



Refining the role of epicardial adipose tissue in non-alcoholic fatty liver disease

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Introduction

Obesity is a rapidly growing public health challenge, with global prevalence having increased substantially over four decades, from less than 3% and 6% in 1975, to 11% and 15% in 2016, among male and female, respectively [1]. This development, together with concomitant increases in diabetes, has fuelled a dramatic escalation in the prevalence of non-alcoholic fatty liver disease (NAFLD). NAFLD is now a leading cause of chronic liver disease, and afflicts about a quarter of the global population [2].

Although it is accepted that visceral adipose tissue (VAT) is an independent risk factor for NAFLD and NAFLD related fibrosis [3, 4], there remains an unresolved debate around the role of other ectopic fat depots. This includes for example, depots that surround the heart, pancreas, and kidneys, and their contribution to the dysmetabolic state and NAFLD risk, independent of VAT. Perhaps, one of the most hotly argued topics is the role of epicardial adipose tissue (EAT).

EAT is the visceral fat depot of the heart and is considered a metabolically active organ that produces both pro-inflammatory and anti-inflammatory mediators [5]. EAT amount has high heritability, estimated in twin studies to be up to 80%, with only a modest impact for environmental factors (20%) [6]. Notably, ethnic variation is observed for EAT volume; with multiple reports suggesting that Asians tend to have higher EAT compared to Caucasian populations for the same adiposity, as measured by BMI [7, 8]. EAT is relatively

easily quantified either by echocardiography or computerised tomography. Hence, its assessment could have important clinical implications for the stratification and prediction of cardio-metabolic risk, particularly as EAT is increased in conjunction with a variety of disorders including metabolic syndrome, atherosclerosis and diabetes [9, 10].

Interestingly, epicardial and intra-abdominal fat have the same embryonic origin, with both derived from brown adipose tissue [11]. Hence, echocardiographic EAT could be considered a marker of visceral adiposity. On the basis of findings that NAFLD increases the risk of cardiovascular disease independent of confounding metabolic risk factors [12, 13], it is conceivable that EAT might play a role in NAFLD development and progression, as well as in increasing NAFLD-associated cardiovascular risk. However, current data on the correlation between EAT and NAFLD is conflicting [14, 15].

In many instances, well conducted systematic reviews (with or without meta-analyses) can help to overcome controversies and debates by enabling an objective synthesis of available literature through a meticulous process of careful and systematic identification, critical appraisal and pooling of relevant studies. In the current issue, Liu et al. [16] systematically reviewed the evidence for the association of EAT thickness and volume with NAFLD, and then performed a meta-analysis to evaluate the association. The meta-analysis included thirteen case–control studies ($n = 2260$ patients) and confirmed that EAT was significantly increased in NAFLD patients compared with controls. Among patients with NAFLD, EAT correlated with the severity of hepatic steatosis and fibrosis, and atherosclerotic cardiovascular disease, suggesting a dose–response effect and thereby biological plausibility. Notably, no association was observed between EAT and NASH, but this likely reflects the fact that only two studies in the meta-analysis (comprising just 200 patients), had this data. Thus, this analysis was highly likely underpowered to assess for association. Importantly, the authors' power calculations indicated that at least 1000

