Ad libitum Ketogenic Diet reverts WD-pathological effects in liver, but not in skeletal muscle in mice

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INTRODUCTION

Western diet (WD), rich in sugars and saturated fats, is a critical factor contributing to obesity and its comorbidities. Due to its effects on insulin resistance and inflammation, WD has been associated with many diseases, such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH), and metabolic syndrome (MetS) in both animals and humans.

Ketogenic diets (KDs) are nutritional regimens characterized by very low carbohydrate intake, high-fat amounts, and adequate protein content, with or without caloric restriction. Energy is provided by ketone bodies from lipid oxidation and protein metabolism. Since growing evidence suggests that KDs are able to reduce inflammation, oxidative stress, and improve mitochondrial function, we hypothesized that it could be a strategy to treat obesity-related diseases, including NAFLD and sarcobesity. To test this hypothesis, after 16 weeks of WD diet, we switched mice to standard diet (SD), ad libitum cholesterol-free KD, or maintained in WD for further 2 and 4 weeks.

FIG.1: Schematic representation of the experimental design

RESULTS

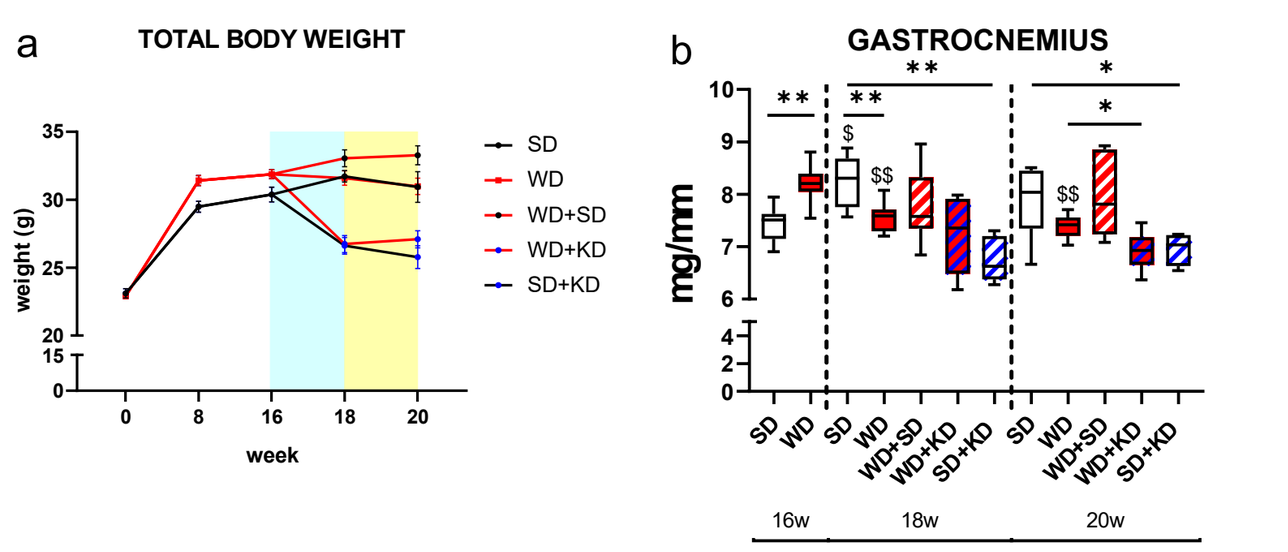


*FIG.2: Total body weight (a), weights of gastrocnemius muscle (b) normalized to tibial length and fat normalized to anus-nose length (c, d). Data are presented as means ± standard error of the mean (S.E.M.), * p<0.05, ** p<0.01 and $ p<0.05, $$ p<0.01 vs 16w. Data were analysed using multiple student's t-test.*

LIVER

KD REDUCES STEATOSIS AND INFLAMMATION WHILE PROMOTING GLYCAEMIC CONTROL

	5° week	6° week	7° week	8° week
ND	Negative	Negative	Negative	Negative
WD	0-5 mg/dl	0-5 mg/dl	5 mg/dl	5mg /dl
KD	10-15 mg/dl	15-20 mg/dl	20-25 mg/dl	30-60 mg/dl

