Effect of Ω3 Fatty Acids on Leptin Knock-out Mice

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Background & Methods
Fish oil, high in Ω3 fatty acids, decreased incidence of fatty livers in our earlier work. The present model used OB/OB (leptin knock-out) mice with naturally occurring fatty livers. Purified Ω3 (20% EPA, 50% DHA) was added to their food pellets, giving a daily dose of 4.65 mg Ω3 (equivalent to a human dose of ~4 grams/day). Original Design was to evaluate fatty livers of 10 untreated OB/OB and compare them to the 10 Ω3 fatty acid-treated group. However, half of the 10 Ω3 fatty acid-treated group died during the 2 months of the study; 80 OB/OB mice with other treatments did well.

My original experiment was to report on liver histopathology change in the Ω-3 vs untreated groups. This report does briefly compare the livers but has added an investigation of the untimely and unexpected deaths and possible mechanisms for it.

Results
• Background: At 2 months, the 5 Ω3 survivors had high blood glucose; two of the five survivors measured 600 mg/dl.
• Secondary Hypothesis: Evaluation of the hearts of the Ω3 survivors will show differences in cardiac structure and morphology from untreated mouse hearts.
• Formalin fixed hearts were sectioned, stained, and photographed.

We accept the null hypothesis for Hypothesis 2: The high blood glucose in Ω3 survivors did not reflect loss of a leptin receptor that might have contributed to death in the Ω3 mice.

• Published studies in man show that diabetes increases myocardial cell apoptosis, necrosis, and death.
• Hypothesis 3: Evaluation of the hearts of the Ω3 survivors will show differences in cardiac structure and morphology from untreated mouse hearts.
• Formalin fixed hearts were sectioned, stained, and photographed. Analysis with guidance from a pathologist (A.M.)
• At 100x a significant decrease in cellularity was seen; at 1000x large areas of cardiac myocytes were totally acellular.

UNEXPECTED EVENTS OCCURRED: Ω3 FATTY ACIDS APPEAR TO BENEFIT THE LIVER. WHY DID 5 MICE DIE?
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Conclusions / Discussion
• This study showed improvement in hepatic steatosis in OB/OB leptin k/o mouse receiving Ω3 fatty acids equivalent to a high clinical dose.
• One half the group died without overt symptoms.
• Survivors had elevated blood glucose at 2 month necropsy; 3 were >600 mg/dl.
• Mechanisms of death were investigated; leptin receptor loss was measured and eliminated as contributory.
• Cardiac myocytes showed aberrant appearance and avascular morphology.
• Proposed: cardiac cell change in structure and morphology, seen in humans with long-term diabetes, contributed to the sudden death of these animals.

References

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