# Optimizing glycaemic control to improve non-alcoholic fatty liver disease (NAFLD)

**Supervisors:** Professor Jeremy Tomlinson
Dr Garry Tan
Associate Professor Leanne Hodson

**Department:** OCDEM, Radcliffe Department of Medicine

**Background**

It is now established that non-alcoholic fatty liver disease (NAFLD) drives increased morbidity and mortality, both through a specific impact upon the liver, but perhaps more importantly, through adverse cardiovascular outcomes (1, 2). Its prevalence continues to rise, and by 2020, NALFD will become the leading indication for liver transplantation worldwide (3). NAFLD is a spectrum of disease ranging from simple steatosis through to inflammation (non-alcoholic steatohepatitis, NASH), scarring, fibrosis with the potential to progress to cirrhosis with the consequent increased risk for the development of hepatocellular carcinoma. NAFLD is more common in patients with type 2 diabetes (T2D) and our own recently published data, generated as part of our local *'think NAFLD'* campaign, suggest that more than 13% of all patients with T2D have advanced fibrosis (4). In addition, NAFLD is associated with worsening of diabetes-related complications (5) and crucially, the development of T2D hastens the progression of NAFLD to the more advanced stages that are associated with the poorest clinical outcome (6). Finally, cross-sectional data suggest that poor glycaemic control is associated with more advanced liver disease in some, but not all clinical studies (7, 8, 9).

Currently there are no licenced pharmacotherapies for NAFLD. Lifestyle intervention alongside cardiovascular risk reduction and optimization of the management of coexistent diabetes are the mainstays of treatment. We, and others have previously shown the histological benefits of specific anti-diabetic agents (including thiazolidinediones (TZD) and GLP-1 analogues) in patients with, and without T2D (10, 11, 12). Furthermore, we have shown the potential to improve weight, glycaemic control as well as liver chemistry through a truly multidisciplinary metabolic hepatology clinic that combines dedicated diabetology and hepatology expertise (13). However, to date, there are no prospectively collected, longitudinal, controlled data to determine whether improvements in glycaemic control (independent of changes in weight or specific anti-diabetic agent) translate to improvements in the natural history of NAFLD in patients with T2D.

**Hypothesis**

The synthesis of hepatic triglyceride from non-lipid precursors (predominantly glucose) through the process of *de novo* lipogenesis (DNL) is an important contributor to the development of hepatic steatosis (14, 15). ***Our hypothesis is that optimization of glycaemic control in patients with T2D will limit hepatic lipid accumulation, at least in part, through decreased DNL.***

**Aims**

1. To undertake the first randomised controlled trial to determine the impact of optimization of glucose control on hepatic DNL and lipid accumulation.
2. To define the changes in hepatic lipid flux that occurring as a result of glycaemic control optimization.

**Plan of investigation**

We will perform the first clinical study to determine if optimizing glycaemic control in patients with hepatic steatosis and T2D who are treated with insulin improves NAFLD. Patients with T2D and sub-optimal glycaemic control (HbA1C ≥ 64mmol/mol, 8%) and evidence of NAFLD (non-invasive serum markers, ultrasound imaging) will be recruited from clinics within the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM). Over a 6-month period, our *'think NAFLD'* data identified >140 patients with T2D, 41% of whom were treated with insulin (mean HbA1C = 68mmol/mol, 8.4%). Patients treated with GLP-1 analogues and / or TZDs will be excluded (from our published data this equates to 11% and 1% of patients with T2D respectively).

Participants will be randomized to standard care or intensive glycaemic control optimization for a period of 6 months utilizing a dedicated algorithm based upon the principles outlined in the VADT study (16). This will incorporate increased frequency of contact with the clinical and research team, increased frequency of blood glucose self-monitoring and aggressive insulin dose titration with the aim of achieving an HbA1C target reduction of ≤ 16.4mmol/mol (1.5%). Glycaemic control will be assessed through measurements of HbA1C and in addition, glucose variability will be measured using continuous glucose monitoring for 2 weekly intervals at baseline and after 3 and 6 months. This will be paralleled by detailed hepatic and metabolic phenotyping performed using an integrative physiological approach incorporating stable isotope tracers to examine the pathways that contribute to lipid accumulation in patients with NAFLD (including DNL) across mixed meal tests as we have described previously (17). Dedicated liver imaging using magnetic resonance techniques (including spectroscopy and multi-parametric MR that can distinguish hepatic steatosis, inflammation and fibrosis) will be performed alongside other non-invasive markers of the stage of liver disease (including liver chemistry, Fibroscan, FIB-4, Enhanced Liver Fibrosis panel). Body composition analysis will be performed using DXA and abdominal subcutaneous adipose tissue biopsies will be taken to determine levels of adipose tissue dysfunction (histomorphometry, gene, protein expression) that has been implicated in the pathogenesis of NAFLD.

