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REVIEW ARTICLE

Zucker Diabetic-Sprague Dawley (ZDSD) rat: Type 2 diabetes translational research model

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Abstract

Type 2 diabetes (T2D) is a prevalent disease and a significant concern for global population health. For persons with T2D, clinical treatments target not only the characteristics of hyperglycaemia and insulin resistance, but also co-morbidities, such as obesity, cardiovascular and renal disease, neuropathies and skeletal bone conditions. The Zucker Diabetic-Sprague Dawley (ZDSD) rat is a rodent model developed for experimental studies of T2D. We reviewed the scientific literature to highlight the characteristics of T2D development and the associated phenotypes, such as metabolic syndrome, cardiovascular complications and bone and skeletal pathologies in ZDSD rats. We found that ZDSD phenotype characteristics are independent of leptin receptor signalling. The ZDSD rat develops prediabetes, then progresses to overt diabetes that is accelerated by introduction of a timed high-fat diet. In male ZDSD rats, glycated haemoglobin (HbA1c) increases at a constant rate from 7 to >30 weeks of age. Diabetic ZDSD rats are moderately hypertensive compared with other rat strains. Diabetes in ZDSD rats leads to endothelial dysfunction in specific vasculatures, impaired wound healing, decreased systolic and diastolic cardiac function, neuropathy and nephropathy. Changes to bone composition and the skeleton increase the risk of bone fractures. Zucker Diabetic-Sprague Dawley rats have not yet achieved widespread use by researchers. We highlight sex-related differences in the ZDSD phenotype and gaps in knowledge for future studies. Overall, scientific data support the premise that the phenotype and disease progression in ZDSD rats models the characteristics in humans. We conclude that ZDSD rats are an advantageous model to advance understanding and discovery of treatments for T2D through preclinical research.

KEYWORDS
hyperglycaemia, obesity, preclinical model, type 2 diabetes, Zucker Diabetic-Sprague Dawley rat

1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic and prevalent disease with characteristics of hyperglycaemia, hyperinsulinaemia, insulin resistance and pancreatic β-cell failure. The estimated prevalence of T2D worldwide is 417 million persons, or 90% of all the adults living with diabetes, which includes ~232 million undiagnosed cases (International Diabetes Federation, 2021). In the USA, 10.5% of the population is living with diabetes, and 34.5% of the adult population have clinical signs of prediabetes, a condition characterized by elevated blood glucose concentrations with sustained sensitivity to regulation by insulin (Centers for Disease Control & Prevention, 2020). Unmanaged hyperglycaemia of persons with diabetes is an initiating event leading to organ and system dysfunction associated with T2D. Primary prevention is one priority strategy to reduce morbidity and mortality associated with T2D (American Diabetes Association Professional Practice Committee, 2022). Since the discovery of insulin over a century ago, basic scientific research has provided discoveries leading to new T2D treatments helping to mitigate the increased burden on health-care services and quality of life for persons living with T2D (Chaudhury et al., 2017). In many cases, the origins or translations of these discoveries have relied on preclinical animal models selected to represent the pathophysiology in human T2D appropriately (Kleinert et al., 2018).

New Findings

- **What is the topic of this review?**
  The Zucker Diabetic-Sprague Dawley (ZDSD) rat is in the early adoption phase of use by researchers in the fields of diabetes, including prediabetes, obesity and metabolic syndrome. It is essential that physiology researchers choose preclinical models that model human type 2 diabetes appropriately and are aware of the limitations on experimental design.
- **What advances does it highlight?**
  Our review of the scientific literature finds that although sex, age and diets contribute to variability, the ZDSD phenotype and disease progression model the characteristics of humans who have prediabetes and diabetes, including co-morbidities.

1.1 | What is the Zucker Diabetic-Sprague Dawley rat?

The Zucker Diabetic-Sprague Dawley (ZDSD) rat is an animal model developed for preclinical experimental research on T2D. A substrain of Charles River Crl;CD (Sprague Dawley) rats were crossbred with Zucker Diabetic Fatty (ZDF) lean homozygous wild-type (+/+) rats, which do not carry the leptin receptor mutation (*fa*) (Peterson et al., 2015; Reinwald et al., 2009). Selective inbreeding of the resulting offspring for >30 generations established the ZDSD rat (Peterson et al., 2015). In principle, the phenotypic and genotypic characteristics of the ZDSD rat might be more advantageous for translation of preclinical findings to the clinic compared with the ZDF strain. For example, the ZDSD rat does not carry the leptin receptor mutation (*fa/fa*). Thus, the mechanisms underlying the T2D in ZDSD rats might be more similar to those in humans, because leptin receptor mutations are rare in humans (Davidson et al., 2014). Zucker Diabetic-Sprague Dawley rats also show age-dependent and reproducible progression that bears a qualitative resemblance to prediabetic changes of blood glucose concentration and insulin sensitivity that occur in humans (Choy, de Winter et al., 2016; Han et al., 2020; Peterson et al., 2015); albeit in some cases spanning decades (Bertram & Vos, 2010; Schlesinger et al., 2022). In addition to using the ZDSD rat to study the prediabetic condition, the extended period of development of T2D, as opposed to shorter periods in other models, has led to uncovering the merit of using the ZDSD rat to study longer-term developmental changes, such as bone turnover and skeletal development (Reinwald et al., 2009). Common morbidities, such as cardiomyopathy, that are associated with higher risk occurrence in prediabetic persons, have also been reported in the ZDSD rat (Sun et al., 2018). Clinical deteriorations associated with human T2D and observed in the ZDSD rat include delayed wound healing, nephropathy and neuropathy (Davidson et al., 2014; Peterson et al., 2015; Suckow et al., 2017). The recent availability of the ZDSD rat and its potential to model human T2D accurately opens new research avenues to advance basic scientific understanding of diabetes and the translation of results from 'bench to bedside'.

We conducted this systematic review to appraise the use of the ZDSD rat as a T2D research model comprehensively and critically. The overarching goal is to summarize the full scope of the published works during the early adoption phase of this animal model. This knowledge might be useful for basic scientists selecting research models and clinical researchers assessing the results of preclinical research studies for translation to clinical care or research.

