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ZDSD Rat

A more translatable rat model for metabolic syndrome, obesity, diabetes, and diabetic complications

What is the ZDSD Rat?

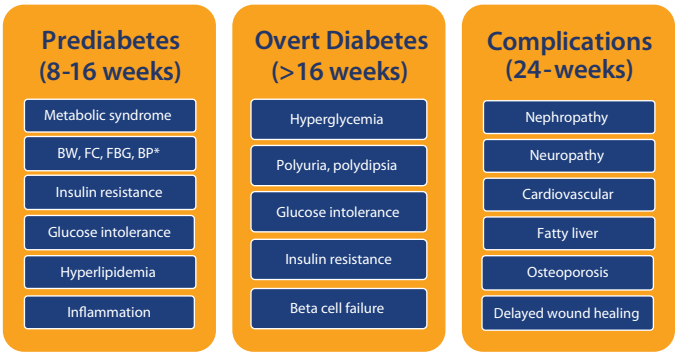
The ZDSD rat is an inbred polygenic model for metabolic syndrome, obesity, diabetes, and diabetic complications. Unlike other rodent models of metabolic disease, the ZDSD rat does not rely on monogenic leptin or leptin receptor mutations for development of obesity and Type 2 diabetes, which more closely mimics human disease development. This results in a more translatable choice for evaluating your therapeutic agents.

The ZDSD rat was developed by crossing the ZDF rat (Lean +/+) with the *CD(SD)* rat and selectively bred for obesity and diabetes traits, followed by inbreeding for more than 35 generations. The resulting ZDSD rat model displays:

- Type 2 diabetes progression similar to the human disease: pre-diabetes (8-16 weeks of age), through overt diabetes (>16 weeks of age), to diabetic complications (24- weeks of age)
- diabetic complications including nephropathy, neuropathy, fatty liver, etc.
- metabolic syndrome characteristics including increased body weight with abdominal fat, insulin resistance, dyslipidemia, and hypertension (**Figure 1**).

Figure 1: Progression of Metabolic Syndrome and Diabetes in the ZDSD Rat

*BW: body weight; FC: food consumption; FBG: fasting blood glucose; BP: blood pressure.



The ZDSD Rat More Closely Mirrors the Human Metabolic Syndrome Phenotype than Conventional Rodent Models

Most rodent models of Type 2 diabetes have a monogenic mutation that is responsible for the initiation of obesity and subsequent insulin resistance. The two most common obesity-causing mutations involve:

- the leptin receptor, observed in
  - Zucker Fatty (ZF) rat
  - Zucker Diabetic Fatty (ZDF) rat
  - *db/db* mouse
- the leptin molecule, observed in
  - *ob/ob* mouse

However, both leptin and leptin receptor mutations are rare in humans. The ZDSD rat does not rely on these leptin receptor mutations, and instead has an early onset of polygenic obesity in the absence of a high calorie diet by two months of age, with early onset diabetes starting around 4 months of age (**Figure 2**). This more closely mirrors the human metabolic syndrome than conventional rodent models (a comparison of the ZDSD rat with conventional rodent models is shown in **Table 1**). The ZDSD rat also displays hyperglycemia, impaired glucose disposal and tolerance, and insulin resistance (**Figure 2**), with a slower progression to overt diabetes when compared with the ZDF rat, due to a slower deterioration of beta cell function. Insulin levels also decline as the diabetic phenotype progresses (**Figure 3**), similar to the human disease, and diabetic complications occur.

