Title: Obesity and Liver Disease in Primary Care

Jiawei Li[a] and Jonathan L. Temple[b], Vi Nguyen[a], Louise Cremonesini[c], Jude A. Oben[ad]

[a] Institute for Liver and Digestive Health, University College London, London, United Kingdom

[b] Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom

[c]Faculty of Health and Society, University of Northampton, Northampton, United Kingdom.

[d]Department of Gastroenterology and Hepatology, Guy's and St Thomas' Hospital, NHS Foundation Trust, London, United Kingdom.

Introduction

Obesity has been described as a pandemic of the 21st century. Nearly two thirds of the adult UK population are now either overweight or obese. Levels of childhood obesity have also risen dramatically over recent decades and continue to rise. In 1995, one in every ten children in the UK aged 2-15yrs old was obese. Now, one child in every six is obese. [1]

Obesity is a chronic metabolic disease that arises from the complex interplay of numerous environmental, behavioural and genetic influences. It is characterised by excessive amounts of adipose tissue (fat), either subcutaneously (under the skin) or viscerally (around the internal organs) and is strongly associated with an increased risk of heart disease, stroke, type II diabetes, as well as numerous psychiatric disorders and cancers.[2] The impact of obesity upon the physical and psychological health of millions of people across the UK is immense and the increasing economic burden this places upon a healthcare system with already limited resources is unsustainable.

Between 1980 and 2013, the number of people, worldwide, who were either overweight or obese rose from 857 million to 2.1 billion. [3] This means that, on planet Earth, there are now more people who are overweight than who are starving.[4] The adoption of a more sedentary lifestyle and a high-calorie diet, rich in fats and simple sugars, are widely acknowledged as the two most important factors contributing to this global phenomenon.

The relationship between obesity and chronic liver disease, specifically Non-alcoholic Fatty Liver Disease (NAFLD), throughout childhood, adolescence and adulthood, remains critically under-appreciated by healthcare professionals and our patients. Important gaps remain in our overall approach to screening, diagnosis, management and follow up, particularly during the transition between paediatric and adult clinical services.

Obesity and Non-alcoholic Fatty Liver Disease

Non-alcoholic Fatty Liver Disease (NAFLD) is now the most common form of chronic liver disease in the Western world, affecting 10-20% and 20-30% of the general paediatric and adult populations, respectively. [2] It describes a spectrum of chronic liver disease, characterised by the excessive accumulation of fat within the liver (hepatic steatosis) in the absence of significant alcohol consumption. 1 in 4 patients with hepatic steatosis will go on to develop a more advanced form of the disease, Non-alcoholic Steatohepatitis (NASH), where steatosis coexists with liver inflammation, liver damage, scarring and, eventually, cirrhosis. [2] NASH is also associated with a greatly increased risk of liver cancer. Some studies have even suggested that patients with steatosis, only, are also at an increased risk of liver cancer.[2] Within 10 years, NAFLD is expected to become the most common cause of liver failure and indication for liver transplantation in childhood and adolescence.[2]

While our understanding of the pathological mechanisms underlying this disease continues to evolve, it is believed to be a manifestation, within the liver, of more widespread metabolic dysfunction and is strongly associated with a number of metabolic risk factors, including type II diabetes, heart disease, high cholesterol and, most significantly, obesity. Indeed, the estimated prevalence of NAFLD in patients who are overweight or obese, is 50-80% and severe obesity (>95th centile BMI), is associated with far worse clinical outcomes, leading some clinicians to describe NAFLD in terms of a disease of 'over-nutrition'. [2]

Although obesity is commonly defined in terms of Body-Mass Index (BMI), this does not always give an accurate indication of the amount of fat a person is carrying in relation to their total body weight. For example, a very muscular individual will demonstrate a BMI that is abnormally high, despite having relatively little body fat. As such, the relationship between BMI and a patient's health, in general, is often less clear than might otherwise be assumed. Increasingly, waist circumference is being favoured as a more useful and appropriate measurement of total body fat. Indeed, a strong association has recently been reported between increasing waist circumference and the risk of type II diabetes. [5] It has, therefore, been suggested that a waist circumference, taken at the level of the umbilicus (belly-button), greater than 94cm (37 inches) in men and 80cm (31 ½ inches) in women indicates obesity. Similar thresholds for obesity in children have yet to be established. [5]

