Advances in NAFLD – is when we eat as important as what we eat?

The timing of energy intake, not just total and type of energy intake, may influence individual risk of non-alcoholic fatty liver disease (NAFLD) development and may offer new hope for management, according to this recent "Advances in Clinical Practice" review in *Gut*. Irregular meal patterns, skipping breakfast, and night-time eating and snacking are associated with metabolic disease and may be important factors in NAFLD risk, adding to the conventional dietary risk factors of high energy intake and unhealthy consumption of ultra-processed foods and saturated fats. Human studies manipulating the timing of energy intake suggest that intermittent fasting and time-restricted eating may be as effective as, and better tolerated than, continuous daily energy restriction and can achieve >5% weight loss, reduce liver steatosis and stiffness, and improve lipid profiles. NAFLD is very common in people with type 2 diabetes and significantly increases the risk of morbidity and mortality from cardiovascular as well as liver disease. There are no currently licensed drug treatments for NAFLD, so management relies on lifestyle changes and weight loss. The authors anticipate a growing role in future guidelines for intermittent fasting and time-restricted eating in the management of metabolic diseases, including NAFLD.

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High energy intake and high consumption of ultra-processed foods, saturated fats and fructose are already recognised as being associated with the pathogenesis of non-alcoholic fatty liver disease (NAFLD). In this "Advances in Clinical Practice" review in *Gut*, Thomas Marjot and colleagues highlight that irregular eating patterns, skipping breakfast and night-time snacking and eating, all common in today's society, may also increase the risk of NAFLD, insulin resistance and type 2 diabetes, likely due to disruption in circadian rhythms. The review explains how these eating patterns contribute to metabolic disorders and summarises the human studies exploring how Ramadan fasting, intermittent fasting and time-restricted eating may contribute to weight loss and have therapeutic potential to help us manage NAFLD and non-alcoholic steatohepatitis (NASH).

Physiology and eating patterns

Although the central body clock in the brain is mainly influenced by timing of light and dark, the liver clock is influenced more by food intake patterns. Thus, fasting and time-restricted eating have emerged as potential ways to prevent and treat NAFLD and other metabolic conditions such as type 2 diabetes.

Food is known to have a greater satiating effect earlier in the day, declining later. Higher intake of carbohydrate (or fat or protein) earlier in the day is known to result in lower intake of the same macronutrient later in the day, likely related to higher levels of satiety hormones such as peptide YY and GLP-1. Improved post-prandial glycaemic control after lunch occurs if the person ate breakfast: the so-called "second meal" phenomenon, thought to be due to higher post-breakfast insulin suppressing plasma non-esterified fatty acid levels, improving skeletal muscle insulin sensitivity and allowing increased storage of glucose as glycogen.

Insulin sensitivity is up to a third higher in the morning compared to the evening, meaning the ability to metabolise dietary glucose and fats is optimal in the morning and becomes progressively impaired later in the day.

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Diabetes Distilled: Even short-term time-restricted eating improves glycaemic control

Time-restricted eating may be an effective additional strategy for glycaemic management in type 2 diabetes.

Diabetes & Primary Care **24**: 129–30

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Overweight individuals given a large breakfast compared with those given a large, isocaloric, evening meal had improved satiety, lower ghrelin levels and greater weight loss. Eating more of the daily food intake later in the day is known to be associated with weight gain, obesity, metabolic syndrome and NAFLD, the latter even after controlling for total daily energy intake.

Both observational and randomised controlled studies showed that variable meal frequency is associated with higher post-meal insulin and LDL-cholesterol levels and greater insulin resistance, compared to regular meals. Using phone apps to record food intake demonstrated that even amongst people who believed they were eating regular meals, irregular food intake occurred 4–15 times per day, with erratic intervals between bouts of eating (Gill and Panda, 2015), while more than half of the participants in another study had food intake spread over more than 15 hours per day.

Intermittent fasting, time-restricted eating and metabolic health

The review provides a useful overview of what is involved in different types of intermittent fasting and how to assist people in implementing time-restricted eating (TRE) for those unfamiliar with these eating patterns. The authors summarise the evidence from human studies on the impact of Ramadan fasting, intermittent fasting and TRE on weight and metabolic disease, and they highlight the potential for intermittent fasting and TRE to contribute to weight loss and NAFLD management.