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Figure 2: Development of Obesity, Hyperglycemia, Impaired Glucose Disposal and Tolerance, and Insulin Resistance in the ZDSD and SD Rat

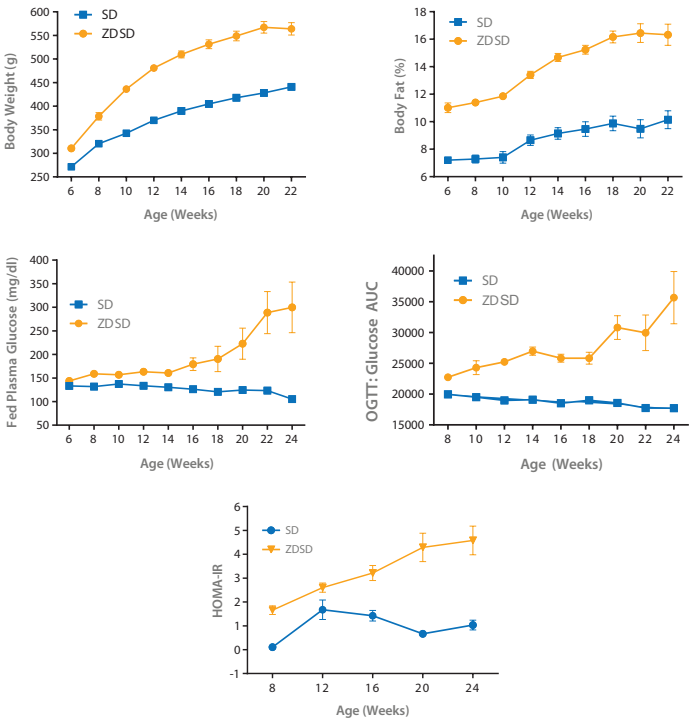
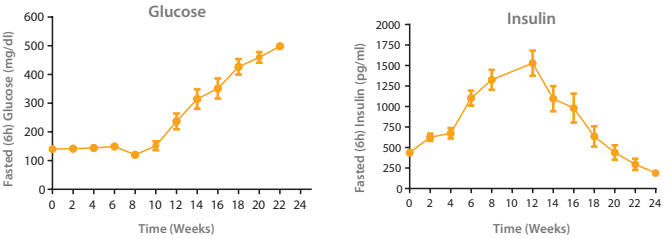


Figure 3: Insulin Levels Decline as Diabetes Progresses in the ZDSD Rat

Rats are 7 weeks of age at Time 0.



The ZDSD Rat Responds to Antidiabetic Therapies

The ZDSD rat has been shown to respond to a variety of antidiabetic therapies. Agents including metformin, rosiglitazone, and exenatide prevented diabetes in ZDSD rats (**Figure 4**). Rosiglitazone has been shown to improve insulin sensitivity in ZDSD rats, with sitagliptin shown to improve glucose tolerance.

Figure 4: Antidiabetic Drug Treatment Prevents Diabetes and Weight Loss in ZDSD Rats

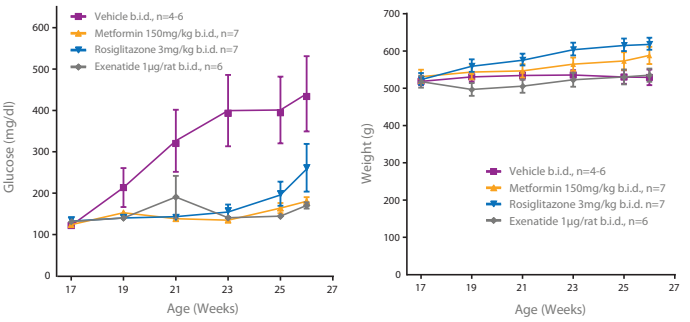


Table 1: The ZDSD Rat vs Conventional Murine Models

Model	ZDSD	ZDF	Zucker	DIO* rat
Leptin pathway	Intact	Lepr^{fa}, defective	Lepr^{fa}, defective	Intact
Obesity	Yes	Yes	Yes	Yes
Insulin resistance	Yes	Yes	Yes	Yes
Glucose intolerance	Yes	Yes	Yes	Yes
Dyslipidemia	Yes	Yes	Yes	Yes
Hypertension	Yes	No	No	?
Hyperglycemia /overt diabetes	Yes, from 19 weeks	Yes, from 8-11 weeks	No	No
Beta cell failure	Late	Early	No	No
Comorbidities	Many	Some	No	No
Translational	+++++	++	+	+

*Diet induced obesity

Dyslipidemia – Why Choose the ZDSD Rat to Evaluate Antilipogenic Compounds?