2 | METHODS

Studies were selected for the review by performing keyword searches using PubMed and by citation tracing articles contained within the reference lists of publications listed by Charles River's technical sheets for the ZDSD rat. Publications between 2009 and 2021 (last search updated June 2021) were included in the study. The search strategy was: 'Zucker Diabetic Sprague' or 'ZDSD', which yielded 16 unique results. Each study was abstracted by A.N.W. and reviewed systematically to identify specific data (blood glucose concentration, diet, age, sex and study time course) as compiled in Tables 1 and 2. Glucose concentrations that were not stated explicitly in the text of studies are interpolated from figures and their captions. Excluded from

TABLE 1 Glucose measurements in Zucker Diabetic-Sprague Dawley rats with Purina 5008 diet alone in peer-reviewed experimental studies

Study	Control	Sex	Endpoint (weeks of age)	Treatment group	Glucose (mg/dl)	Citation
1	ZDF and SD	Male		ZDSD[a,b]	$n = 6$	Reinwald et al. (2009)
			7–11		160 ± 3 to 190 ± 3	
			13		205 ± 22	
			15		300 ± 26	
			17		350 ± 40	
			19		440 ± 36	
			21		520 ± 27	
			23–29	ZDSD	525 ± 13 to 630 ± 9	
				SD	100 ± 5 to 125 ± 5	
				ZDF obese	460 ± 33 to 510 ± 33	
				ZDF lean	125 ± 8	
			33	ZDSD	687 ± 58	
				SD	96 ± 2	
				ZDF obese	543 ±16	
				ZDF lean	98 ± 6	
2	SD	Male		ZDSD	$n = 23$	Peterson et al. (2015)
			7–11	Fed[c,d]	127 ± 2 to 123 ± 2	
				Fasted[b,d]	125 ± 2 to 160 ± 2	
			13–15	Fed[c,d]	146 ± 3 to 150 ± 9	
				Fasted[b,d]	148 ± 2 to 149 ± 2	
			19	Fed[c,d]	227 ± 2	
				Fasted[b,d]	152 ± 15	
			21	Fed[c,d]	300 ± 26	
				Fasted[b,d]	237 ± 28	
			27	Fed[c,d]	478 ± 16	
				Fasted[b,d]	425 ± 30	
			31	Fed[c,d]	527 ± 11	
				Fasted[b,d]	498 ± 10	
4	SD	Male		ZDSD[c,e]	$n = 8$	Sun et al. (2018)
			14	Morning	130 ± 13	
				Evening	150 ± 13	
			18	Morning	130 ± 13	
				Evening	160 ± 13	
			22	Morning	165 ± 25	
				Evening	230 ± 25	
			30	Morning	420 ± 25	
				Evening	410 ± 50	
			34	Morning	460 ± 50	
				Evening	460 ± 50	
				SD[c,e]	$n = 8$	
			14–34	Morning	100 ± 10	
				Evening	110 ± 10 to 90 ± 10	

(Continues)

TABLE 1 (Continued)

Study	Control	Sex	Endpoint (weeks of age)	Treatment group	Glucose (mg/dl)	Citation
5	SD	Male		ZDSD[a,c]	$n = 9$	Hutter (2019)
			23		167 ± 14	
			25		264 ± 47	
			26		222 ± 35	
			31		381 ± 65	
			32		388 ± 73	
			33		413 ± 69	
			34		436 ± 66	
				SD[a,c]	$n = 7$	
			23–34		100 ± 11 to 101 ± 11	
6	SD	Male	10	ZDSD	$n = 8$	Han et al. (2020)
				SD	$n = 8$	
			10	ZDSD[f,g]	150 ± 3	
				SD[f,g]	135 ± 6	
			14	ZDSD[f,g]	111 ± 3	
				SD[f,g]	101 ± 3	
			18	ZDSD[f,g]	162 ± 6	
				SD[f,g]	142 ± 6	
			22	ZDSD[f,g]	153 ± 24	
				SD[f,g]	109 ± 3	
			23	ZDSD[c,g]	196 ± 35	
				SD[c,g]	86 ± 4	
			26	ZDSD[f,g]	195 ± 36	
				ZDSD[c,h]	153 ± 13	
				SD[f,g]	115 ± 7	
				SD[c,h]	93 ± 7	

Abbreviations: SD, Sprague Dawley; ZDF, Zucker Diabetic Fatty; ZDSD, Zucker Diabetic-Sprague Dawley. *Note*. Studies are listed in chronological order of publication according to PubMed and Google Scholar database searches as of June 2021. Purina 5008 diet is 4.15 kCal/g, having calories provided by 27% protein, 16% fat and 57% carbohydrates. Control group describes the conditions used as a reference within the study. Glucose values represent the mean with SEM as reported in tables in the original publications or estimated from graphs and figures by the authors of this review. Glucose was measured in whole blood, plasma or serum. Blood was collected from the distal tail vein directly or by transection of the tail. If specifically considered in the experimental design, the values for fasted and non-fasted animals and sampling period (afternoon vs. evening) are reported. Sample sizes are included where reported by the study authors.

Superscripts denote the following methodological details: [a]daytime or afternoon fed (non-fasting) glucose; [b]clinical chemistry analyser; [c]blood glucometer; [d]non-fasting and 6 h fasting glucose measured at 6:00 a.m. and noon, respectively; [e]non-fasting glucose; [f]commercial kit; [g]4 h fasting glucose; and [h]12 h fasting glucose.

Tables 1 and 2 are five search results that included reviews, editorial articles and publications where the diet protocols were not stated. However, we have considered these articles and cited their additional insights where appropriate in this review.

3 | RESULTS AND DISCUSSION

3.1 | Diet-accelerated diabetes in the ZDSD rat

A characteristic of this model is that male ZDSD rats will become hyperglycaemic when fed Purina 5008 diet (i.e., Formulab/Labdiet 5008), which has a modestly (5–10%) higher energy content compared with standard diet for rodents in biomedical research [e.g., Purina 5008 vs. Labdiet 5001 (in kilocalories per gram): gross energy, 4.15 vs. 4.07; physiological fuel value, 3.50 vs. 3.36; and metabolizable energy, 3.31 vs. 3.02]. The sources of calories provided in Purina 5008 versus 5001 diets are as follows (as a percentage): protein, 27 vs. 29; fat, 16 vs. 13; carbohydrates, 57 vs. 58. Table 1 lists studies where only the Purina 5008 diet was used in the study design. It is important to recognize that Purina 5008 is the normal diet fed ad libitum to ZDSD rats from weaning. Purina 5008 is also the diet for ZDF fats and is the same diet used during the 12-year breeding programme that established the ZDSD rats.

