THE PATHOPHYSIOLOGIC AND MOLECULAR BASIS OF NONALCOHOLIC STEATOHEPATITIS-ASSOCIATED CARDIOMYOPATHY (NAC)

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BACKGROUND

There is a paucity of data on the pathophysiological and molecular basis of myocardial dysfunction in non-alcoholic steatohepatitis (NASH). The Diet-induced animal model of NAFLD (DIAMOND) develops fatty liver, NASH and bridging fibrosis after 4, 16 and 36 weeks respectively, on a typical western diet (WD).

HYPOTHESIS: NASH-associated cardiomyopathy (NAC) is driven by pathways similar to those seen in NASH.

AIMS

(1) To determine if the DIAMOND model reproduces the myocardial dysfunction seen in humans with NASH
(2) To determine the histological, cell signaling and transcriptomic drivers of cardiac physiological changes.

METHODS

DIAMOND mice were fed chow diet (CD) or WD for 8 to 52 weeks (n=6-8/group). Trans-thoracic echocardiography was performed. H&E, Sirius Red stains and electron microscopy (EM) were performed. Molecular analysis (PCR/Western blot) of pathways related to NASH pathogenesis, and unbiased analysis (RNA Seq) to evaluate the transcriptome were performed.

RESULTS

DIAMOND mice fed WD SW exhibit obesity (A), hepatomegaly (B), Fatty Liver, NASH and advanced fibrosis (C).

Figure abbreviations: CD NW, chow diet, normal water; WD SW, Western diet, sugar water; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; BF, bridging fibrosis.

NB: * p value <0.05; ** p value < 0.001.

CONCLUSION

- DIAMOND mice have been shown to develop steatohepatitis (NASH) and associated liver fibrosis while on a WD SW diet.
- As in the liver, these mice exhibit inflammatory and fibrotic changes in the myocardium, namely, non-alcoholic steatohepatitis-associated cardiomyopathy (NAC).
- The hallmark of these myocardial changes is Diastolic Dysfunction (HFpEF).
- The similar pathophysiology b/n NAC and NASH provide potential therapeutic targeting for both entities.

REFERENCES

1. Asgharpour et al.; J Hep 2016