Patients with Type 2 diabetes and metabolic syndrome often present with dyslipidemia, displaying elevated cholesterol and triglycerides, and decreased HDLc, which has been shown to impact on cardio-vascular and renal comorbidities. In ZDSD rats on a normal diet, hypertriglyceridemia manifests as early as 12 weeks of age, and levels progress up to 500mg/dl by 15 weeks of age. Increases in cholesterol are not as dramatic as triglycerides, and may be induced by feeding a high fat diet (a comparison of the ZDSD rat with the ZDF rat is shown in **Figure 5**). The ZDSD model responds to classic reference agents including rosiglitazone, and response to treatment with niacin is shown in **Figure 6**.

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Figure 5: Comparison of ZDSD Rat with Available Dyslipidemic Models

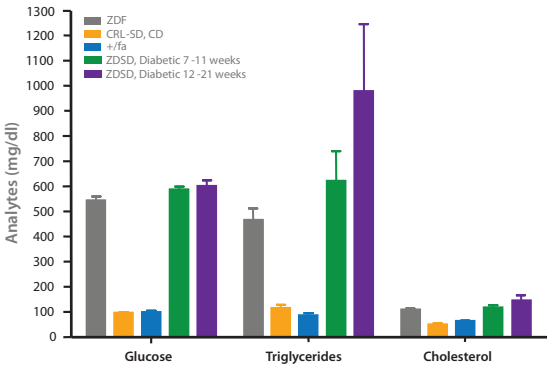
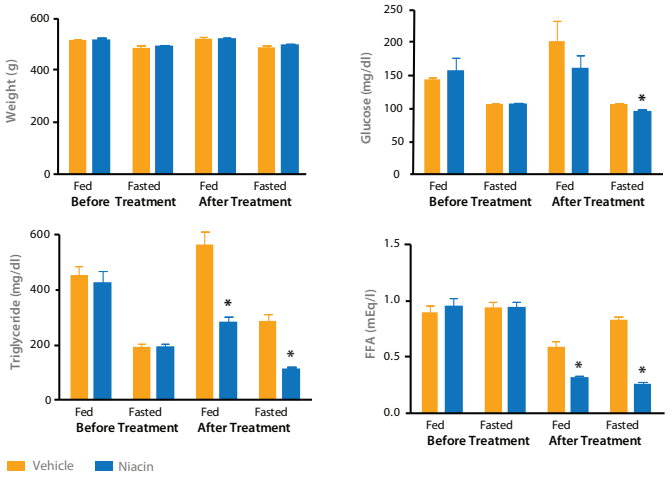


Figure 6: ZDSD Rat Responds to Niacin Treatment

Treatment: 100mg/kg, q.d. for 7 days.



Hypertension – An Integral Component of Metabolic Syndrome

High blood pressure is a key symptom of metabolic syndrome and is a major contributor to the increased risk of cardiovascular disease, kidney disease, and ischemic stroke seen in these patients. Examination of the interactions of all the components of the syndrome in rats is complicated by the absence of high blood pressure in current models (e.g. the ZF rat). ZDSD rats present elevated biomarkers for an activated renin–angiotensin–aldosterone system (RAAS), endothelial dysfunction, and aberrant vasoconstriction and direct evidence of hypertension have been confirmed in the prediabetic state via the tail-cuff method as well as telemetry.

Renal Injury (Nephropathy) – Why Choose the ZDSD Rat to Evaluate Diabetic Nephropathy Therapies?

Obesity and metabolic syndrome are clear predictors of chronic kidney disease, largely due to the potentiation of chronic inflammation by insulin resistance. In addition, the lipoprotein abnormalities, increased hemodynamics, hypercoagulability, and vascular dysfunction associated with metabolic syndrome have all been implicated as causative factors in renal disease. Biomarkers for renal dysfunction (i.e. IL6, TNF-α, NGAL, KIM-1, VEGF etc.) as well as significant albuminuria, elevated free fatty acids with oxidative stress, and histological analysis have shown the ZDSD rat to exhibit nephropathy that closely mimics that observed in obese, insulin resistant patients (**Figure 7**). The ACE inhibitor lisinopril was shown to significantly decrease urinary albumin in diabetic ZDSD rats (**Figure 8**).

