Scientists provide novel insights into the effects of alternate day fasting on atherosclerosis

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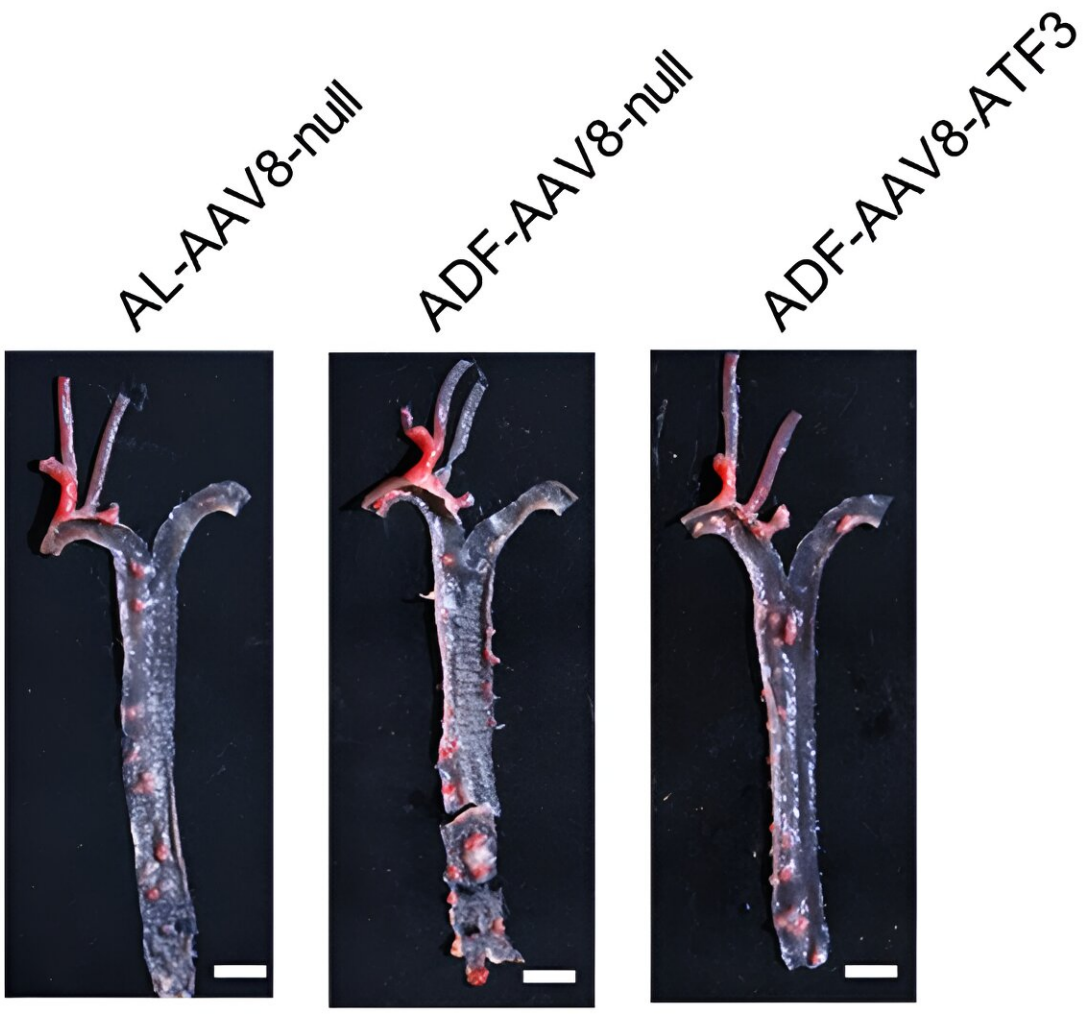

Hepatocyte-specific overexpression of ATF3 attenuates the effects of ADF on atherosclerotic plaque formation. Credit: Frontiers Journals

Atherosclerosis is the major contributor to cardiovascular mortality worldwide. Diet-induced metabolic abnormalities including obesity, hyperglycemia, dyslipidemia, insulin resistance (IR), and non-alcoholic fatty liver disease are considered atherogenic risk factors.

Alternate day fasting (ADF) has gained growing attention due to its dramatic effects on improving disordered metabolic parameters. However, the roles of ADF in obesity-related cardiovascular diseases remain to be addressed, as the effects of ADF on atherosclerotic plaque formation remain inconsistent and controversial in atherosclerotic animal models.

Using atherogenic mice lacking apolipoprotein E ($Apoe^{-/-}$), scientists from Nanfang Hospital of Southern Medical University and Shanxi Medical University Second Hospital have worked jointly and reported that ADF aggravated Western diet (WD)–induced atherosclerotic lesion formation, and they also validated that such effects were mediated by inhibiting the expression of hepatic activating transcription factor 3 (ATF3) under ADF intervention.

The findings suggest the potentially harmful effects when ADF intervention is applied to the population at high risk of atherosclerosis. This study, titled "Alternate day fasting aggravates atherosclerosis through the suppression of hepatic ATF3 in $Apoe^{-/-}$ mice," was published online in *Life Metabolism*.

In this study, 11-week-old male $Apoe^{-/-}$ mice fed with WD were randomly grouped to ad libitum and ADF group. ADF aggravated WD-induced early and advanced atherosclerotic lesion formation in $Apoe^{-/-}$ mice. Although ADF protected $Apoe^{-/-}$ mice from obesity, hyperglycemia, and fatty liver and promoted energy expenditure, it

deteriorated cholesterol profiles as hepatic cholesterol content and circulating cholesterol levels were increased.

Liver RNA sequencing results in these mice demonstrated that ADF treatment significantly inhibited the hepatic integrated stress response (ISR) and decreased hepatic ATF3 expression. Hepatocyte-specific overexpression of Atf3 attenuated the effects of ADF on atherosclerotic plaque formation, indicating that the suppressed ATF3 expression in the liver was one of the contributing factors that mediated the modulatory effects of ADF on hepatic cholesterol accumulation and circulating cholesterol profile.

The expression of ATF3 had a significant relevance with the expression of Krüppel-like factor 6 (KLF6), which is a zinc finger transcription factor. In hepatocytes treated with ISR stressor, the expression of ATF3 could be regulated by KLF6, and both the expressions of ATF3 and KLF6 were regulated by the hepatic cellular ISR pathway. Mechanistically, ADF inhibited hepatic ISR and decreased the expression of KLF6 and ATF3.

This study provided novel insights into the effects of ADF on atherosclerosis by verifying that the deteriorated cholesterol profiles under ADF intervention might contribute to the worsened atherosclerosis in $Apoe^{-/-}$ mice fed with WD. In addition, the study indicated that ADF inhibited hepatic ISR signaling pathway and KLF6 expression, and unraveled the previously unknown regulative effects of transcription factor KLF6 on hepatic ATF3 expression.

ATF3 could act as a downstream component of ISR in the liver and the study shed light on the role of hepatic ATF3 in mediating the effects of ADF on atherosclerosis, thus providing evidence supporting the diverse effects of hepatic ISR in regulating cholesterol metabolism and atherosclerosis.

More information: Yajuan Deng et al, Alternate day fasting aggravates atherosclerosis through the suppression of hepatic ATF3 in Apoe −/− mice, *Life Metabolism* (2024). DOI: 10.1093/lifemeta/loae009