

Ultimately, long-term adherence to a healthy eating pattern that can fulfil an individual's values and preferences, while at the same time meeting their nutritional needs and treatment goals, 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 OBESITY

Due to the metabolic weight adaptation that occurs with any amount of weight loss, pharmacotherapy plays a role in both enhancing weight loss and avoiding weight regain.

Both daily liraglutide (Saxenda) 3.0 mg and weekly semaglutide (Wygovy) 2.4 mg are GLP-1 receptor agonists (GLP-1 RA) approved for obesity management. Currently, Wygovy is not available in Singapore. Semaglutide in the Ozempic preparation is available locally for patients with T2DM.

GLP-1 RAs have become a very popular option in obesity and T2DM management, because of robust clinical benefits – weight loss, glycaemic control, and cardiometabolic benefits. Studies have suggested that GLP1-RAs normalise liver transferase levels and reduce liver fat on imaging. A recent RCT comparing different doses of semaglutide in patients with NASH showed that treatment resulted in higher percentage of steatohepatitis resolution. These results are largely driven by weight loss.[12]

Two other drugs worth mentioning are SGLT2 inhibitors and pioglitazone. Studies show the potential of SGLT2 inhibitors in patients with both T2DM and NAFLD in reducing hepatic steatosis. Pioglitazone is a PPAR-gamma receptor that improves insulin resistance through targeting adipose tissue and improving lipid storage/redistribution. It can improve liver fat and has benefits in NASH resolution. However, pioglitazone is associated with dose-dependent weight gain and edema and should be used with caution in those with heart failure.[3,13]

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 FOR OBESITY

Bariatric surgery can be considered for patients with BMI >32.5kg/m^2 and the presence of obesity-associated complications. It is well established that bariatric surgery induces sustained weight loss, and can improve multiple comorbidities, leading to improved MACE. Bariatric surgery has been shown to improve fertility rates, and in NAFLD, it has been shown to improve steatosis. Caution against surgery is necessary in those with advanced fibrosis or cirrhosis, as liver decompensation can occur. The decision to recommend bariatric surgery should involve a multi-disciplinary team consisting of a bariatric surgeon, an endocrinologist, dietitians, a psychologist, and a physiotherapist.

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 0.5mg 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

NAFLD and PCOS are both obesity-related diseases that have close links with insulin resistance. In patients with high risk factors, early screening using fibrosis calculations can help to risk stratify those at intermediate to high risk of developing advanced liver fibrosis. 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.

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. (n.d.). Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. Epidemiology & Disease Control Division and Policy, R. &. (n.d.). NATIONAL POPULATION HEALTH SURVEY 2020.
3. 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 May;28(5):528-562. doi: 10.1016/j.eprac.2022.03.010. PMID: 35569886.
4. Teoh WS, Ramu D, Indran IR, Chua MWJ, Thu WPP, Yong EL. Diagnosis and management of polycystic ovary syndrome: Perspectives of clinicians in Singapore. Ann Acad Med Singap. 2022 Apr;51(4):204-212. doi: 10.47102/annals-acadmedsg.2021474. PMID: 35506403.
5. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice

guideline. J Clin Endocrinol Metab. 2013 Dec;98(12):4565-92. doi: 10.1210/jc.2013-2350. Epub 2013 Oct 22. Erratum in: J Clin Endocrinol Metab. 2021 May 13;106(6):e2462. PMID: 24151290; PMCID: PMC5399492.
6. Barber TM, Franks S. Obesity and polycystic ovary syndrome. Clin Endocrinol (Oxf). 2021 Oct;95(4):531-541. doi: 10.1111/cen.14421. Epub 2021 Jan 31. PMID: 33460482.
7. Wharton S, Lau DCW, Vallis M, Sharma AM, Biertho L, Campbell-Scherer D, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020 Aug 4;192(31):E875-E891. doi: 10.1503/cmaj.191707. PMID: 32753461; PMCID: PMC7828878.
8. Williams T, Mortada R, Porter S. Diagnosis and Treatment of Polycystic Ovary Syndrome. Am Fam Physician. 2016 Jul 15;94(2):106-13. PMID: 27419327.
9. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab. 2018 Jun 5;27(6):1212-1221.e3. doi: 10.1016/j.cmet.2018.04.010. Epub 2018 May 10. PMID: 29754952; PMCID: PMC5990470.
10. Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, Shoghi A, et al. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. Cell Metab. 2020 Jan 7;31(1):92-104.e5. doi: 10.1016/j.cmet.2019.11.004. Epub 2019 Dec 5. PMID: 31813824; PMCID: PMC6953486.
11. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. Obesity (Silver Spring). 2013 Dec;21(12):2504-12. doi: 10.1002/oby.20460. Epub 2013 Jul 2. PMID: 23512957.
12. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021 Mar 25;384(12):1113-1124. doi: 10.1056/NEJMoa2028395. Epub 2020 Nov 13. PMID: 33185364.
13. Karjoo S, Auriemma A, Fraker T, Bays HE. Nonalcoholic fatty liver disease and obesity: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. Obesity Pillars. 2022;3. doi:doi.org/10.1016/j.obpill.2022.100027

RECOMMENDED READING LIST

1. Managing polycystic ovary syndrome in primary care
Lau ACY, How CH, King TFJ
SMJ 2018; 59(11) 597-571
Doi: 10.11622/smedj.2018135
2. Obesity in adults: a clinical practice guideline
Wharton S, Lau DCW, Sharma AM, Biertho L, Campbell-Scherer D, Adamo K et al.
CMAJ 2020 August 4;192:E875-91.
doi: 10.1503/cmaj.19170

LEARNING POINTS

- **Persons with T2DM have a higher prevalence of NAFLD, 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 are crucial in the management of NAFLD.**
- **Consider the use of GLP1-RAs, SGLT2 inhibitors, and Pioglitazone appropriately in the management of NAFLD and T2DM.**