Figure 7: Diabetic Nephropathy in the ZDSD Rat

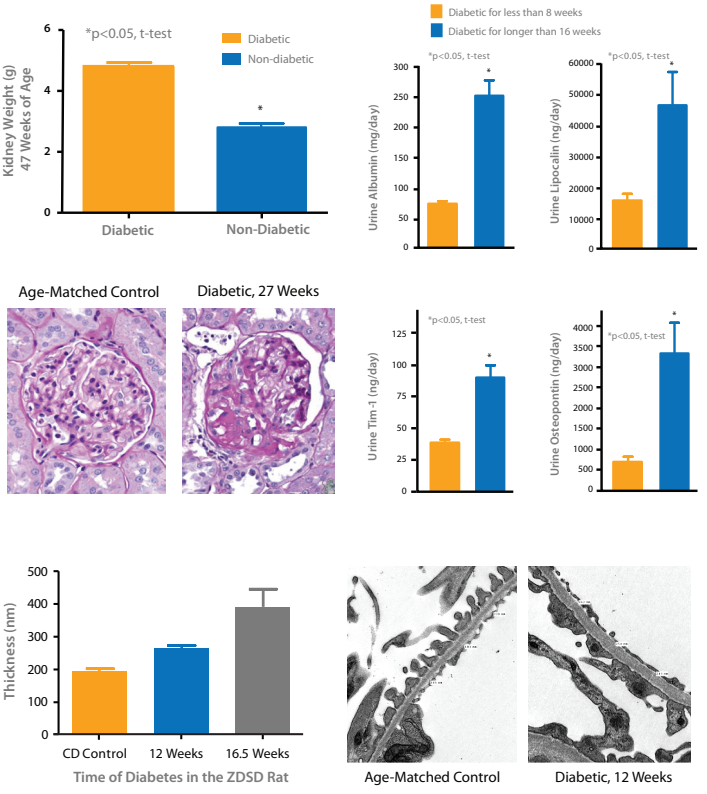


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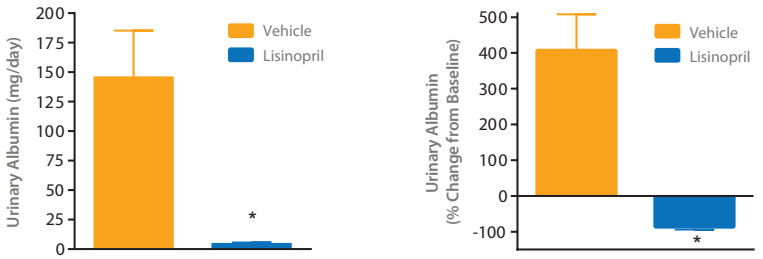
Figure 8: Lisinopril Decreases Urinary Albumin in ZDSD Rats



Summary

The ZDSD rat is a more translatable rat model for obesity, metabolic syndrome, diabetes, and diabetic complications. With an intact leptin pathway, more closely mimicking human disease initiation, the ZDSD rat displays insulin resistance, elevated glucose levels, and glucose intolerance from an early age, providing a *bona fide* prediabetic state that lasts for two months. The progression of human Type 2 diabetes is mirrored in this model, with advancement through insulin resistance, hypertension, dyslipidemia, obesity, and overt diabetes, and with diabetic complications such as nephropathy, osteoporosis, delayed wound healing, neuropathy, and increased cardiovascular/inflammatory markers developing over a reasonable timeframe. Response to a range of agents such as TZDs, metformin, GLP-1 agonists, sitagliptin, niacin, ACE inhibitors, rimonabant, and glyburide has also been observed in the ZDSD rat, showing the model to be highly translatable to the human condition.

Discover the benefits of using the ZDSD rat today to successfully translate your metabolic syndrome, obesity, diabetes, and diabetic complication research into the clinic. Contact us today at **busdev@crownbio.com** for a free consultation about selecting the models that meet your project needs.