Intermittent fasting – eating 25% of usual caloric intake on "fasting days" – appears to be as effective for weight loss as daily caloric restriction but is possibly more sustainable over the longer term. Alternate-day fasting and 5:2 diets have achieved 3–8% weight loss in randomised controlled trials over 8–12 weeks, similar reductions to those achieved with continuous daily energy restriction, but around 30% of this is likely to be regained in the 6 months after the altered eating pattern ceases, exactly as occurs with continuous restriction.

Limiting the eating window to 6–10 hours, even without guidance to decrease caloric intake, results in around a 30% calorie reduction but may be associated with smaller weight reduction (3–4%) than a similar calorie reduction as part of continuous calorie control (around 5–7%). Early TRE (where the final meal is eaten mid-afternoon) is associated with better weight reduction, glycaemic control, satiety hormone profiles and hunger scores that late TRE (fasting until around 1–2 pm and eating dinner in the evening) in randomised trials. TRE may be easier to discuss and implement than intermittent fasting, since no calorie counting is required.

Alongside the weight reductions, these altered eating patterns are recognised to provide cardiovascular and immune system benefits. Early concerns that intermittent fasting might increase disordered eating has not been demonstrated in clinical trials.

Effects on liver disease

In human studies, both intermittent fasting and low-carbohydrate/high-fat diets demonstrated improved steatosis in an open-label randomised trial, but only the 5:2 diet significantly improved liver stiffness. Alternate-day fasting for 8 weeks in people with NAFLD improved ALT and steatosis on ultrasound scan more than *ad libitum* eating. Alternate-day fasting was associated with >5% weight loss and improvement in dyslipidaemia by 4 weeks, with additional weight loss by 12 weeks. However, the authors warn that these eating patterns should not be recommended in people with established cirrhosis.

Circadian misalignment is known to be associated with liver metabolic dysfunction, and irregular dietary patterns predispose to steatosis and inflammation. TRE can reprogramme circadian rhythms and improve the key factors stimulating NAFLD, namely weight and insulin resistance.

There is already limited evidence that TRE using an 8-hour eating window compared to a normal control diet is associated with weight loss of nearly 5%, decreased fat mass and improved triglycerides over 12 weeks in nearly 100 people recruited because of increased liver stiffness; however, there was no significant change in liver stiffness, likely due to the short study duration.

Other randomised controlled trials have demonstrated that early TRE (eating window

6 am to 4 pm) over 12 weeks reduced body weight more and had greater impact on intrahepatic fat and plasma glucose than eating the same restricted calories across six meals throughout the day. Stringent calorie restriction combined with TRE (8 am to 4 pm) compared with calorie restriction alone over 12 months was more effective in improving insulin resistance, and both groups achieved weight loss of >10% with significant reductions in intrahepatic triglycerides and liver stiffness. A number of large randomised trials are planned or underway exploring the potential of TRE in management of chronic diseases, including NAFLD.

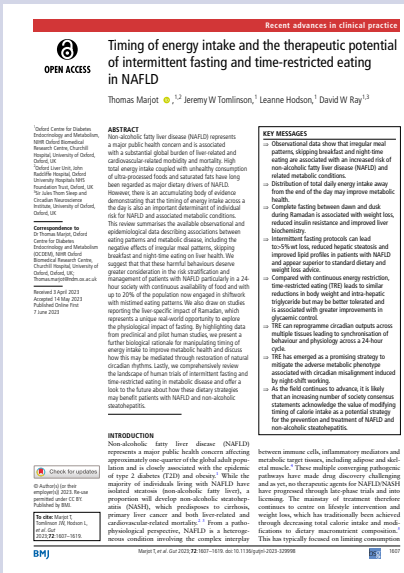
Concluding remarks

Around a quarter of the global adult population now has NAFLD, and this is more common in the people we look after with type 2 diabetes than in the general population. NAFLD is often unrecognised if liver function tests are normal, yet progression to NASH is more common in those with type 2 diabetes, with an associated risk of fibrosis, cirrhosis and hepatocellular carcinoma. As well as the risk of liver disease progression, NAFLD further increases the already raised risk of cardiovascular disease in those with type 2 diabetes.

Currently there are no licensed drugs for NAFLD and the mainstay of treatment is lifestyle interventions: decreasing fructose, ultra-processed food and saturated fat intake, aiming to achieve weight loss. The Mediterranean diet has been shown to improve liver function tests and liver steatosis, as well as evidence that it may reduce the risk of primary and secondary cardiovascular events.