TABLE 2 Blood glucose characteristics of Zucker Diabetic-Sprague Dawley with high-fat diet feeding protocol in peer-reviewed experimental studies

Study	Control group	Sex	High fat diet (weeks of age)	Endpoint (weeks of age)	Treatment group	Glucose (mg/dl)	Citation
7	ZDSD with control diet	Male	9–18	18	HFD (6)[b,c]	161 ± 63[h]	Davis et al. (2013)
			12–18	18	HFD (6)[b,c]	437 ± 63[h]	
			16–18	18	HFD (6)[b,c]	469 ± 63[h]	
			no HFD switch	18	Control (6)[b,c]	186 ± 45[h]	
8	SD	Male	17–19[g]	30	Control (9)	139 ± 8	Hammond et al. (2013)
					ZDSD (9)	633 ± 90	
9	SD	Female	20–32[g]	20	Control (5)	126 ± 9	Gonzalez et al. (2014)
					ZDSD (4)	114 ± 16	
				32	Control (5)	131 ± 16	
					ZDSD (4)	472 ± 38	
10	ZDSD	Female	20–32[g]	20	ZDSD (24)[c]	118 ± 16[h]	Hill Gallant et al. (2014)
				23	ZDSD (8)[c]	191 ± 49[h]	
				24	ZDSD (8)[c]	334 ± 43[h]	
				25	ZDSD (8)[c]	373 ± 8[h]	
				27	ZDSD (8)[c]	407 ± 35[h]	
				29	ZDSD (8)[c]	383 ± 17[h]	
				31	ZDSD (8)[c]	442 ± 44[h]	
				32	ZDSD (8)[c]	474 ± 16[h]	
11	SD	Male	20–32[g]	32	Control	142 ± 3[h]	Gallant et al. (2013)
					ZDSD	630 ± 23[h]	
12	SD	Male	16–22[g]	34	Control (10)[a,b,c,e,f]	140 ± 5[h]	Davidson et al. (2014)
						93 ± 1[h]	
					ZDSD (9)[a,b,c,e,f]	564 ± 11[h]	
						468 ± 8[h]	
13	SD	Male	16–22[g]	16–29	Controls (26)[a,c]	86 ± 5	Creecy et al. (2016)
				16	ZDSD (48)[a,c]	104 ± 54	
				17	ZDSD (32)[a,c]	209 ± 134	
				18	ZDSD (32)[a,c]	317 ± 109	
				19	ZDSD (32)[a,c]	383 ± 115	
				20	ZDSD (32)[a,c]	354 ± 118	
				21	ZDSD (32)[a,c]	318 ± 98	
				22	ZDSD (32)[a,c]	328 ± 95	
				23	ZDSD (18)[a,c]	321 ± 89	
				24	ZDSD (18)[a,c]	314 ± 120	
				25	ZDSD (18)[a,c]	317 ± 81	
				26	ZDSD (18)[a,c]	308 ± 44	
				27	ZDSD (18)[a,c]	342 ± 85	
				28	ZDSD (18)[a,c]	382 ± 95	
				29	ZDSD (18)[a,c]	379 ± 91	

(Continues)

TABLE 2 (Continued)

Study	Control group	Sex	High fat diet (weeks of age)	Endpoint (weeks of age)	Treatment group	Glucose (mg/dl)	Citation
14	SD and ZDSD pre-HFD	Male	17–19[g]	17	SD (10)[c,e]	120 ± 2[h]	Suckow et al. (2017)
					ZDSD L (6)[c,e]	149 ± 3[h]	
					ZDSD H[c,e]	392 ± 12[h]	
				18	SD (10)[c,e]	117 ± 12[h]	
					ZDSD L (6)[c,e]	164 ± 12[h]	
					ZDSD H[c,e]	451 ± 36[h]	
				19	SD (10)[c,e]	137 ± 12[h]	
					ZDSD L (6)[c,e]	152 ± 12[h]	
					ZDSD H[c,e]	507 ± 12[h]	
15	SD	Male	18–21[g]	10–18	SD (10)[a,c,d,e]	115 ± 15[h]	(Peterson et al., 2017)
					ZDSD (16)[a,c,d,e]	144 ± 15[h]	
				20	SD (10)[a,c,d,e]	107 ± 15[h]	
					ZDSD (16)[a,c,d,e]	191 ± 15[h]	
				22	SD (10)[a,c,d,e]	124 ± 15[h]	
					ZDSD (16)[c,e]	210 ± 30[h]	
				24	SD (10)[c,e]	116 ± 15[h]	
					ZDSD (16)[a,c,d,e]	363 ± 35[h]	
				26	SD (10)[a,c,d,e]	116 ± 15[h]	
					ZDSD (16)[a,c,d,e]	431 ± 35[h]	
				28	SD (10)[a,c,d,e]	122 ± 15[h]	
					ZDSD (16)[a,c,d,e]	546 ± 15[h]	
				30	SD (10)[a,c,d,e]	128 ± 15[h]	
					ZDSD (16)[a,c,d,e]	554 ± 15[h]	
16	SD	Male	16–18[g]	16	Control (20)	134 ± 15	(Bhamb et al., 2019)
					ZDSD (22)	131 ± 11	
				20	Control (20)	177 ± 19	
					ZDSD (22)	331 ± 174	
				32	Control (14)	223 ± 144	
					ZDSD (12)	439 ± 172	
17	SD	Male	16–19[g]	20	Control (14)[c]	157 ± 25	(Glaeser et al., 2020)
					ZDSD (18)[c]	504 ± 155	

Abbreviations: SD, Sprague Dawley; ZDSD, Zucker Diabetic-Sprague Dawley; ZDSD L ('light') and ZDSD H ('heavy') refers to body weight subgroups identified as non-diabetic and diabetic, respectively, according to the criterion in the study for elevated blood glucose. *Note.* Studies are listed in chronological order of publication according to PubMed and Google Scholar database searches as of June 2021. Control group describes the conditions used as a reference within the study. Sample sizes (numbers in parentheses) are included where reported by the study authors.

