Increased expression of ATP-binding cassette transporter A1 (ABCA1) by cilostazol may be a possible mechanism for its protective effect against hepatic steatosis

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BACKGROUND

Cilostazol, a selective inhibitor of phosphodiesterase 3 (PDE3), which has been widely used in patients with atherosclerotic diseases, is known to have additional beneficial effects on dyslipidemia. However, the mechanism whereby cilostazol increases plasma high-density-cholesterol(HDL) is not completely understood. ATP-binding cassette transporter A1(ABCA1), a membrane protein, which mediates the transport of cellular cholesterol and phospholipid to lipid-deficient apolipoproteins, is known to play a critical role in the regulation of intracellular cholesterol levels in hepatocytes.

OBJECTIVES

The aim of this study was to investigate the effect of cilostazol on expression of hepatic ABCA1 in a human hepatocellular carcinoma cell line(HepG2) and high-fat-induced dyslipidemic mice. The study was also designed to evaluate whether cilostazol have an effect on hepatic steatosis by increased ABCA1 through HDL-cholesterol level, to maybe a possible mechanism for ameliorating hepatic steatosis.

MATERIALS & METHODS

***in vitro* study**

Subject: HepG2

Treatment: Cilostazol (CILO), Palmitate (PA)

siRNA: siABCA1 transfection

Oil-Red-O staining: lipid cholesterol accumulation

Immunoblot: ABCA1 protein expression

***in vivo* study**

Subject: C57BL/6 (male, 7 weeks old) Duration: 9 weeks

Experimental Groups:

1> (n=10) Chow + vehicle (CC)

2> (n=14) High Fat (60% kcal) + vehicle (HD)

3> (n=9) High Fat (60% kcal) + cilostazol(30mg/kg/day) (HC)

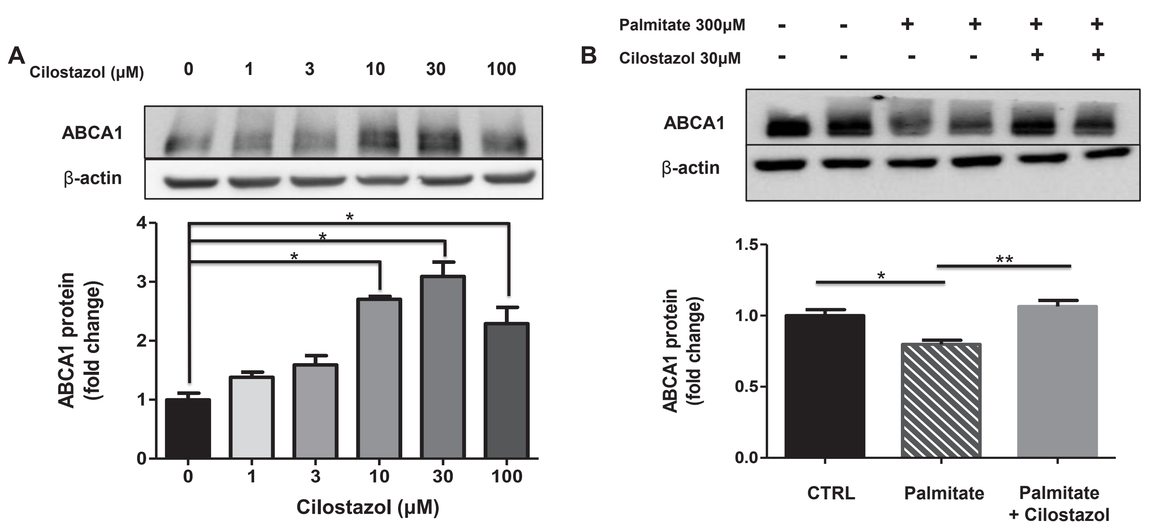
Oral glucose tolerance test (OGTT)

H&E staining – lipid and cholesterol accumulation in liver

Immunoblot: ABCA1 protein expression

RESULTS

Figure 1. Cilostazol increased ABCA1 expression in HepG2 cells. Immunoblot analysis of ABCA1 in HepG2 with cilostazol in dose-dependent manners (A) and ABCA1 in HepG2 with palmitate and cilostazol (B).