TAB.1: Quantification of ketone bodies of the diets at different weeks

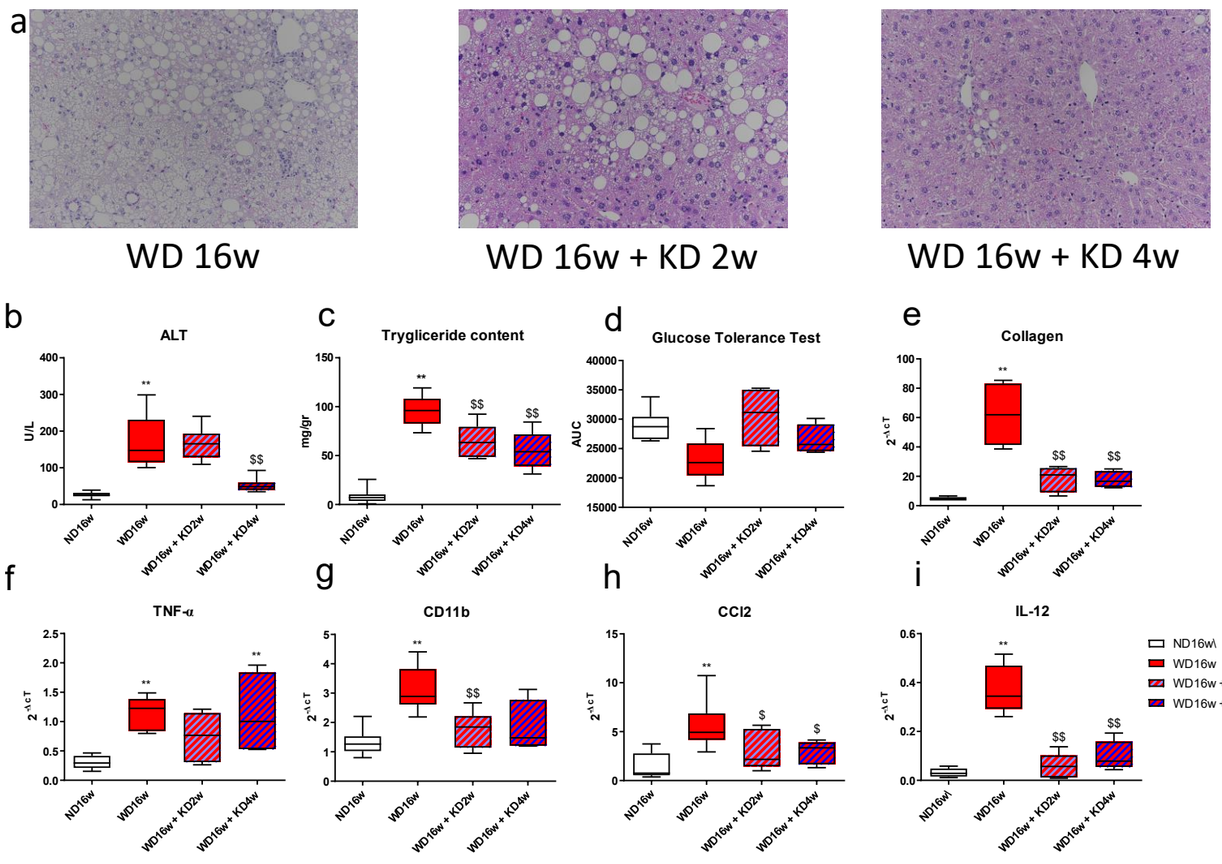
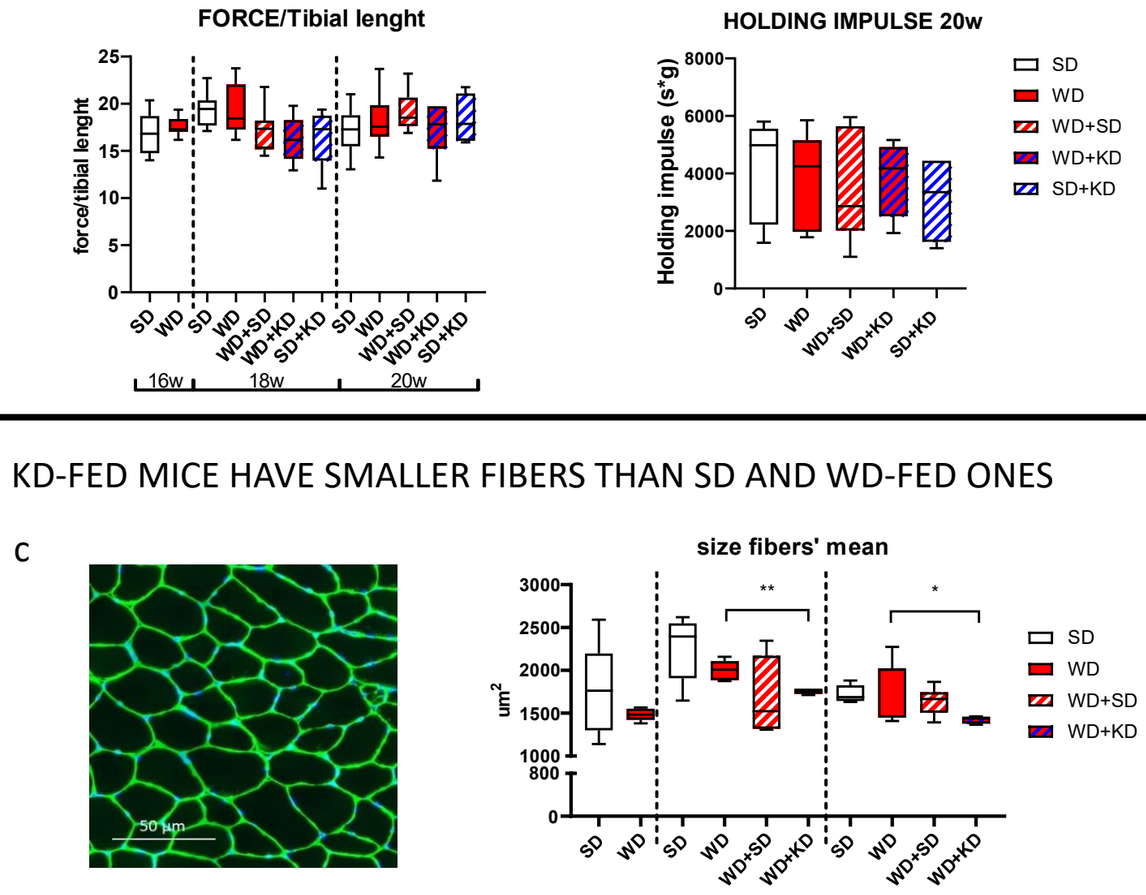