**References**


1. Ekstedt M, Hagström H, Nasr P *et al.* Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology*. 2015;61:1547-54
2. Dulai PS, Singh S, Patel J *et al.* Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology*. 2017;65:1557-1565
3. Wong RJ, Cheung R, Ahmed A. Non-alcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology*. 2014;59:2188-95

4. Marjot T, Sbardella E, Moolla A *et al.* Prevalence and severity of non-alcoholic fatty liver disease are underestimated in clinical practice: impact of a dedicated screening approach at a large university teaching hospital. *Diabet Med*. 2018;35:89-98
5. Yan LH, Mu B, Guan Y *et al*. Assessment of the relationship between non-alcoholic fatty liver disease and diabetic complications. *J Diabetes Investig*. 2016;7:889-894
6. McPherson S, Hardy T, Henderson E *et al.* Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62:1148-55
7. Katoh S, Peltonen M, Wada T *et al.* Fatty liver and serum cholinesterase are independently correlated with HbA1c levels: cross-sectional analysis of 5384 people. *J Int Med Res*. 2014;42:542-53
8. Zhang Q, Yu Y, Yang M *et al.* Association between glycosylated hemoglobin and non-alcoholic fatty liver disease in health examination population. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2017;42:529-535
9. Cusi K, Sanyal AJ, Zhang S *et al.* Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab*. 2017;19:1630-1634
10. Armstrong MJ, Hull D, Guo K *et al.* Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol*. 2016;64:399-408
11. Armstrong MJ, Gaunt P, Aithal GP *et al*. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387:679-90
12. Sanyal AJ, Chalasani N, Kowdley KV *et al.* Pioglitazone, vitamin E, or placebo for non-alcoholic steatohepatitis. *N Engl J Med*. 2010;362:1675-85
13. Motohashi K, Moolla A, Marjot T *et al.* The impact of a dedicated metabolic hepatology clinic for the treatment of non-alcoholic fatty liver disease. *Endocrine Abstracts* 2017
14. Donnelly KL, Smith CI, Schwarzenberg SJ *et al.* Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest*. 2005;115:1343-51
15. Diraison F, Moulin P, Beylot M. Contribution of hepatic de novo lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease. *Diabetes Metab*. 2003;29:478-85
16. Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129-39
17. Pramfalk C, Pavlides M, Banerjee R *et al.* Fasting Plasma Insulin Concentrations Are Associated With Changes in Hepatic Fatty Acid Synthesis and Partitioning Prior to Changes in Liver Fat Content in Healthy Adults. *Diabetes*. 2016;65:1858-67

**Supervisor's recent relevant publications**


- Marjot T, Sbardella E, Moolla A, Hazlehurst J, **Tan GD,** Ainsworth M, Cobbold JFL, **Tomlinson JW**. Prevalence and severity of non-alcoholic fatty liver disease are underestimated in clinical practice: impact of a dedicated screening approach at a large university teaching hospital. *Diabet Med*. 2018;35:89-98
- Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, Nasiri M, Yu J, Gough SC, Newsome PN, **Tomlinson JW**. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. *J Hepatol*. 2016;64:399-408
- Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, **Tomlinson JW,** Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387:679-90
- Pramfalk C, Pavlides M, Banerjee R, McNeil CA, Neubauer S, Karpe F, **Hodson L**. Fasting Plasma Insulin Concentrations Are Associated With Changes in Hepatic Fatty Acid Synthesis and Partitioning Prior to Changes in Liver Fat Content in Healthy Adults. *Diabetes*. 2016;65:1858-67
- Pramfalk C, Pavlides M, Banerjee R, McNeil CA, Neubauer S, Karpe F, **Hodson L.** Sex-Specific Differences in Hepatic Fat Oxidation and Synthesis May Explain the Higher Propensity for NAFLD in Men. *J Clin Endocrinol Metab*. 2015;100:4425-33