Softened food reduces weight loss in the STZ-induced diabetic nephropathy model in mice

Diabetes Complications Pharmacology, DC research, Novo Nordisk A/S

Background
Streptozotocin (STZ) treatment of mice is a widely used model of diabetes and diabetic nephropathy. However, this model is well known to have issues with high weight loss and high euthanization rates due to the toxic nature of STZ resulting in: (1) overall low animal welfare, (2) a need for large group sizes, (3) a need for extensive health monitoring and supportive measures i.e. insulin and saline injections.

The initiative
To overcome these issues, we hypothesized that STZ-induced diabetic mice given ground, water-softened food once daily in addition to normal chow would result in: (1) reduced acute weight loss, (2) reduced euthanization rate due to humane endpoints, (3) less supportive insulin and saline injections, (4) overall improved animal welfare.

Study
This hypothesis was investigated in a 15 week STZ-induced diabetic nephropathy study where the mice were given normal chow or chow plus a portion of ground, water-softened chow once daily. Upon 10% weight-loss mice were given supportive insulin and saline and at 20% weight loss the mice were euthanized. Blood glucose, HbA1c and albuminuria were monitored to evaluate the impact of the initiative on diabetes and diabetic nephropathy.

Results
Giving the STZ-induced diabetic animals ground, water-softened food in addition to normal chow resulted in significantly reduced acute weight loss during the initial 3 weeks post STZ injection. Throughout the study, fewer mice experienced significant weight loss (>15%) when given softened food and fewer mice needed supportive injections of insulin and saline. Without softened food, more mice reached the humane endpoint but due to the extent of supportive measures this did not reach statistical significance. Furthermore, a lower faecal excretion of stress hormone in the mice given softened food indicates a lower stress level in these mice.

The initiative did not affect the induction or magnitude of diabetes or diabetic nephropathy, suggesting an intact disease model despite this initiative.

Impact of initiative and future plans
This initiative is REFINING the animal model significantly by reducing weight loss and lowering the need for supportive insulin and saline indicating an overall improved general well-being of the animals.

This initiative REDUCES the number of animals needed in studies as fewer animals reach significant weight loss and the humane endpoint.

Implementing this initiative could potentially lead to pharmacology studies with more power and less variation thereby lowering the risk of inconclusive results. This study indicates that up to 30% of mice subjected to STZ potentially could be saved by including softened food. In our department, up to 2500 mice per year could be affected, but if implemented in other departments and outside Novo Nordisk it is estimated that it could affect many thousands of animals annually. Currently, this initiative has been assessed in the STZ-induced diabetes/diabetic nephropathy model but could potentially be considered in any animal model where high weight loss is an issue.

We plan to publish the results of this study so researchers using this model or other models with weight loss issues could consider implementing this in their protocols.