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Adding more fat to a high-fat diet only exacerbates hepatic insulin resistance

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Non-alcoholic fatty liver disease (NAFLD) is one of the many clinical consequences of obesity and increases one's risk of developing diabetes ~5-fold, and is present in up to ~2/3 of those with type 2 diabetes (Hazlehurst *et al.* 2016). The current obesity epidemic necessitates an urgent need to find effective and accessible weight loss interventions. Recently, the 'ketogenic' diet (KD), which is the consumption of a high-fat and low carbohydrate diet (Jornayvaz *et al.* 2010; Roberts *et al.* 2017; Grandl *et al.* 2018), has produced weight loss and improved some markers of metabolic dysregulation in humans and rodents (Foster *et al.* 2003; Roberts *et al.* 2017).

The ability of a diet so high in fat content (sometimes ~90% of kilocalories from fat) to improve glucose tolerance is somewhat surprising, since as few as 3 days of a high-fat diet (HFD; 60% of kilocalories from fat) causes hepatic fat accumulation and insulin resistance in rats (Kraegen *et al.* 1991; Jornayvaz *et al.* 2010). The importance of this rapid hepatic fat accumulation is that early impairments in glucose homeostasis typically result from the inability of insulin to suppress hepatic glucose output, leading to decreased glucose tolerance, whereas insulin resistance in muscle and adipose tissue takes longer to develop (Rask-Madsen & Kahn, 2012).

In a recently published article in *The Journal of Physiology*, Grandl and colleagues provide evidence that while a short-term (3 day) KD is associated with an improved fasting metabolic profile, including lower blood glucose and insulin, a KD (~90% of kilocalories from fat, 9% of kilocalories protein, > 1% of kilocalories carbohydrate) exacerbates systemic glucose intolerance compared to a traditional Western-style high-fat diet (HFD; 60% of kilocalories from fat, 20% of kilocalories protein, 20% of kilocalories carbohydrate) (Grandl *et al.* 2018). Importantly, glucose intolerance was related to hepatic insulin resistance and the resulting inability of insulin to suppress hepatic glucose output (Grandl *et al.* 2018).

The main strength of this study was the use of both [3-^{3}H]-labelled glucose to estimate endogenous glucose production and 2-[1-^{14}C]-labelled deoxyglucose to measure tissue-specific glucose uptake after steady-state glucose infusion had been reached during a hyperinsulinaemic euglycaemic clamp. Notably, both high (18 mU kg^{-1} min^{-1}) and low (12 mU kg^{-1} min^{-1}) insulin infusions were unable to suppress hepatic glucose output in KD-fed animals. At the same time, the glucose infusion rate required to maintain euglycaemia in KD-fed mice was significantly lower than in chow-fed animals, while traditional HFD was not (Grandl *et al.* 2018). Also, in line with these data, plasma analysis in insulin-stimulated conditions reveal an impairment in glucose tolerance, displayed by increased area under the curve (AUC) during a glucose tolerance test in KD-fed animals, more so than HFD, though both were significantly elevated. Notably, under fasted conditions, where lipid oxidation dominates substrate utilization, HFD-fed animals have increased basal insulin and HOMA-IR index compared to KD. These data suggest that animals consuming the KD are less able to withstand a glucose challenge despite appearing more metabolically healthy under fasted conditions (Grandl *et al.* 2018). This metabolic inflexibility was also evident in the respiratory exchange ratio where KD groups had even lower values (indicative of elevated fat oxidation) compared to traditional HFD.

Research into ketogenic diets has produced conflicting and polarizing results, but Grandl *et al.* present evidence for impaired glucose metabolism following brief KD compared to HFD under insulin-stimulated conditions. These data, observed after only 3 days of feeding, almost completely recapitulate phenotypes observed after more prolonged KD (5 weeks) and align with others showing rapid high-fat diet-induced hepatic fat accumulation and its association with hepatic insulin resistance and increased glucose output (Kraegen *et al.* 1991; Jornayvaz *et al.* 2010). However, this paper did not measure hepatic lipid accumulation or purported mediators of lipid-induced insulin resistance, such as inflammatory markers or protein kinase C (Jornayvaz *et al.* 2010). As expected, massive lipid accumulation following chronic KD, at least compared to chow-fed mice (Jornayvaz *et al.* 2010), has previously been observed, but it would be interesting to compare KD to traditional high-fat diets directly. Unfortunately, Grandl and colleagues also did not assess hepatic insulin signalling. Thus, despite convincing evidence of impaired hepatic insulin sensitivity via multiple clamp experiments, we cannot know where along the insulin pathway these impairments may be and what is contributing to them within the liver itself. Future work should closely investigate the temporal development of hepatic insulin resistance during KD and traditional HFD to provide a more mechanistic explanation for Grandl's results (Grandl *et al.* 2018).

Another important consideration is that liver insulin resistance in KD-fed mice was only evident under fasted insulin-stimulated conditions (Grandl *et al.* 2018). Rigorous KD followers would not be expected to experience oscillations in glucose-stimulated insulinaemic conditions, and thus the relevance of hepatic insulin resistance may be minimal. However, intermittent followers of the KD may be negatively impacted by the inability of insulin to suppress hepatic glucose output, as they would develop exacerbated KD-induced hepatic insulin resistance, then subsequently challenge their system with high glucose and insulin. This has implications for a human population that is likely to have poor adherence to such a stringent and restricted diet plan.

Grandl's article shows that KD-associated glucose intolerance is most likely the result of increased liver glucose output rather than impaired glucose uptake by other tissues (Grandl *et al.* 2018). While a mechanism was not elucidated, results of the current study demonstrate that the inability of insulin to suppress hepatic glucose output is exacerbated in KD-fed animals compared to both chow-fed and traditional HFD animals (Grandl *et al.* 2018). Notably, systemic glucose intolerance is worsened

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in KD-fed animals when compared to traditional Western-style HFD. While KD is a strategy used for weight loss in obese models (Foster *et al.* 2003), the present study presents evidence for acute KD-induced hepatic insulin resistance.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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