Superscripts denote the following methodological details: [a]fed or [a]12 h fasted blood glucose were measured by [c]glucometer; no superscript a, b or c, method not reported; [d]morning period data; [e]sampled from tail vein or tail-tip transection; [f]data from glucose tolerance test; study used the high-fat diet: [g]Purina 5SCA or (no superscript g), Research Diet D12468. Glucose values represent the mean, with variation given as [h]SE or (no subscript h) SD as reported in tables in the original publications, or estimated from graphs and figures by the authors of this review.

Zucker Diabetic-Sprague Dawley rats have mild hyperglycaemia, with fasted blood glucose being >125 mg/dl, proposed as a prediabetic stage, as early as 7 weeks of age (Peterson et al., 2015). During feeding with Purina 5008 diet, most studies reported a state of diabetes (as defined by blood glucose concentrations >250 mg/dl) in ZDSD rats between 20 and 25 weeks of age; the blood glucose concentration remains high to >30 weeks of age (Table 1). This latter criterion was applied equally to fed and fasted blood glucose concentrations. Fed blood glucose concentrations rising above the diabetic criterion were detected ≤2 weeks earlier than fasted blood glucose (Peterson et al., 2015). However, when ZDSD rats are fed Purina 5008 alone, there is a marked heterogeneity in the time to onset of diabetes. These reports include hyperglycaemia developing later in subsets of ZDSD rat cohorts (Peterson et al., 2015) and a study where the

majority of ZDSD rats fed only Purina 5008 ($n = 44$) had not reached the threshold for significant hyperglycaemia by 26 weeks, and were therefore considered still prediabetic (Hutter, 2019).

Likewise, serum glucose concentrations were higher in ZDSD on Purina 5008 compared with Sprague–Dawley (SD) rats from 10 to 18 weeks of age, but did not differ between groups after 22 weeks of age (Table 1; Han et al., 2020). However, that study used a small sample size ($n = 8$ per group) and reported significant interindividual variation in blood glucose at 22–26 weeks of age (Han et al., 2020). The variability between studies for the time elapsed before the development of a diabetic phenotype in ZDSD rats fed Purina 5008 diet alone raises important considerations for experimental design using this model.

The age at which ZDSD rats develop diabetic phenotypes can be decreased by using a diet with a high fat content (HFD; i.e., a 'Western diet'). All the studies in Tables 1 and 2 reported using Purina 5SCA except for study 7 in Table 2, which used Research Diet D12468. Calories are provided in Purina 5SCA versus D12468 by (as a percentage): protein, 8.9 vs. 10; fat, 48.5 vs. 48; carbohydrate, 42.7 vs. 42. For both diets, soy protein isolate and lard are the protein and fat ingredients, respectively. The gross energy densities (in kilocalories per gram) of 5SCA versus D12468 are 4.75 versus 4.79. In conditions of HFD feeding for as short a period as 2 weeks, ZDSD glucose concentrations increased to >300 mg/dl at 18 weeks of age (Table 2). Table 2 shows that switching from Purina 5008 to HFD caused a rapid increase in blood glucose, which persisted until they were >30 weeks old. Interestingly, ZDSD rats fed a HFD at a young age (9–18 weeks) were resistant to obesity-related disease and had lower blood glucose concentrations than ZDSD rats fed HFD from 12 to 18 or from 16 to 18 weeks of age (Davis et al., 2013). The mechanism underlying this observation has not been determined, but histological analyses identified an increased number and size of adipocytes in ZDSD rats fed HFD at younger versus older ages (Davis et al., 2013). This apparently 'healthy obese' state coincided with younger HFD-fed ZDSD rats also showing a decrease in the expression of anti-adipogenic and pro-inflammatory factors in adipose tissue (Davis et al., 2013). Therefore, the timing of the dietary interventions is an important factor for the ZDSD model and warrants attention in both the design and interpretation of studies.

The acceleration of T2D in ZDSD rats with a HFD is reproducible in males; however, sex-related differences are noted in this model. In the few studies where female ZDSD rats have been used, they are described as resistant to development of T2D. Male ZDSD rats can develop T2D spontaneously without HFD feeding, whereas female ZDSD rats require a HFD to induce and maintain a diabetic state (Hill Gallant et al., 2014). Heterogeneity in the time course is also significant for female ZDSD rats, evidenced by a study in which only half of the population developed overt diabetes when fed a HFD from 20 to 32 weeks (Gonzalez et al., 2014).

The factors driving the sex-related differences have not been investigated in the ZDSD rat. Female ZDF rats exhibit sex differences in the development of diabetes when fed diets differing in the fat content; that is, female ZDF rats become obese, but remain normoglycaemic on a 'lower than high-fat diet', whereas male ZDF rats become spontaneously diabetic, even on the control diet (Corsetti et al., 2000). According to Topp et al. (2007), an increase in β-cell mass with preserved β-cell function allows for adaptation to insulin resistance in high fat-fed obese female ZDF rats. In addition, sex-dominant differences in hepatic carbohydrate and lipid metabolism of high-fat diets, including detoxifying biotransformation pathways, were proposed, based on analyses of mRNA expression using whole-genome arrays, from female and male ZDF rat livers (Gustavsson et al., 2011). Sex hormones, such as oestrogens, protect against insulin resistance and glucose intolerance in high sucrose-fed rats (Horton et al., 1997) and high fat-fed mice (Riant et al., 2009). We speculate that a combination of oestrogens and sex-predominant liver metabolism and detoxification pathways could contribute to sex differences in ZDSD rats in a similar manner. Studies mainly report using SD rats as the control group; however, it has been proposed that age-matched non-diabetic ZDSD rats could be used as alternative or additional control groups (Gonzalez et al., 2014; Hill Gallant et al., 2014). The use of female animals in preclinical models is essential for understanding sex-related differences of T2D progression and translation of future findings to an understanding of human disease mechanisms. Further characterization of sex-related differences warrants attention (King, 2012; Reinwald et al., 2009).