*FIG.3: Representative images of liver section stained with H&E of mice at 16w, 18w, and 20w (a). Quantification of ALT level (b) from blood samples and trygliceride content (c). Relative mRNA expression level of different genes (e-i). Data are presented as means ± standard error of the mean (S.E.M.), * p<0.05, ** p<0.01 vs ND16w and $ p<0.05, $$ p<0.01 vs WD16w. Data were analysed using multiple student's t-test.*

MUSCLE

FUNCTIONAL TESTS DO NOT SHOW DIFFERENCES BETWEEN TREATMENTS



KD-FED MICE HAVE SMALLER FIBERS THAN SD AND WD-FED ONES

*FIG.4: Representation and relative score of grasping test (a) and hanging wire test (b). Representative image of CSA immunofluorescence and quantification of the fiber size mean in gastrocnemius muscle section (c). Data are presented as means ± standard error of the mean (S.E.M.), * p<0.05, ** p<0.01 Data were analysed using multiple student's t-test.*

CONCLUSION

We demonstrated that both KD and SD are able to revert detrimental effects induced by WD in mouse liver, improving the pathological features and lowering the hepatic inflammatory responses associated with NASH. KD resulted in ketosis and mimicked fasting conditions promoting body weight loss and glycaemic control. However, KD did not have positive effects on skeletal muscle strength, mass, and histologic morphology after WD-induced muscle atrophy.Despite the positive effect on WD-induced liver damage and increased body weight, ad libitum KD does not seem to have protective effects againsT WD-associated loss of muscle mass and functionality. However, we cannot rule out that muscles might need a longer recovery period than the liver.

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