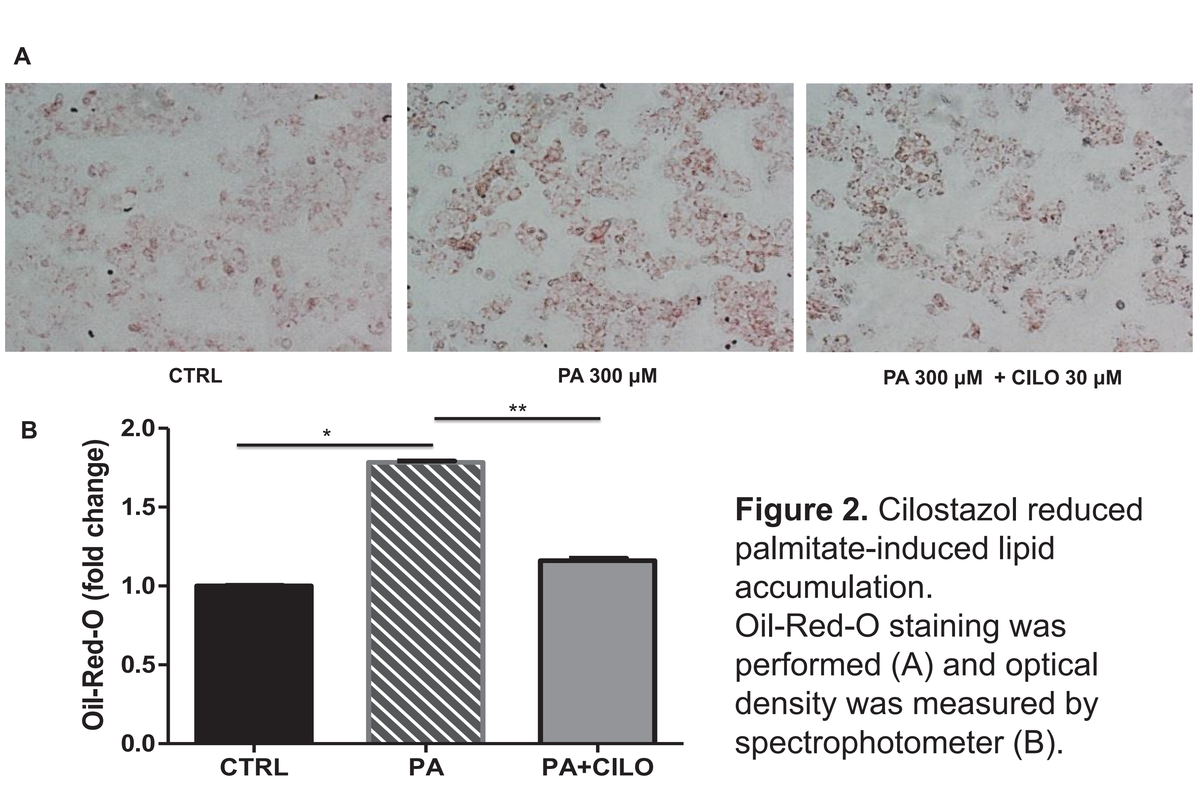


Figure 2. Cilostazol reduced palmitate-induced lipid accumulation.
Oil-Red-O staining was performed (A) and optical density was measured by spectrophotometer (B).

Figure 3. Lipid accumulation were reduced in HepG2 cells incubated without siCTRL(A), but had no effect in HepG2 cells incubated with siABCA1(B). optical density was measured by spectrophotometer (C,D) and HepG2 cells were incubated with siABCA1 for 24h (E).