This detailed exploration of the interaction between timing of eating, dietary patterns and circadian rhythms on the pathogenesis of NAFLD and metabolic disease sets the scene for considering intermittent fasting and TRE as additional tools we can use to support people with weight loss and managing NAFLD. This is likely to be supported by inclusion of intermittent fasting and TRE in national and international guidelines in the near future. ■

Gill S, Panda S (2015) A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab* **22**: 789–98



Recent advances in clinical practice

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Timing of energy intake and the therapeutic potential of intermittent fasting and time-restricted eating in NAFLD

Thomas Marjot, Jeremy W Tomlinson, Leanne Hodson, David W Ray

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) represents a major public health concern and is associated with a substantial global burden of liver-related and cardiovascular-related morbidity and mortality. High total energy intake coupled with unhealthy consumption of ultra-processed foods and saturated fats have long been regarded as major dietary drivers of NAFLD. However, there is an accumulating body of evidence demonstrating that the timing of energy intake across a the day is also an important determinant of individual risk for NAFLD and associated metabolic conditions. This review summarises the available observational and epidemiological data describing associations between eating patterns and metabolic disease, including the negative effects of irregular meal patterns, skipping breakfast and night-time eating on liver health. We suggest that that these harmful behaviours deserve greater consideration in the risk stratification and management of patients with NAFLD particularly in a 24-hour society with continuous availability of food and with up to 20% of the population now engaged in shiftwork with mistimed eating patterns. We also draw on studies reporting the liver-specific impact of Ramadan, which represents a unique real-world opportunity to explore the physiological impact of fasting. By highlighting data from preclinical and pilot human studies, we present a further biological rationale for manipulating timing of energy intake to improve metabolic health and discuss how this may be mediated through restoration of natural circadian rhythms. Lastly, we comprehensively review the landscape of human trials of intermittent fasting and time-restricted eating in metabolic disease and offer a look to the future about how these dietary strategies may benefit patients with NAFLD and non-alcoholic steatohepatitis.

KEY MESSAGES

- Observational data show that irregular meal patterns, skipping breakfast and night-time eating are associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) and related metabolic conditions.
- Distribution of total daily energy intake away from the end of the day may improve metabolic health.
- Complete fasting between dawn and dusk during Ramadan is associated with weight loss, reduced insulin resistance and improved liver biochemistry.
- Intermittent fasting protocols can lead to>5% wt loss, reduced hepatic steatosis and improved lipid profiles in patients with NAFLD and appear superior to standard dietary and weight loss advice.
- Compared with continuous energy restriction, time-restricted eating (TRE) leads to similar reductions in body weight and intra-hepatic triglyceride but may be better tolerated and is associated with greater improvements in glycaemic control.
- TRE can reprogramme circadian outputs across multiple tissues leading to synchronisation of behaviour and physiology across a 24-hour cycle.
- TRE has emerged as a promising strategy to mitigate the adverse metabolic phenotype associated with circadian misalignment induced by night-shift working.
- As the field continues to advance, it is likely that an increasing number of society consensus statements acknowledge the value of modifying timing of calorie intake as a potential strategy for the prevention and treatment of NAFLD and non-alcoholic steatohepatitis.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a major public health concern affecting approximately one-quarter of the global adult population and is closely associated with the epidemic of type 2 diabetes (T2D) and obesity.[1] While the majority of individuals living with NAFLD have isolated steatosis (non-alcoholic fatty liver), a proportion will develop non-alcoholic steatohepatitis (NASH), which predisposes to cirrhosis, primary liver cancer and both liver-related and cardiovascular-related mortality.[2] From a pathophysiological perspective, NAFLD is a heterogeneous condition involving the complex interplay between immune cells, inflammatory mediators and metabolic target tissues, including adipose and skeletal muscle.[3] These multiple converging pathogenic pathways have made drug discovery challenging and as yet, no therapeutic agents for NAFLD/NASH have progressed through late-phase trials and into licensing. The mainstay of treatment therefore continues to centre on lifestyle intervention and weight loss, which has traditionally been achieved through decreasing total calorie intake and modifications to dietary macronutrient composition.[4] This has typically focused on limiting consumption

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Diabetes & Primary Care **21**: 5–6

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