COMMENT

Is adipose tissue lipolysis always an adaptive response to starvation?: implications for non-alcoholic fatty liver disease

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ABSTRACT

The physiological response to starvation involves increased muscle proteolysis and adipose tissue lipolysis that supply amino acids and non-esterified fatty acids ('free fatty acids') for gluconeogenesis, oxidation and ketogenesis. In the present issue of Clinical Science, Moller and co-workers show that, in humans, IHL (intrahepatic lipid) content, measured using 1H-magnetic resonance spectroscopy, increases following 36 h of fasting, with a direct association with plasma levels of 3-hydroxybutyrate. The observation raises interesting questions as to how IHL levels increase in a situation of increased mitochondrial fatty acid oxidation and ketogenesis. Possible mechanisms for increased IHLs include reduced apoB-100 (apolipoprotein B-100) production and hepatic lipid export, and/or impaired mitochondrial function resulting from increased oxidative stress, with diversion of fatty acids for esterification. The accumulation of IHL during prolonged fasting may, therefore, reflect a maladaptive response to increased non-esterified fatty acid delivery to the liver that unmasks a subtle defect in mitochondrial function. This could have implications for the pathogenesis of the common human disorder of non-alcoholic fatty liver disease. The accumulation of IHLs observed with prolonged fasting may also explain exacerbations of steatohepatitis seen sometimes with rapid weight loss, anorexia nervosa and parenteral nutrition. The findings also suggest caution against promoting excessive ketogenesis with weight-loss regimens.

The metabolic response to starvation has been well described and involves homeostatic mechanisms that result in energy expenditure being derived from the oxidation of lipids and proteins [1]. This is consequent on major hormonal changes, with reduction in plasma insulin and increase in glucagon concentrations secondary to a fall in plasma glucose. Molecular mediators such as PPAR (peroxisome-proliferator-activated receptor) α, FGF21 (fibroblast growth factor 21) and FoxA2 (forkhead box A2) are also involved [2–4]. With exhaustion of liver glycogenolysis after 1 day of starvation, plasma glucose concentrations are maintained by gluconeogenesis from amino acids derived from muscle proteolysis, and cerebral function is maintained by a switch from glucose to ketone body oxidation in the brain. Critical to the adaptive response of the later stages of starvation is an increase in adipose tissue lipolysis and fatty acid delivery to the liver that provides energy for gluconeogenesis; ketogenesis also results in the formation of ketone bodies that are preferentially oxidized by the brain and limit muscle proteolysis. But is adipose tissue lipolysis always a favourable adaptive response to starvation?

In the present issue of Clinical Science, Moller et al. [5] have studied the impact of prolonged fasting on IHLs

Key words: fasting, fatty liver, 3-hydroxybutyrate, lipid, 1H-magnetic resonance spectroscopy, non-alcoholic fatty liver disease (NAFLD).

Abbreviations: AMPK, cAMP-activated protein kinase; apo, apolipoprotein; IHL, intrahepatic lipid; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome-proliferator-activated receptor; PGC-1α, PPAR-γ co-activator; ROS, reactive oxygen species.

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(intrahepatic lipids) using $^1$H-magnetic resonance spectroscopy. By contrast with no changes after a 12-h fast, the authors [5] observed a significant increase of 156 % in IHLs after a 36-h fast in six lean non-diabetic men. The absolute increase in IHLs was, however, less than 5 % and, hence, not in the pathological range of hepatic steatosis [6]. The increase in IHLs was significantly correlated with an increase in plasma levels of 3-hydroxybutyrate, a major circulating ketone body, but not with plasma alanine transaminase levels. Although a small study in a restricted group of individuals, these findings raise questions about the physiology of starvation, with important implications for NAFLD (non-alcoholic fatty liver disease).

One interesting question is why should IHLs accumulate concurrent with hepatic ketogenesis, a process characterized by increased fatty acid entry into mitochondria? Hepatic steatosis is determined by a balance between fatty acid supply to the liver and intrahepatic lipogenesis on the one hand, and the rates of β-oxidation and lipid export by the liver on the other [6]. Probable explanations for the increase in IHLs in the study by Moller et al. [5] relate to an increase in hepatic lipogenesis and/or a reduction in apo (apolipoprotein) B-100 secretion by the liver. Increased rates of proteolysis and channelling of amino acid precursors towards gluconeogenesis in starvation could limit the hepatic secretion of apoB-100 and contribute to the accumulation of IHLs by decreasing hepatic output of triacylglycerols (triglycerides), but this remains conjectural. Another explanation may be that high rates of fatty acid β-oxidation lead to uncoupling of mitochondrial oxidative phosphorylation, with generation of ROS (reactive oxygen species) [7]. Starvation in experimental animals decreases hepatic glutathione levels, providing another mechanism for increased ROS [8]. ROS and lipid peroxidation further impair mitochondrial biogenesis by damaging molecular targets, potentially including the expression and/or activity of the transcriptional co-activator PGC-1α (PPAR-γ co-activator) and AMPK (cAMP-activated protein kinase). Impaired, or uncoupled, mitochondrial function may then contribute to an ‘overflow’ of fatty acids that are redirected into the esterification pathway and expand the storage pool of triacylglycerols.