Clinical Presentation of NAFLD

While the risk of NAFLD and NASH-cirrhosis certainly increases with age, clinical cases have been reported in patients as young as 2 and 8yrs old, respectively. Most paediatric cases, however, present, clinically, above the age of 10 years and tend to show a more aggressive clinical course than is observed in adult NAFLD. As a result of this, and other histopathological differences between paediatric and adult NAFLD, diagnostic algorithms and risk prediction

scores, such as the NAFLD Activity Score, which have been developed for use in adult patients, are of limited use in children and should not be relied upon. [2]

Patients of all ages often remain asymptomatic until significant liver damage has occurred. Diagnosis is often incidental on physical examination or routine blood testing. Indeed, previous studies have shown that 7-11% of abnormal liver function tests (LFTs) and 74% of liver biopsies, in obese patients with metabolic risk factors, can be attributed to NAFLD.[2] However, LFTs can remain normal, even in cases of advanced liver damage and, thus, are by no means definitive in terms of diagnosis or prognosis. When symptoms do present, they are often non-specific and include abdominal pain due to stretching of the liver capsule, as well as fatigue, irritability, headaches and difficulty concentrating. Liver enlargement may be appreciated on manual palpation but can be difficult to assess in obese patients. Acanthosis nigricans, a skin condition associated with type II diabetes, may also be observed. It should also be noted that, while obesity is the single most important risk factor for NAFLD in both adult and paediatric disease, NAFLD can develop in patients of normal weight but this is comparatively rare. [2]

Due to its high population prevalence, NAFLD can readily co-occur with other forms of chronic liver disease, including infective hepatitis, autoimmune hepatitis and alcohol-induced liver disease, worsening clinical outcomes that, otherwise, can be improved by treating the metabolic risk factors underlying NAFLD, such as obesity and insulin resistance, concurrently.[2] In this context, it is also vital to note that, given the apparent similarities in the clinical presentations of alcoholic-induced liver disease and NAFLD, diagnosis of the former should not exclude the diagnosis and treatment of the latter, out of hand, even when there is evidence of extreme alcohol consumption. Indeed, the two conditions can co-occur and there remains no absolute clinical definition at to what is ‘significant’ alcohol consumption and what is not.

An increasing body of evidence suggests that there is a strong genetic contribution to the development of NAFLD, particularly in paediatric cases. A strong family history of NAFLD increases the likelihood that the disease will present and that clinical outcomes for that patient will be more severe.[2] Furthermore, certain ethnic groups display greater susceptibility to NAFLD than others. Hispanic children demonstrate the highest prevalence of NAFLD (36%), which is greater than that of Asians (10.2%), Afro-Caribbeans (14%) and non-Hispanic whites (8.6%), despite these populations exhibiting similar rates of obesity.[2] Hispanic patients have also been shown to be at a higher risk of type II diabetes and tend to display more features of the metabolic syndrome than non-Hispanic whites, which may further contribute to their greater risk.[2] Mutations in numerous genes, such as those related to fat metabolism and storage, have been associated with NAFLD and are thought to largely explain these ethnic differences.

Of particular concern is the rising prevalence of obesity among women of child-bearing age, as recent evidence suggests that maternal obesity is, itself, associated with an increased risk of obesity and NAFLD among their children, in addition to more frequent and more severe complications during pregnancy. Increasing recognition of the developmental origins of health

and disease, including the critical role of maternal physiology around the time of birth, foetal intrauterine growth and neonatal diet, in predisposing children towards diverse metabolic dysfunctionalities, including NAFLD, raises the possibility of targeted intervention and education before and during pregnancy, to minimise risk. Indeed, several studies have demonstrated that controlled maternal weight loss before pregnancy is effective in reducing the lifetime risk of their offspring developing NAFLD.[9] The biological processes that underlie this phenomenon, whereby maternal physiology 'programs' their offspring's metabolism, are only beginning to be understood but appear to focus on numerous tiny changes to the way in which many different genes are expressed in different cell types, both within the liver and beyond.[9]

Making the Diagnosis

Non-alcoholic Fatty Liver Disease is not, as it has sometimes been described in the literature, a diagnosis of exclusion. Rather, it should be considered actively in all patients who are overweight or obese, particularly in the context of high blood pressure, evidence of liver enlargement, acanthosis nigricans or type II diabetes, as well as in those who demonstrate a strong family history of NAFLD or, in severe cases, are jaundiced.

