Time to consider a holistic approach to the treatment of non-alcoholic fatty liver disease in obese young people?

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During the last decade, evidence has accumulated to show that NAFLD is a "multisystem" disease often associated with obesity and other cardiometabolic disorders [1]. NAFLD not only increases risk of liver-related complications, but also increases risk of developing type 2 diabetes (T2D) [2], cardiovascular disease (CVD) [3], chronic kidney disease[4], and certain extra-hepatic cancers[5]. Thus, there is now important evidence to support a holistic approach to the treatment of NAFLD in adulthood and that approach extends to risk management of other diseases beyond the liver.

With the burgeoning 21st century problem of obesity in childhood, it is now apparent that NAFLD is also a common disease in young people with overweight or obesity[6]. Bearing in mind the evidence in adults that NAFLD increases risk of extra-hepatic diseases, this also raises the possibility that NAFLD in childhood may not be harmless; and that NAFLD may also have important implications for the health of young people as they grow older[7].

Simon *et al*. have previously reported important data from a nationwide cohort of Swedish adults with histologically-confirmed NAFLD and without pre-existing CVD at baseline (n=10,422)[8]. In that retrospective cohort study, the authors showed that over a median of 13.6 years of follow-up, NAFLD was associated with a ~65% increased risk of major adverse cardiovascular events (MACE), (even after adjustment for common cardiometabolic risk factors). Furthermore, risk of incident MACE increased monotonically with worsening of NAFLD severity.

In this issue of GUT, Simon *et al*. have extended that previous analysis. Using the same nationwide cohort that included all Swedish children and young adults ≤25 years old with histologically-confirmed NAFLD, and without underlying CVD at baseline (n=699), the authors investigated multivariable-adjusted hazard ratios (aHRs) and 95%CIs for incident MACE outcomes (i.e. ischemic heart disease, stroke, heart failure or cardiovascular mortality)[9]. In secondary analyses, the authors also explored rates of cardiac arrhythmias. In parallel to their study in adults, NAFLD was defined from prospectively-recorded histopathology, and further categorized as simple steatosis or steatohepatitis. Patients with NAFLD were matched to ≤5 population controls without NAFLD (n=3,353)[9]. Although this is a young cohort (and as expected the numbers of CVD events was small), incident MACE was confirmed in 33 NAFLD patients, and 52 controls, over a median follow-up of 16.6 years. NAFLD patients had higher rates of MACE than controls (3.1 vs. 0.9/1000 person-years[PY]; difference=2.1/1000PY; aHR=2.33, 95%CI=1.43-3.78), including higher rates of ischaemic heart disease (difference=1.4/1000PY; aHR=3.07, 95%CI=1.62-5.83) and congestive

heart failure (difference=0.5/1000PY; aHR=3.89, 95%CI=1.20-12.64). Similar to their previous data in adults, rates of incident MACE outcomes appeared to be further increased with the presence of NASH at baseline (aHR=5.27, 95%CI=1.96-14.19). Moreover, in support of the above MACE data, in secondary analyses, young patients with NAFLD also had higher rates of cardiac arrythmias (aHR=3.16, 95%CI=1.49-6.68), especially atrial fibrillation.

This is the first study to date to examine the incidence of fatal and nonfatal MACE in children and young adults with biopsy-proven NAFLD. However, it is important to consider that this was a retrospective study with NAFLD defined histologically, and not all young adults with NAFLD undergo liver biopsy. This could introduce some selection bias and reduce the generalisability of the findings of the study. Also, given the small numbers of MACE outcomes, it is also important to consider the robustness of the statistical analyses. It is plausible that the fully adjusted Cox regression models could be (partly) over-adjusted. However, it should be noted that there was only a modest change in the risk estimates between the minimally adjusted and fully adjusted regression models (without a substantial widening of the confidence intervals). It is also possible that there was residual confounding as some cardiometabolic risk factors may be under-reported in the Swedish Registers. The authors also lacked detailed descriptive data regarding adiposity measures, age of puberty, smoking or alcohol use. Interestingly, Simon *et al*. also observed attenuated risk estimates when inserting time-varying risk factor covariates as exposures, in time-dependent regression modelling. These latter data suggest that NAFLD might (at least in part) increase CVD risk, via it promoting the development of cardiometabolic risk factors. Thus, persistence of NAFLD over time might adversely influence the development of known cardiometabolic risk factors, and these risk factors may mediate (at least in part) the development of CVD.

What messages should we take home from these important data? We know from data in adults that weight loss is effective in treating the early stages of NAFLD (before advanced fibrosis and cirrhosis have developed). Weight loss is also very effective in decreasing risk of T2D and other cardiometabolic disorders. Thus, it is crucial that young people with NAFLD be helped to lose weight. If lifestyle modifications alone are not sufficient, there is a case for advocating treatment with glucagon-like peptide-1 (GLP-1) receptor agonists in order to promote weight loss in obese children and young adults with NAFLD. Recent data show that GLP-1 receptor agonists are safe and effective in reducing weight and related cardiometabolic disorders in children and adolescents

with obesity[10]. There is also now a wealth of data in adults showing that these agents attenuate CVD risk. Thus, it only seems a matter of time before NAFLD in obese young people will become another indication for this class of incretin-receptor agonist drugs.

Since NAFLD also increases risk of T2D and other cardiometabolic disorders, the findings from Simon *et al*.[9] raise important implications for the early management of obese young people with NAFLD. Whilst we don't advocate the widespread use of multi-drug treatments for obese young people with NAFLD (that would also involve a considerable cost), it is perhaps time to debate the pros and cons of not treating these young people with drugs that have meaningful cardiovascular benefits (and proven long-term safety profiles). Maybe, these important data from Simon *et al.* [9] suggest that it is time to consider a holistic approach to the treatment of NAFLD in obese young people.

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