Evaluation of Zucker Diabetic Fatty and ZSF1-Obese Rats as Potential Models for Diabetic Retinopathy

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1 ABSTRACT

The most common animal model for assessing diabetic retinopathy is the Streptozotocin (STZ)-induced rodent model. This model involves injection of STZ followed by glucose monitoring to confirm the diabetic state. Development of ocular lesions takes several weeks and study duration may be longer, during which time the health of the animals may be declining due to the diabetic state. This study was designed to monitor ZDF and ZDF-1 obese rats as a potential spontaneous model of diabetic retinopathy.

Fifteen rats (2 ZDF rats and 13 ZSF1-obese rats) were evaluated for ocular changes indicative of spontaneous development of diabetic retinopathy. Additionally, 4 ZSF1-lean rats were evaluated as controls. Adult animals were used. Over a period of 11 weeks, the animals were evaluated approximately biweekly via ophthalmic examinations and optical coherence tomography (OCT). Slit lamp biomicroscopy was used to assess the anterior chamber and lens. Indirect ophthalmoscopy was used to assess the posterior chamber. OCT was conducted using the Heidelberg Spectralis to collect infrared reflectance (IR)+OCT scans.

One ZDF animal was noted with focal retinal degeneration, while the second ZDF animal was noted with irregular retinal pigmentation. Ophthalmic findings for all other animals were limited to lens capsule and lens nucleus opacities. Once the opacities reached the point where visualization of the fundus was blurred, the animals were released from study. For each rat, there were no substantial changes in OCT scans over the course of the evaluation period. There were no differences in OCT scans between the three rat strains.

After 11 weeks of monitoring, there was no spontaneous development of diabetic retinopathy lesions that were detectable by OCT. Ophthalmic examinations demonstrated retinal changes in both ZSF1-obese animals. The ZDF strain does not appear to provide a spontaneous model of diabetic retinopathy that would be useful in the contract research setting; however, further evaluation via fluorescein angiography may provide useful data for characterizing retinal changes. Further evaluation of more ZSF1-obese animals is warranted.

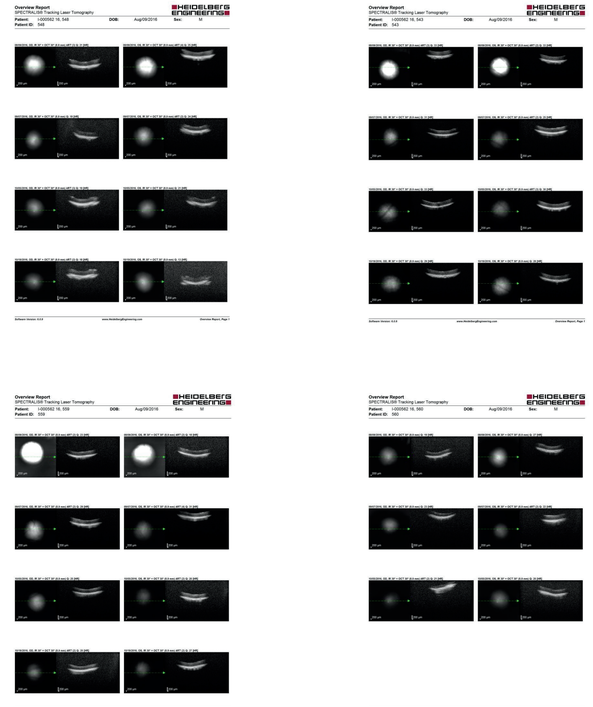
2 MATERIALS AND METHODS

Ophthalmic examinations consisted of slit lamp biomicroscopy (KOWA handheld biomicroscope) to assess the anterior chamber and indirect ophthalmoscopy (Keeler All-pupil with Volk 28 diopter and 20 diopter lenses) to evaluate the lens, vitreous, retina and optic nerve. Examinations were conducted on Days 4, 17, 31, 45, 59, and 73 relative to the start of observations.

Optical coherence tomoography (OCT) was conducted using the Heidelberg Spectralis. The simultaneous imaging mode was used to capture infrared reflectance confocal scanning laser ophthalmoscopy (cSLO) images and optical coherence tomography scans.

3 RESULTS

Animal ID	Strain	Ophthalmic Examinations
538	Zucker Diabetic Fatty	Days 4, 17, 31, 45 OU slight to moderate posterior lens capsule opacity; Day 59 OS and Day 73 OU prominent lens nucleus
539	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59 OU slight to severe posterior lens capsule opacity; Days 59 and 73 OU prominent lens nucleus; fundus not visible after Day 31
540	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
541	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity; Days 59 and 73 OU prominent lens nucleus
542	ZSF1-lean	Days 4, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
543	ZSF1-lean	Days 4 (OU), 17 (OD), 31 (OD), 45 (OU), 59 (OU), and 73 (OU) slight to moderate posterior lens capsule opacity
544	ZSF1-lean	Days 4, 17, 31, 45, 59, and 73 OU very slight to moderate posterior lens capsule opacity
545	ZSF1-lean	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
546	ZSF1-lean	Days 4, 17, 31, 45 OU slight to severe posterior lens capsule opacity; Days 31 and 45 OS pigmented corneal opacity; Days 59 and 73 OU prominent lens nucleus; OD fundus not visible on Day 46
547	Zucker Diabetic Fatty	Days 4, 17, 31, 45 OU slight to moderate posterior lens capsule opacity; Day 31 OS pigmented corneal opacity
548	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity; Days 59 and 73 OS prominent lens nucleus
549	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity; Days 59 and 73 OD prominent lens nucleus
550	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
551	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
552	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
553	Zucker Diabetic Fatty	Day 4 OU lens opacity; unable to clearly visualize retina; no further evaluation
554	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to severe posterior lens capsule opacity; Day 73 OD prominent lens nucleus; OS fundus not visible on Day 45
555	Zucker Diabetic Fatty	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity
556	Zucker Diabetic Fatty	Day 4 OU Lens opacity; unable to clearly visualize retina; no further evaluation
557	ZSF1-Obese	Day 4 OU Lens opacity; unable to clearly visualize retina; no further evaluation
558	ZSF1-Obese	Day 4 OU Lens opacity; unable to clearly visualize retina; no further evaluation
559	ZSF1-Obese	Days 4, 17, 31, 45, 59, and 73 OU slight to moderate posterior lens capsule opacity; Days 59 and 73 OS **irregular retinal pigmentation**
560	ZSF1-Obese	Day 2 OU **slight focal retinal degeneration**; Days 17, 31, and 45 OD **moderate focal retinal degeneration**; Day 59 OD **retinal hyperpigmentation**; Days 4, 17, 31, 45, and 59 OU slight to severe posterior lens capsule opacity; Day 59 OD prominent lens nucleus; OD fundus not visible on Day 45



4 CONCLUSIONS

Diabetic retinopathy causes changes that can lead to leakage from retinal vasculature and macula edema. These changes lead to loss of vision, and disease models play an important role in developing new therapies to prevent blindness. After 11 weeks of monitoring, there was no spontaneous development of diabetic retinopathy lesions that were detectable by OCT. Ophthalmic examinations demonstrated retinal changes in both ZSF1-obese animals. The ZDF strain does not appear to provide a spontaneous model of diabetic retinopathy that would be useful in the contract research setting; however, further evaluation vial fluorescein angiography may provide useful data for characterizing retinal changes. Further evaluation of more ZSF1-obese animals is warranted.