Differential diagnosis should first be based on the clinical features, then on blood tests, including serum ALT and AST levels, abdominal ultrasound and, finally, liver biopsy, which is currently considered the gold standard for the diagnosis of NAFLD, facilitating differentiation between steatosis and NASH, as well as determining the presence and severity of liver scarring and indicating the likelihood of disease progression.[2]

However, radiological and histopathological findings should be interpreted with caution, as the extent of liver steatosis can diminish in advanced disease, rendering abdominal ultrasound insensitive. Even liver biopsy is not always reliable, especially in paediatric cases, as fatty lesioning within the liver tends to be less diffuse and the histopathological changes more subtle and, hence, easier to miss.[2]

As such, maintenance of a high clinical suspicion, in both primary and specialist care settings and by all members of the multidisciplinary team, remains the most potent of diagnostic tools, enabling early referral to gastroenterology services and subsequent diagnosis and appropriate therapeutic intervention designed to stymie disease progression.

Management

At present, weight loss, achieved through dietary modification and increased physical exercise, forms the core of all therapeutic intervention. Numerous studies have shown that a moderate increase in physical exercise and reduction in caloric intake, has the potential to significantly improve clinical outcomes for patients with existing NAFLD. The key challenge here lies in engaging patients with interventional services and promoting adherence in the long-term. As such, lifestyle intervention should be tailored towards patients as individuals, taking account of

the cultural and socioeconomic determinants of diet and exercise habits, as well as differences in patient perceptions of obesity and body image, before setting clear and achievable goals derived by the patient and healthcare professional, in partnership. The adoption of similar lifestyle modifications by family members and, in some cases, behavioural therapy may aid compliance. More effective and straightforward tools for monitoring day-to-day quality and quantity of dietary intake and physical activity, particularly in children, as well as greater efforts to educate and provide guidance for parents and their children, regarding maintaining a healthy diet and the importance of physical activity, are needed.

Several studies have shown that even a moderate reduction in weight, 5% in steatosis and 10% in NASH, has the potential to reduce liver steatosis, improve insulin sensitivity and significantly improve clinical outcomes. [2] There is also evidence to suggest that vigorous exercise, defined as more than 6 times resting energy expenditure, is more beneficial than longer intervals of moderate exercise. [2]

Effective therapeutic strategies should also address any metabolic risk factors associated with NAFLD, such as type II diabetes, high cholesterol and cardiovascular disease. Type II diabetes, for example, is the most common metabolic abnormality associated with NAFLD and, perhaps, the most useful indicator of disease severity and progression in adults and children. As such, drugs that can improve insulin sensitivity, such as metformin, have a key role in the therapeutic management of this disease, potentially reversing even advanced liver damage and improving long-term clinical outcomes.

Current AASLD guidelines recommend limiting overall dietary fat intake to less than 5% of total caloric intake, whilst limiting trans-fats to <1% and saturated fats to <7%. [2] The consumption of other micronutrients, such as fructose, which is a constituent of sucrose, corn syrup, fruit juice, soft-drinks and various sweeteners, should also be reduced. Unlike glucose, fructose is metabolised exclusively in the liver, increasing hepatic steatosis and increasing the risk of liver scarring and cirrhosis. [2]

Growing evidence also suggests that dietary supplementation with vitamin D, vitamin E and omega-3 fatty acids may also have a role in reducing the severity of liver steatosis, scarring and risk of disease progression. Heavy alcohol consumption is a risk factor for chronic liver disease and should be avoided in patients with NAFLD.

Whilst still under development, additional drug therapies, specifically designed to slow or reverse the progression of NASH, may also have a role, depending on the extent and severity of liver scarring and inflammation. [2] The aim of such therapy would be to forestall and, in some cases, reverse the progression of NAFLD to end-stage liver disease.

The efficacy of any intervention should be assessed after a six-month period and, if ineffective, additional therapeutic options might then be considered, including pharmacological therapy or surgical intervention. [2,7,8] Collaboration between hepatologists and other relevant specialties,

including endocrinology, paediatrics, dietetics, cardiology and primary care should be encouraged in order to optimise treatment.