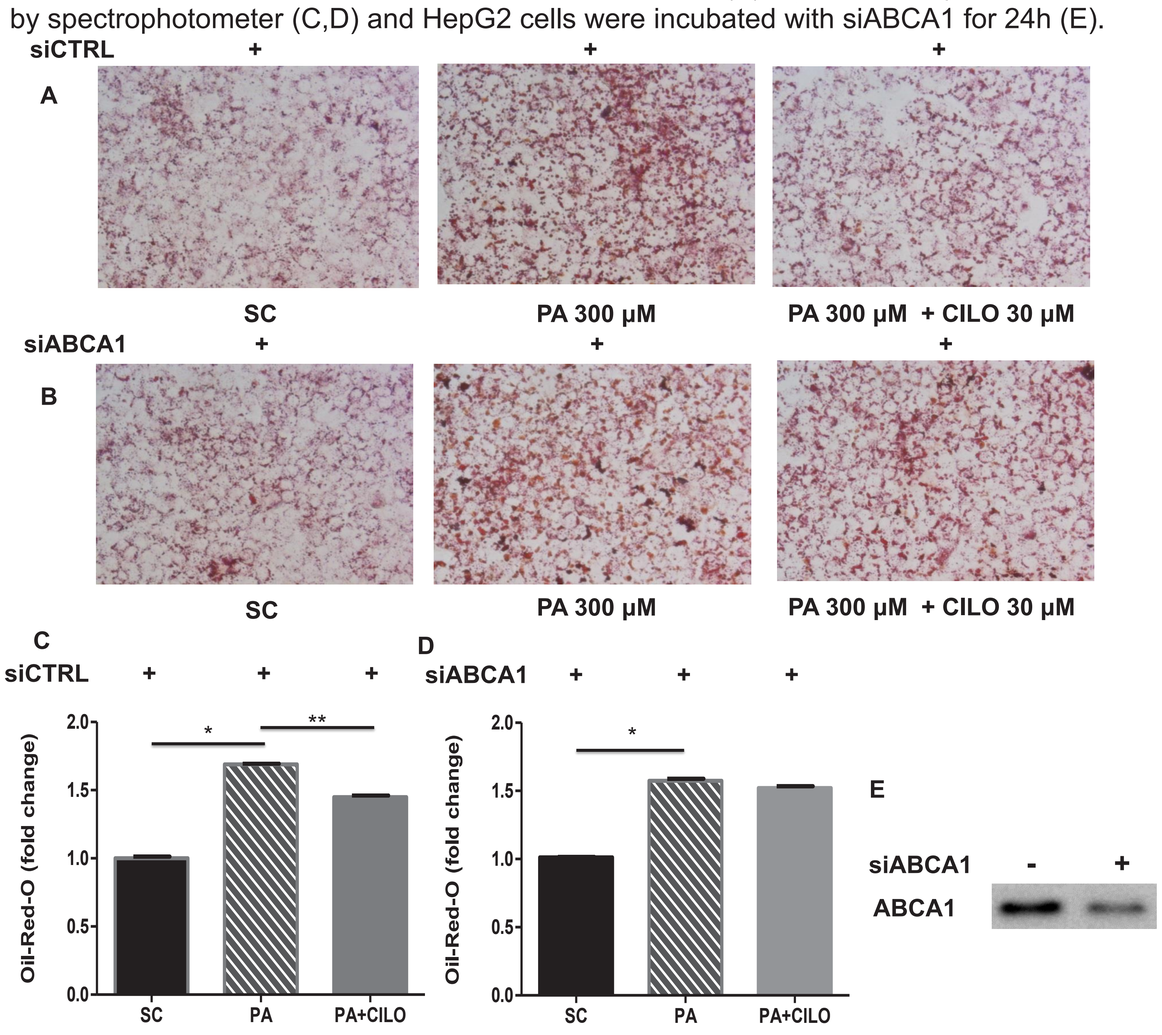


Figure 4. Cilostazol ameliorated hyperglycemia and lipid accumulation in high-fat diet induced obesity mice. Body weight (A) and OGTT (B) were measured. Liver weight/body weight ratio (C) and liver weight (D) were determined. H&E staining (E) and immunoblot (F) analysis were performed in each experimental group.

