A translational mouse model for NASH and advanced fibrosis in association with atherosclerosis

Anita van den Hoek1, Nicole Worms1, Anita van Nieuwkoop1, Christa de Ruiter1, Aswin Menke1, Sridhar Radhakrishnan2, Martine Morrison1, Kanita Salic1, Robert Kleemann1, Reinout Stoop1, Roelien Hanemaaijer1

1 Department of Metabolic Health Research, The Netherlands Organization for Applied Scientific Research (TNO), Leiden, The Netherlands.
2 Research Diets Inc., New Brunswick, USA.

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a fast-growing liver disorder in the Western world and is associated with an increased incidence of cardiovascular disease and type 2 diabetes. Animal models adequately mimicking this condition and that display both the metabolic and histological features of human NASH/fibrosis are scarce.

AIM

To investigate whether Ldlr−/- Leiden mice on a high fat diet represent a suitable and rapid NASH/fibrosis model to study severe stages of fibrosis in the context of obesity and associated insulin resistance and CVD.

METHOD

• Ldlr−/- Leiden mice were fed high-fat diets (no added cholesterol) containing lard or milk fat for 28 weeks. Effects on body weight, plasma and liver biochemical variables, liver histology, adipose tissue inflammation (lard-based diet) or hepatic inflammation and fibrosis (lard-based diet) were assessed. The response to treatment (week 18-28) with 10 mg/kg/d FXR agonist obeticholic acid (OCA) on NASH and fibrosis was also evaluated.

• Additionally, disease induction at earlier timepoints in the milk-fat group were investigated by taking a liver biopsy at t=12 weeks and sacrifice at t=22 weeks.

RESULTS

Ldlr−/- Leiden mice on high fat diets develop NASH with progressive fibrosis

At t=28 weeks:

<table>
<thead>
<tr>
<th>Diet name</th>
<th>High fat diet (HFD)</th>
<th>Fast food diet (FFD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>45% kcal Lard</td>
<td>41% kcal Milk fat</td>
</tr>
<tr>
<td>Protein</td>
<td>20% kcal Casein</td>
<td>14% kcal Casein</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>35% kcal a.o. Sucrose</td>
<td>44% kcal a.o. Fructose</td>
</tr>
</tbody>
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Body weight (g)

- Chow: 38.3 ± 1.5
- HFD: 52.3 ± 1.1
- FFD: 48.7 ± 1.5

Glucose (mM)

- Chow: 7.7 ± 0.4
- HFD: 7.7 ± 0.2
- FFD: 6.5 ± 0.3

Insulin (ng/mL)

- Chow: 2.9 ± 0.6
- HFD: 14.7 ± 4.2
- FFD: 3.9 ± 0.4

ALT pooled/group (U/L)

- Chow: 46.6
- HFD: 290.0
- FFD: 364.0

CONCLUSIONS

Ldlr−/- Leiden mice fed high-fat diets recapitulate features of the metabolic syndrome and NASH with progressive liver fibrosis and simultaneous atherosclerosis development.

By adaptation of the fat content of the diet, either insulin resistance and adipose tissue inflammation (lard-based diet) or hepatic inflammation and fibrosis (lard-based diet) can be emphasized.

This represents a novel translational animal model of NASH/fibrosis in association with atherosclerosis that can be used to investigate the effects of new drugs or drug combinations.

CONTACT INFORMATION

Roeland.Hanemaaijer@tno.nl
A.vandenhoek@tno.nl