Vitamin D and sex affect metabolic function and the development of NAFLD

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Background: Both dietary fat and vitamin D deficiency have been linked with insulin resistance and increased incidence of non-alcoholic fatty liver disease (NAFLD). While disparities in disease rates between males and females have been observed, differences in the susceptibility to, and the mechanisms of disease progression are still to be well characterized. This study aimed to assess the impact of vitamin D deficiency on liver and metabolic function in both sexes, in response to a normal and high fat diet.

Methods: Male and female C57/BL/6 mice underwent a 5 week dietary intervention aimed at inducing an increase in adiposity and vitamin D deficiency. At weaning, mice received one of four diets, which were either low (5% wt/wt) or high fat (22% wt/wt), and either vitamin D replete or deficient. At ~8 weeks of age mice were subject to a glucose tolerance test to assess insulin sensitivity. Mice were allowed to recover and 2-3 days later were euthanized *via* IP injection of sodium pentobarbital (60mg/kg bodyweight). Gonadal fat pads were excised and weighed as a marker of visceral adiposity, while the liver was dissected and fixed for histological analysis. Hepatic fat accumulation was assessed using stereological point counting.

Results: Female mice had significantly greater hepatic fat accumulation *versus* males ($P<0.001$) across all comparisons (eg. low and high fat diets, vitamin D replete and deficient). A high fat diet replete in vitamin D, resulted in increased visceral adiposity ($P<0.001$) and hepatic fat accumulation ($P<0.001$) in both males and females. Vitamin D deficiency, independent of dietary fat, also increased hepatic fat accumulation in both sexes ($P=0.003$). Male mice were more insulin resistant than females (greater AUC; $P<0.001$) and had greater visceral adiposity ($P<0.001$) in both low and high fat fed animals. Only female mice however developed greater insulin resistance in response to high fat feeding (increased AUC and glucose peak; $P<0.01$).

Conclusion: This study is the first to demonstrate vitamin D deficiency alone can result in hepatic fat accumulation, with females at greater risk than males. Fat accumulation in the liver preceded any significant changes in insulin sensitivity and therefore may be one of the earliest signs of metabolic dysfunction. Whether hepatic inflammation is occurring in conjunction with fat accumulation, in response to a high fat diet or vitamin D deficiency could not be determined from this study, but should be investigated as a possible mechanism contributing to the development of insulin resistance. In addition, further studies are required to determine if vitamin D supplementation can be used to prevent or rescue hepatic fat accumulation.