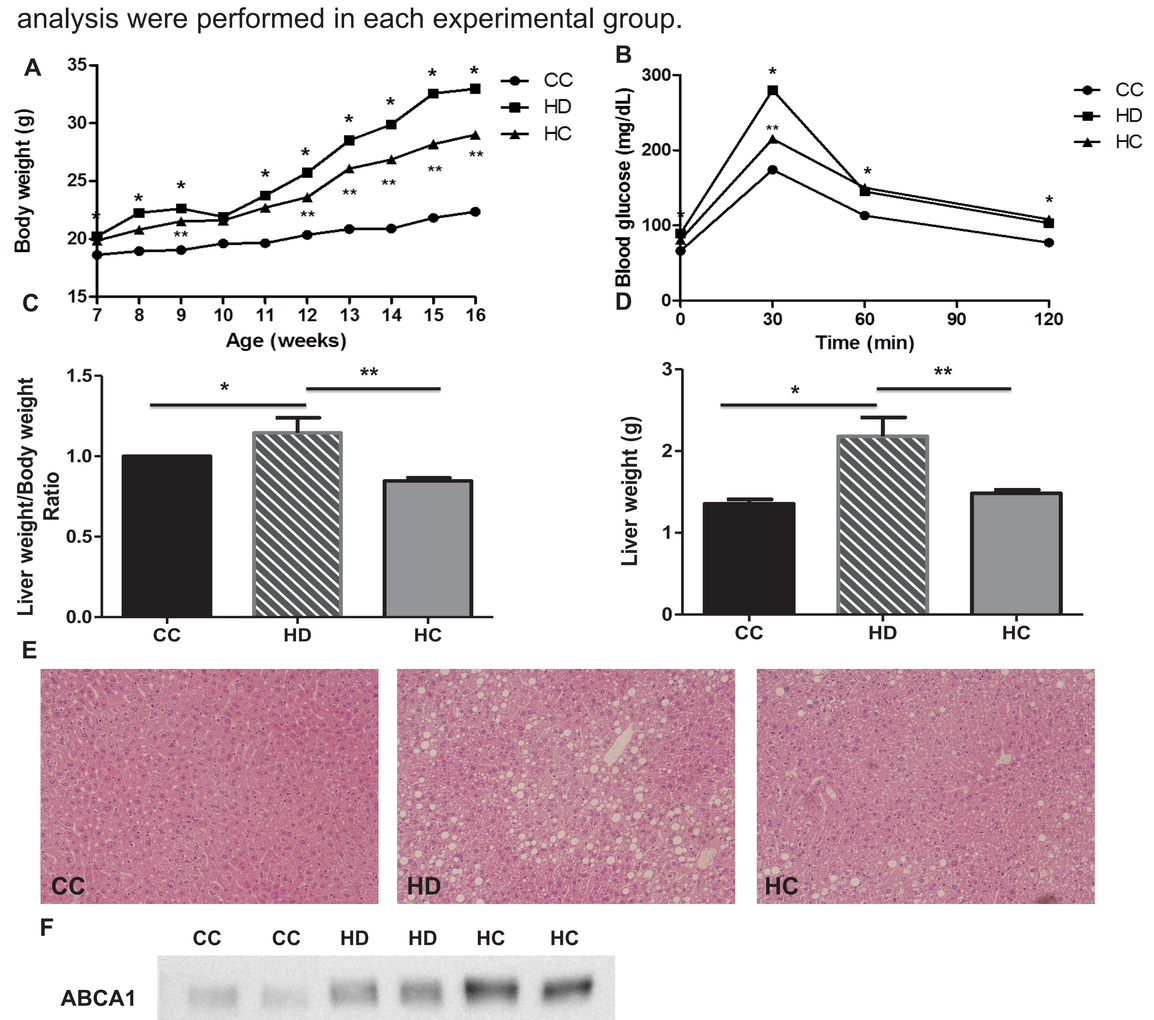
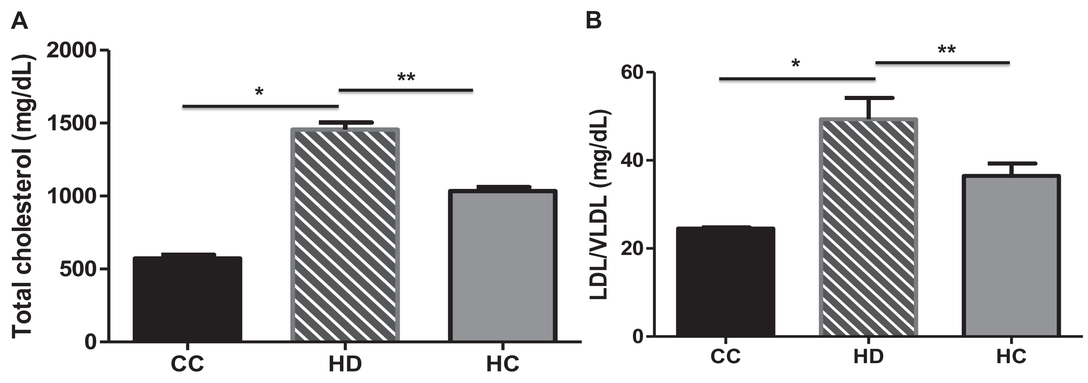


Figure 5. Cilostazol reversed plasma Total cholesterol (A) and LDL/VLDL (B) levels induced by high-fat diet.



CONCLUSION

Cilostazol ameliorated hepatic steatosis and increased ABCA1 expression in diet-induced obesity. Knockdown of ABCA1 in hepatocytes inhibited the protective effect of cilostazol on lipid accumulation in vitro. This implicates that cilostazol may have a beneficial role in the treatment of non-alcoholic fatty liver disease.

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