In severe cases of NAFLD or other chronic liver disease complicated by NAFLD, partial or full liver transplantation may be indicated. However, the average waiting time is, currently, 145 days and complications following the procedure much more likely in obese patients.[11]

Weight Loss Surgery

Weight loss surgery, which encompasses a wide range of procedures, has been shown to significantly improve clinical outcomes in patients with NAFLD.[2] However, at present, it is only recommended for severely obese adult patients with significant steatohepatitis, in whom therapeutic lifestyle intervention has been unsuccessful.[2] In such patients, it has been shown to significantly reduce the extent and severity of liver damage, steatosis and inflammation, as well as improving insulin sensitivity. However, its use in cases of established NASH and NASH-cirrhosis remains controversial.

A more recent and less invasive procedure involves the endoscopic insertion of a fluid-filled intra-gastric silicone balloon into the patient's stomach, reducing its functional volume and, consequently, the amount of food that can be consumed. Six months after insertion, the balloon is removed. The intra-gastric balloon represents an attractive alternative to other surgical weight loss procedures and has been shown to be effective in helping patients to lose weight.[12]

Conclusions

Non-alcoholic Fatty Liver Disease (NAFLD) is now the most common form of chronic liver disease, affecting 10-20% and 20-30% of the general paediatric and adult population, respectively.[2] Within the next 10yrs it is expected to become the leading cause of liver pathology, liver failure and indication for liver transplantation in childhood and adolescence in the Western world.[4] Despite this, NAFLD remains under-studied, under-recognised and, potentially, undermanaged.

The single most important risk factor for NAFLD is obesity. Raising awareness of the severe health risks of obesity and obesity-associated diseases, as well as addressing the many and often widespread misconceptions regarding their prevalence, natural history and prognosis and highlighting the importance of early and appropriate therapeutic intervention, are key in improving clinical outcomes for patients. This will require greater collaboration between healthcare professionals, academics, health policy-makers and, most importantly, the general public.

The importance of the effective clinical management of any metabolic risk factors, as well as improving the interconnectedness of diverse health disciplines, especially during the transition from paediatric to adult clinical services and in those patients at the extreme end of the obesity

spectrum, in whom non-surgical therapies for weight loss are currently non-existent, cannot be over-estimated.

In the absence of definitive radiological and histopathological diagnostic tests, maintenance of a high clinical suspicion, in both primary and specialist care settings and by all members of the multidisciplinary team, remains the most potent of diagnostic tools, enabling early diagnosis and appropriate therapeutic intervention.

References

1. Niblett, P. Statistics on Obesity, Physical Activity and Diet—England, 2015. Available online: http://www.hscic.gov.uk/catalogue/PUB16988
2. Temple, J.L.; Cordero, P.; Li, J. ; et al . A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence. *Int. J. Mol. Sci.* 2016, *17*, 947.
3. Ng, M; Flemming, T; Robinson, M. ; et al.; Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study. *Lancet* 2014, 384 (9945), 766-781.
4. *Obesity and Overweight Fact sheet*; World Health Organisation; 2016; http://www.who.int/mediacentre/factsheets/fs311/en/ (Last Accessed on 13.08.2016)
5. *Measurement of Obesity*; Public Health England, 2017; http://www.noo.org.uk/NOO_about_obesity/measurement (Last Accessed on 20.01.2017)
6. Chalasani, N.; Younossi, Z.; Lavine, J.E.; et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. *Am. J. Gastroenterol.* 2012, 107, 811–826.
7. Ratziu, V.; Bellentani, S.; Cortez-Pinto, H.; et al, G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J. Hepatol.* 2010, *53*, 372–384.
8. Cordero, P.; Li, J.; Temple, J.L.; et al. Epigenetic mechanisms of maternal obesity effects on the descendants. *Parent. Obes. Intergener. Progr. Conseq.* 2016
9. Cordero, P.; Li, J.; Oben, J.A. Epigenetics of obesity: Beyond the genome sequence. *Curr. Opin. Clin. Nutr. Metab. Care* 2015, 18, 361–366.
10. *Liver Transplant-Waiting List*; NHS Choices; 2015; http://www.nhs.uk/Conditions/Liver-transplant/Pages/When-it-should-be-done.aspx/ (Last Accessed on 20.01.2017)
11. Nguyen, V; Li, J; Cordero, P; et al. Intra-Gastric Balloon (IGB): an endoscopic treatment option for obesity and NAFLD. *Hepatolo*. 2016, 63 (1 SUPP), 567A-568A