In response to starvation, the rate of ketogenesis is significantly higher in lean than obese individuals, and this may reflect a homoeostatic control that limits muscle proteolysis in the former group. The ratio of circulating concentrations of 3-hydroxybutyrate/acyetoacetate, a reflector of mitochondrial redox activity, also increases more in lean than in obese subjects [9]. Measurement of this ratio, as well as urinary and plasma isoprostane levels, in the study by Moller et al. [5] might have elucidated whether an increase in oxidative stress could explain the increase in IHLs. AMPK and PGC-1α activities are also critically regulated by leptin and adiponectin levels, and measurement of these adipokines that regulate energy flux might have proved informative [10]. Hepatic fatty acid and triacylglycerol metabolism is also dependent on a wider spectrum of proteins, including microsomal triacylglycerol transfer protein, uncoupling proteins, fatty acid CoA oxidase, stearoyl CoA desaturase, PPARα and apoE. Whether genetic variations in these proteins contribute to the 5-fold variation in the change in IHLs reported by Moller et al. [5] in response to prolonged fasting also warrants further investigation.

NAFLD is increasing globally and is now recognized to be not only a risk factor for cirrhosis, but also for Type 2 diabetes and cardiovascular disease [11,12]. What are the implications of the study by Moller et al. [5] for NAFLD? The pathogenesis of NAFLD essentially revolves around a ‘two hit’ hypothesis, in which the ‘first hit’ relates to an increase in hepatic lipogenesis due to insulin resistance and the ‘second hit’ relates to inflammation and increase in oxidative stress [13]. Increasing dietary fat content can also increase IHL in overweight individuals, as suggested by Westerbacka et al. [14]. In this situation, the mechanism underlying the accumulation of IHLs could involve increased hepatic uptake of fatty acids and triacylglycerols from post-prandial lipoproteins [15]. The mechanisms underlying hepatic steatohepatitis are gradually being better understood and, although clinical trials have hinted at the benefit of new pharmacotherapies such as PPARγ agonists [16] beyond weight loss alone, new approaches to treating this increasingly important clinical disorder need to be tested. Whether the human model described in the study by Moller et al. [5] can be employed to explore the therapeutic potential of new agents for NAFLD remains a possibility.

By extension, the findings from the present study by Moller et al. [5] may explain why rapid weight loss, in particular following intestinal bypass, has been reported to accelerate hepatic inflammation and fibrosis in obese subjects [17,18]. Similar changes including fulminant hepatic failure have been described in anorexia nervosa, a severe form of prolonged protein–energy malnutrition [19]. In the special situation of severely malnourished patients, re-feeding with parenteral nutrition can also lead to an acceleration of hepatic steatosis and hepatic failure [20]. The putative mechanisms in all of these situations relate to mitochondrial dysfunction and oxidative stress and a decrease in the synthesis and hepatic secretion of apoB-100. Conversely, gradual weight loss has been known to reduce NAFLD and is currently the primary clinical intervention recommended to reduce NAFLD in humans [11]. The findings by Moller et al. [5] suggest that, in any weight-loss regimen in obese subjects, avoidance of more than moderate ketosis is preferable to avoid a paradoxical increase in intrahepatic fat or aggravation of hepatic inflammation or fibrosis.

In summary, the small physiological study by Moller et al. [5] suggests that, in early starvation, peripheral adipose tissue lipolysis could lead to maladaptive
accumulation of IHL. The findings, however, need confirmation in a larger sample size and with other subject groups. Further investigations should examine the impact of early starvation, re-feeding and aerobic exercise on IHLs in more overweight individuals, in women, and in older and younger subjects, as well as the impact of these changes on oxidative stress, inflammatory markers and mitochondrial function. Whether the accumulation of IHL measured by magnetic resonance spectroscopy in response to early starvation predicts individuals at risk of developing NAFLD with weight gain also remains an intriguing question.

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