3.2 | Metabolism and phenotype characteristics

3.2.1 | Insulin resistance and glucose metabolism

To evaluate the diabetic phenotype and glucose metabolism, insulin tolerance tests (ITTs) and glucose tolerance tests (GTTs) have been performed in three studies using male ZDSD rats. These tests were conducted in ZDSD rats fed Purina 5008 alone (Han et al., 2020; Peterson et al., 2015) and in ZDSD rats fed Purina 5008 with a 6-week period of HFD feeding (Davidson et al., 2014). No studies have yet reported using hyperinsulinaemic clamp methods in ZDSD rats.

A threefold decrease in insulin sensitivity index (calculated from GTT) occurred in ZDSD rats from 7 to 19 weeks of age (Peterson et al., 2015). Fasted (6 h) insulin concentrations increased threefold between the ages of 7 and 19 weeks, then declined rapidly, falling below their starting points by 27 weeks of age (Peterson et al., 2015). At 7 weeks of age, oral glucose loading produced a 4.3-fold increase in maximum insulin concentration relative to the fasted state (Peterson et al., 2015). This insulin response in the GTT declined steadily with age (Peterson et al., 2015). By 15 weeks, the time-to-peak plasma insulin concentration after glucose loading was 30 min, a doubling of the initial time at 7 weeks age in ZDSD rats (Peterson et al., 2015). The duration of the insulin response to oral glucose loading was 2 h in all ZDSD rats. The insulin area under the curve (AUC), calculated during the GTT, doubled in size between 7 and 19 weeks of age, then this trend

reversed course and fell to 20% of its initial value by 31 weeks of age. These measurements of the time course of responses to insulin, insulin concentrations and insulin production are interpreted as evidence of a prediabetic state characterized by declining insulin sensitivity and compensatory increased insulin production lasting up to 19 weeks of age, which declines to a chronic state at 27–31 weeks of age (Peterson et al., 2015).

As noted, the observed heterogeneity in the hyperglycaemia within ZDSD groups presents challenges for experimental design and data interpretation. Han et al. (2020) observed heterogeneity in the age that their ZDSD cohort showed the onset of hyperglycaemia and 'overt' diabetes. They also observed weight loss in some ZDSD rats after hyperglycaemia. In 17- and 23-week-old rats after a 4 h fast, glucose concentrations were higher in the entire cohort of ZDSD rats than in SD controls both before and after insulin injection during the 60 min time course of the ITT. Han et al. (2020) proposed subgrouping this cohort ($n = 8$) of ZDSD rats according to weight loss attributable to hyperglycaemia (125–249 mg/dl) and diabetes (>250 mg/dl), and age-matched non-diabetic ZDSD rats. Accordingly, this sub-analysis indicated that blood glucose concentrations were higher for the full time (60 min) or only the initial 15 min of the ITT in the diabetic ZDSD and non-diabetic ZDSD rats, respectively, when compared with SD control animals (Han et al., 2020).

Together, the evidence characterizes the ZDSD rat as a model of diabetes that progresses from normal insulin sensitivity to insulin resistance and, finally, to decreased insulin production. Hyperinsulinaemic clamp studies should be conducted to investigate the insulin resistance in the ZDSD rat.

Glucose tolerance test results in ZDSD rats are consistent with the insulin kinetics and responses described above, with progressively lower glucose utilization as evidenced by higher glucose concentrations and lower glucose disposal rates with ageing (Han et al., 2020; Peterson et al., 2015). For example, glucose disposal was fourfold less at 31 compared with 7 weeks of age (using Purina 5008 only; Peterson et al., 2015). At 34 weeks of age, after a HFD feeding protocol from 16 to 22 weeks of age, glucose clearance in ZDSD rats was lower than in SD rats (Davidson et al., 2014). Decreased usage of glucose for metabolism is characteristic of T2D, and these data from separate studies show that this persistent defect in glucose metabolism occurs independent of a HFD protocol.

A persistent decrease in glucose utilization results in a chronic exposure to elevated glycaemia in T2D. Glycated haemoglobin (HbA1c) is a biomarker used in the clinical management of T2D in humans. Glycated haemoglobin reflects red blood cell exposure to glucose, and the levels have been shown to demonstrate a strong positive correlation with blood glucose concentration (International Expert Committee, 2009). Levels of HbA1c indicate the cumulative exposure of haemoglobin to elevated blood glucose over the lifespan of circulating red blood cells and, as a result, are less prone to short-term dynamic fluctuations compared with sentinel blood glucose monitoring (Reinwald et al., 2009).

A constant linear increase in HbA1c has been reported for male ZDSD rats from 7 to 31 weeks of age. The initial HbA1c value reported in 7-week-old ZDSD rats is 3.45% and is comparable to that of SD rats (3.36–3.60%). By 31 weeks of age, HbA1c levels increased threefold in male ZDSD rats (Peterson et al., 2015). Interestingly, we note that the 33% higher HbA1c levels in ZDSD relative to ZDF (*fa/fa*) rats at 33 weeks of age is consistent with 26% higher blood glucose (non-fasted) in ZDSD relative to the ZDF (*fa/fa*) rat (Reinwald et al., 2009). The constant increase in HbA1c during a period of apparent normoglycaemia from 7 to 15 weeks and prediabetes from 15 to 19 weeks of age might be indicative of periods of hyperglycaemia that go undetected in the study designs. However, consistent with the observations of sex-related differences in the hyperglycaemia, Hb1Ac did not differ between female ZDSD and SD rats (4.4 vs. 4.2%) at 20 weeks of age, but with introduction of HFD for 12 weeks, the HbA1c was elevated by >2.5-fold in the ZDSD rats (Gonzalez et al., 2014; Hill Gallant et al., 2014). In comparison, the implementation of a HFD for a shorter period of 2 weeks (from 17 to 19 weeks of age) also led to significantly higher HbA1c levels in male ZDSD rats than in age- and diet-matched SD rats (Hammond et al., 2013). These higher HbA1c levels were sustained in ZDSD rats to 30 weeks of age (Peterson et al., 2017). Together, the evidence validates HbA1c as a biomarker to monitor the time progression of persistent hyperglycaemia and diabetes in ZDSD rats.