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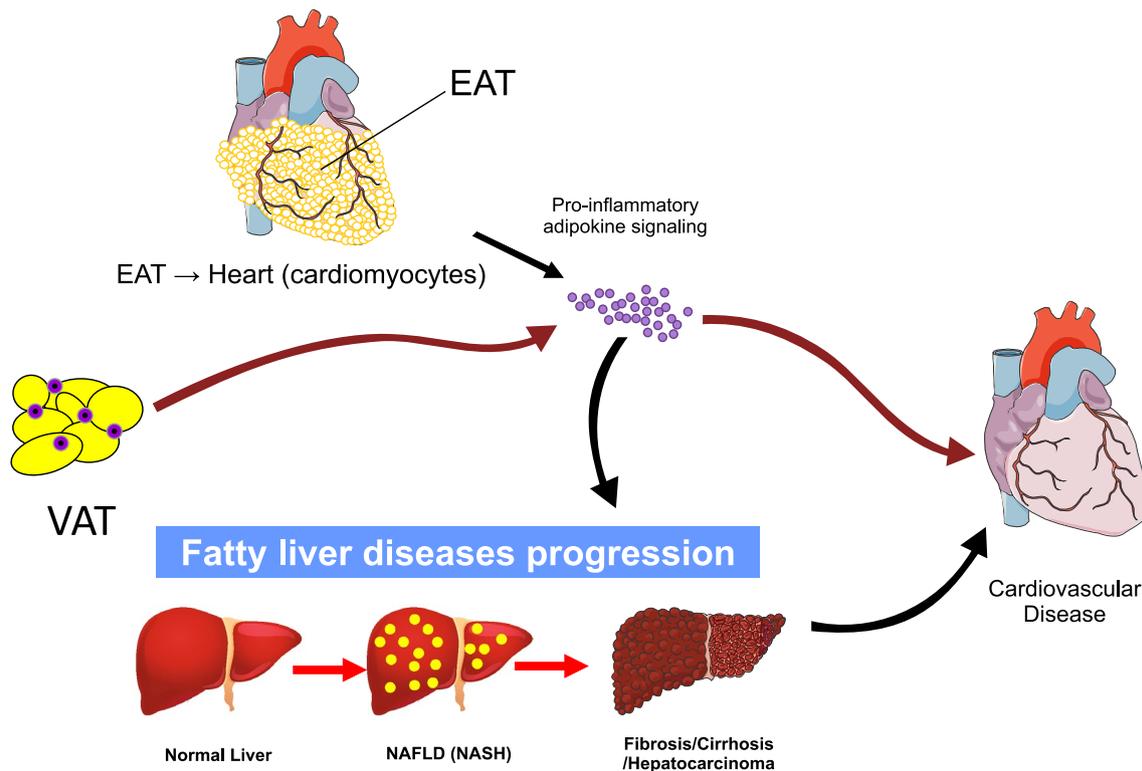


Fig. 1 Role of epicardial and visceral adipose tissue in non-alcoholic fatty liver disease. VAT: *Visceral Adipose Tissue*, EAT: *Epicardial adipose tissue*

patients would be required in such an analysis, for a more definitive conclusion. Thus, additional studies are required to examine the link between steatohepatitis with EAT. In addition, the cross-sectional nature of all the included studies influences any assessment of causality and whether EAT precedes NAFLD or vice versa, or in fact if they are both concomitant phenotypes that occur in the context of systemic metabolic dysfunction.

A further critical concern in relation to inferences of causality is that excess EAT is more commonly present associated with visceral obesity, than in isolation without visceral obesity. Thus, when studies do not concomitantly examine both VAT and EAT in relation to NAFLD risk, whether there is any independent contribution of EAT to NAFLD histology, is difficult to ascertain. Further, a previous study has suggested that metabolic syndrome has a greater impact on EAT than NAFLD and that subjects with NAFLD and diabetes tend to have more EAT than those without diabetes. In this regard, it should be noted that adipose secreted proteins (adipokines) and inflammatory mediators, typically act in an autocrine or paracrine manner, with less systemic spill over [17]. In contrast, according to the “portal hypothesis” for VAT, the direct infusion of mediators into the portal circulation and thence to the

liver [18], indicates that causal metabolic associations are more likely associated with VAT than EAT. However, more detailed studies need to be undertaken to dissect and clarify this issue (Fig. 1). Notably, recent data suggest that EAT mass and related cardiovascular risk can be attenuated through weight loss, exercise and some pharmaceutical drugs such as lipid-lowering agents, sodium-glucose transporter 2 inhibitors and the glucagon-like peptide 1 analogues [19–23].

In summary, ectopic fat depots and perhaps EAT likely play crucial roles in the development and progression of NAFLD, and increase the risk of cardiovascular diseases in these patients. However, while the data in this report increase current knowledge, more detailed studies need to be undertaken and reported, to characterise the precise roles of EAT as opposed to other ectopic fat depots in the pathogenesis of NAFLD. As with most science, the current report serves as an impetus to undertake more research in order to clarify the questions raised.

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Compliance with ethical standards

Conflict of interest Mohammed Eslam and Jacob George declare no competing interests for this manuscript.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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