3.2.2 | Lipids and cholesterol

Lipid profiles of ZDSD rats provide evidence of lipid metabolism trending towards dysfunction. At 33 weeks of age (in the absence of an HFD protocol), blood concentrations of free fatty acids (FFAs) and cholesterol in diabetic ZDSD rats were 1.7- and 2.8-fold higher than those of SD control animals (Reinwald et al., 2009). A threefold increase in triglyceride concentrations was reported in ZDSD rats between 7 and 19 weeks of age, which was 2.5-fold higher at 31 weeks of age (Peterson et al., 2015). A subsequent study found similar results using serum samples from 4-h-fasted ZDSD compared with SD rats (Han et al., 2020). The authors reported 10% larger livers (relative to total body mass) having normal histology in ZDSD rats, and reported that liver triglycerides, when normalized to liver weights, did not differ between strains (Han et al., 2020). We suggest that these data signify a small (10%) increase in liver triglycerides, with no detected histological changes. That study also found elevated mRNA levels of fatty acid binding and transport proteins (*Cd36*, *Fabp1* and *Fabp4*) along with fatty acid oxidation proteins (e.g., *Cpt1a*) in ZDSD rats at 34 weeks of age compared with SD rats. When fed HFD between 16 and 22 weeks of age, the serum levels of FFA, free cholesterol and triglycerides were 3.7-, 2.6- and 5.9-fold higher in ZDSD rats than in SD control animals (Davidson et al., 2014). Increased liver lipid levels were evidenced in histology sections prepared with Oil Red staining in ZDSD compared with control rats (Davidson et al., 2014).

There is less information available about the lipid profile of female ZDSD rats. Female 32-week-old ZDSD rats, previously fed HFD, have elevated serum triglyceride levels, but it is unclear whether this phenotype is conditional on the HFD (Hill Gallant et al., 2014).

3.2.3 | Destruction of pancreatic β-cells

Pancreatic islet β-cell failure is a characteristic of human T2D, with ≤50% loss of function found at the time of diagnosis (Chatterjee et al., 2017; Holman et al., 2008). Significant destruction of the pancreatic β-islet cells is observed as early as 15 weeks of age in ZDSD rats (Han et al., 2020). A two- to threefold lower insulin and glucagon staining of pancreatic cross-sections was reported for male ZDSD compared with SD rats at 15 and 26 weeks of age (Han et al., 2020). An earlier study (Peterson et al., 2015) with ZDSD rats used a homeostasis model assessment of β-cell function (HOMA-IR) to estimate the insulin secretory capacity of pancreatic cells. A more direct measurement can be made using hyperinsulinaemic clamp. Using the HOMA-IR approach, the researchers reported a >95% decline in insulin secretory capacity between 19 and 31 weeks for ZDSD rats (Peterson et al., 2015). Compared with control animals, a larger pancreatic mass was found in ZDSD rats, but its cause was not determined (Reinwald et al., 2009).

Pancreatic β-islet cell failure has not been explored in female ZDSD rats. Peterson et al. (2015) did not measure the mass of the pancreas but speculated that the evidence of pancreatic islet destruction coupled with an increase pancreatic mass could signify a compensatory mechanism to restore euglycaemia in ZDSD rats.

3.2.4 | Obesity

Body masses increase steadily in ZDSD rats from 7 to 21 weeks of age and reach a plateau at 23 weeks before beginning a decline (8.2% over 8 weeks) (Choy, de Winter, et al., 2016; Davidson et al., 2014; Peterson et al., 2015). In clinical T2D patients, health monitoring of disease progression can be modelled using the weight–HbA1c–insulin–glucose model (Choy, Kjellsson, et al., 2016). This approach, with some modifications for weight change in ZDSD rats modelled on the excess growth rate of obese SD rats and fasting plasma glucose concentrations, has been applied to understanding the ZDSD phenotype (Choy, de Winter, et al., 2016). Based on their model, which uses data from rats fed Purina 5008 diet alone (Peterson et al., 2015), the youngest aged ZDSD rats showed the most excess growth compared with other ages. At 7 weeks of age, the excess growth rate of ZDSD rats was 80% higher than that of SD rats (Choy, de Winter, et al., 2016). The SD rat body weights catch up to ZDSD rats, with both strains having a body mass >500 g at 30 weeks of age (Peterson et al., 2017; Reinwald et al., 2009). These changes in body weight in ZDSD rats differ from the ZDF (*fa/fa*) rats, which remain larger than lean ZDF (*fa/+*) animals (Reinwald et al., 2009). In comparison to HFD protocols used at 16–23 weeks, one study reported weight loss as early as 18 weeks of age in ZDSD rats, which was 3 weeks earlier than the control (SD) animals (Creecy et al., 2016), and another study reported 8% larger body weights of SD compared with ZDSD rats by 34 weeks (Davidson et al., 2014). Even with a shorter HFD treatment period, from 17 to 19 weeks of age, weight loss persisted in ZDSD rats at 30 weeks (Hammond et al., 2013). The decrease in body mass in older animals has been interpreted as evidence of T2D disease progression and described as unintentional weight loss by the authors of the modelling study. In discussing their predictive model, dehydration attributable to polyuria and muscle breakdown and cell apoptosis were speculated as contributors to the weight loss (Choy, de Winter, et al., 2016). In this regard, the ZDSD body mass phenotype at older ages differs from the usual presentation of clinical T2D.

Most studies reported that ZDSD rats developed obesity with diabetes, whereas one study using HFD reported that both diabetic and non-diabetic ZDSD rats were larger than SD rats at 17 weeks. The researchers interpreted these observations as evidence that the obesity and diabetes are independent events (Suckow et al., 2017). Adipose tissue generates leptin, a hormone that regulates body weight through food intake and adipose tissue mass (Friedman & Halaas, 1998). Despite intact leptin receptor signalling pathways, ZDSD rats become obese. Diabetic ZDSD rats had 15-fold lower circulating leptin concentrations and 70% less insulin compared with SD rats at 33 weeks of age. In contrast, ZDF (*fa/fa*) rats had a twofold higher leptin concentration and 44% less insulin than control (lean ZDF) animals (Reinwald et al., 2009). Dysregulation of leptin receptor signalling in the CNS leads to irregular feeding behaviours in rodents, especially overeating (hyperphagia). However, the ZDSD rat also shows a hyperphagia that has been quantified in a couple of studies as an increase in ad libitum consumption (ranging from 30 to 250%) of Purina 5008 diet by ZDSD compared with SD rats from weeks 14 to 26 (Han et al., 2020) and at 33 weeks of age (Reinwald et al., 2009). Hutter (2019) reported that ZDSD rats having blood glucose concentrations in the upper quartile range of their cohort ate 50% more Purina 5008 than ZDSD rats in the lower quartile blood glucose range (medians, 355 vs. 140 mg/dl) at 26 weeks of age. At 26 weeks of age, food consumption was 20% less than at 14 weeks of age in ZDSD rats, whereas food consumption declined by 50% in the age-matched SD control animals (Han et al., 2020; Hutter, 2019; Reinwald et al., 2009). Our review of the literature found no evidence that hypothalamic leptin–melancortin feeding pathways have been characterized extensively in the ZDSD rat, for example, by gene expression studies.

Visceral fat and organ weights have been compared in studies examining the obesity phenotype. A premise is that changes in body mass associated with obesity should be associated with increased adipose tissue mass and distinguished from generalized higher growth (Reinwald et al., 2009). Kidney, liver, heart, peritoneal and retroperitoneal fat depot weights (normalized to body mass) were higher in ZDSD and ZDF rats compared with the control groups (non-diabetic or lean control groups; Han et al., 2020; Reinwald et al., 2009). Mixed results have been reported for epididymal fat depot weight (Han et al., 2020; Reinwald et al., 2009). Subcutaneous and brown fat depots did not differ between ZDSD and SD rats (Han et al., 2020). Increased liver weight might be a result of hepatic steatosis (Davidson et al., 2014) and in line with higher circulating FFAs and triglycerides (Reinwald et al., 2009).

3.3 | Cardiovascular complications and diseases

Cardiovascular disease is the largest cause of morbidity and mortality for people living with T2D (Chatterjee et al., 2017). Cardiomyopathies, peripheral artery disease and hypertension, endothelial dysfunction, wound healing and nephropathies have been studied in the ZDSD rat.

3.3.1 | Cardiomyopathies

Heart failure is a major risk associated with T2D (Selvin et al., 2014). Heart failure with preserved or normal ejection fraction (diastolic heart failure) is observed in T2D. Patients with diastolic heart failure show physical changes to the heart, with endothelial dysfunction, hypertrophy, cardiomyocyte stiffness and advanced glycation end products (Meagher et al., 2018).

Using echocardiography, the ejection fraction and fractional shortening were higher in ZDSD compared with SD rats at 18–22 weeks of age, but with chronic T2D the ejection fraction decreased to levels below those of control SD rats at 34 weeks of age (67 vs. 82%; Sun et al., 2018). The difference in ejection fraction is accounted for by 30% larger end-diastolic volumes and 2.5-fold larger end-systolic volumes, with no difference in stroke volume in ZDSD versus SD rats. Dobutamine stress testing using ZDSD rats revealed worsened left ventricular wall contraction at 34 weeks and was interpreted as decreased cardiac systolic reserve (Sun et al., 2018). Diastolic ventricular relaxation function was modestly compromised at 34 weeks of age. Decreases in the transmitral blood flow velocity during early phase diastole and the transmitral flow velocity profile, defined by the ratio of peak flow in early diastole to peak flow in late diastole, were provided as evidence of this functional change in ZDSD rats (Sun et al., 2018). Left ventricular wall dimensions also changed over this time course. Left ventricular posterior wall thickness was larger in ZDSD than SD rats at 18 weeks, but wall thickness did not differ from SD rats at 34 weeks. Structural changes to the ventricular wall coincided with significant enlargement of the left ventricular inner diameters of ZDSD compared with SD rats at 34 weeks. A marginally slower heart rate (20%) was observed in ZDSD rats at 34 weeks of age, but cardiac output did not differ from SD control animals. Interestingly, cardiac histopathological and heart failure biomarkers (serum B-type natriuretic peptide) did not change in ZDSD rats and did not differ from control animals (Sun et al., 2018). The biphasic pattern observed for cardiac function with ZDSD rat ageing warrants attention to pressure–volume determinations to identify potential mechanisms, such as increased wall stress and decreased compliance, and to assess the impact of the diastolic dysfunction.

In summary, at 34 weeks of age the ZDSD diabetic cardiomyopathy is characterized as systolic and diastolic changes associated with reduced ejection fraction, which on the one hand, differs from clinical observations of T2D, but on the other hand, is consistent with eventual development of uncompensated heart failure and higher cardiovascular mortality risk in T2D.

3.3.2 | Endothelial dysfunction

Endothelial cell dysfunction is an early and crucial element of blood vessel diseases. Critical limb ischaemia is a severe condition in diabetes that occurs because of blood vessel disease, with endothelial dysfunction as a key factor (Avogaro et al., 2011). Hyperglycaemia is considered a primary initiating cause for endothelial dysfunction in diabetes. However, endothelial dysfunction is also associated with postprandial hyperlipidaemia and cardiovascular risk, such as atherosclerosis (Ansar et al., 2011). The endothelium has many functions, including the regulation of vascular tone by release of contracting and relaxing factors that act upon vascular smooth muscle. In the context of vascular tone, endothelial dysfunction can be described as an imbalance between these opposing vasoactive agents (Xu et al., 2021).

Endothelial dysfunction has been examined directly in only a single study of ZDSD rats, but it used comparable methodology to that applied in other diabetic rat models previously. Specifically, the researchers recorded internal diameters of *ex vivo* pressurized epineurial arterioles (small-diameter blood vessels supplying nerves) and reported reduced endothelium-dependent vasodilatory responses with acetylcholine and calcitonin gene-related peptide in ZDSD compared with SD rats (Davidson et al., 2014). Epineurial arteriole dilatations induced by acetylcholine were found to be mediated by both nitric oxide and endothelium-derived hyperpolarizing factors (EDHFs). The EDHF component of endothelium-dependent blood vessel dilatation mechanisms has been shown to be impaired in a similar manner in type 1 (streptozotocin-induced) and type 2 (ZDF) models (Coppey et al., 2003). Decreased vasodilatation of epineurial arterioles leading to lower blood flow supply to the sciatic nerve in ZDSD rats could contribute to neuropathy, as evidenced by the decreased nerve conduction velocity previously found in other models of T2D (Coppey et al., 2002; Davidson et al., 2014). Endothelial function differs across vasculatures and disease models. As an example, evidence of decreased vasodilatory mechanisms were not observed in small coronary and mesenteric arteries from ZDSD rats, according to statements made of data not shown by Davidson et al. (2014), whereas the vasodilatory responses of mesenteric and coronary arteries of ZDF (*fa/fa*) rats were reduced (Oltman et al., 2006; van Timmeren et al., 2007). Given the broad influence of the endothelium, which ranges from the conduit arteries down to the microvasculature and capillaries, further study of the endothelial and vascular smooth muscle function in ZDSD rats is warranted to gain a better understanding of the diabetic phenotype and to assess the use of this model for cardiovascular research.

In the context of using the ZDSD rat as a preclinical model for study of cardiovascular disease, it is important to consider the HFD or Western diets that are part of the model and have been studied extensively for many years. Using otherwise normal strains of SD rats, Western diet or other HFD protocols will produce diet-induced obesity and are associated with increased inflammatory markers and oxidative stress that affect the function of blood vessels, the heart and kidneys

and damage the cardiovascular system (Elrashidy et al., 2019; García-Prieto et al., 2015; Lin et al., 2014; Sweazea et al., 2010).

3.3.3 | Delayed wound healing

Impaired wound healing in T2D can be attributable to a combination of impaired growth factors, angiogenic responses, macrophage infiltration and other physiological factors (Brem & Tomic-Canic, 2007). Wound recovery and preservation of peripheral arterial blood flow to limbs could have profound effects for diabetic care, particularly in avoidance of limb amputations in critical limb ischaemia (Brem & Tomic-Canic, 2007; Game, 2012).

Excisional wounds made in both diabetic and non-diabetic ZDSD rats fed HFD from 17 to 19 weeks of age show delayed healing processes compared with age-matched SD control animals (Suckow et al., 2017). The precise mechanisms of delayed wound healing in ZDSD rats have yet to be determined. Generally, the closure of excisional wounds occurs by processes of epithelialization, angiogenesis and scar formation, which involve epithelial cells, endothelial cells, immune cells and myofibroblasts in rodents. Increased levels of inflammatory mediators produced by some of these cells are known to contribute to relevant affected processes in obesity and diabetes. In addition, decreased immune responses to infectious agents, hence increased infection rates can also contribute to delayed wound healing. In preclinical studies looking at spinal fusion surgeries, ZDSD rats were prone to higher infection rates than the SD control group (Bhamb et al., 2019).

3.3.4 | Hypertension

Hypertension is identified in about half of patients living with T2D and metabolic syndrome (Savoia & Touyz, 2017; Si et al., 2014). Zucker Diabetic-Sprague Dawley rats were reported as being hypertensive when compared with control animals at ages as early as 18 weeks and continuing to 34 weeks, as evidenced by elevated systolic arterial blood pressure (20 mmHg higher in ZDSD rats) measured by the tail-cuff technique (Sun et al., 2018). However, the cause of the elevated systolic blood pressure was undetermined in that study. Arterial elasticity did not differ between ZDSD and SD rats, as evidenced by pulse wave velocity and carotid arterial diameters measured at diastole and systole (Sun et al., 2018).

There are only a few studies that report blood pressure measurements in ZDSD rats. Differences in diastolic arterial blood pressure between ZDSD rats and comparative strains have not been observed consistently. In one study, researchers reported no differences between ZDSD and SD control animals, whereas in another the researchers found higher diastolic arterial blood pressures in ZDSD than SD rats at 22–34 weeks; both studies used similar tail-cuff blood pressure measurement methods (Han et al., 2020; Sun et al., 2018). Using radiotelemetry to obtain more accurate and precise blood pressure measurements, the ZDSD blood pressure phenotype was shown to be hypertensive versus the normotensive Wistar–Kyoto rat strain (Jackson et al., 2015). Specifically, at 19 weeks of age male ZDSD rats ($n = 9$) had higher systolic blood pressure (145 ± 2 mmHg), mean arterial blood pressure (119 ± 1 mmHg) and diastolic blood pressure (99 ± 1 mmHg) than the Wistar–Kyoto control animals ($n = 9$; values in millimetres of mercury: systolic, 127 ± 1; mean, 105 ± 1; and diastolic, 88 ± 1). As correctly noted by the authors of the radiotelemetry study, the ZDSD genetic background is not shared with the Wistar–Kyoto rat, hence mechanisms might differ. With regard to the size of the difference, the arterial pressures of ZDSD rats were below the range reported for the spontaneously hypertensive rat strain in the same study ($n = 12$; values in millimetres of mercury: systolic, 181 ± 5; mean, 139 ± 2; and diastolic, 130 ± 3), which suggests that the ZDSD phenotype is a moderate hypertension.

Given the evidence of hypertension in the ZDSD rat, anti-hypertensive treatment in combination with drugs for glycaemic control have been assessed in this model. Clinical studies that have looked at the effects of dipeptidyl peptidase 4 (DPP4) inhibitors with the blood pressure-lowering drug enalapril [angiotensin-converting enzyme (ACE) inhibitor] have found mixed responses in T2D patients (Jackson et al., 2008; Marney et al., 2010; Ogawa et al., 2011). In ZDSD rats, sitagliptin, a DPP4 inhibitor, was combined with the ACE inhibitor enalapril (Jackson et al., 2015). Sitagliptin lowered systolic and mean arterial blood pressures of ZDSD rats and did not compromise the lowering of systolic, diastolic and mean arterial blood pressure by the ACE inhibitor (Jackson et al., 2015).

The ZDSD rat is an attractive model that captures the complexities of metabolic syndrome, including hypertension. However, there is some variability that exists in demonstrating a hypertensive phenotype, which should be investigated further and accounted for when performing future studies.

3.3.5 | Nephropathy

Hypertension accelerates the development of diabetic nephropathy and end-stage renal disease (Peterson et al., 2017; Si et al., 2014). Nephropathy is a result of the combination of microvascular and renal tubule changes in T2D (John, 2016). As early as 22–24 weeks of age, the presence of urine biomarkers for tubular damage [β2-microglobulin, cystatin C, clusterin and urine kidney injury molecule-1 (KIM-1)] have been detected in ZDSD rats. By 30 weeks, these biomarkers are seven to ninefold higher than in SD control animals (Peterson et al., 2017). Excreted concentrations of urinary KIM-1, osteopontin and lipocalin-2 are also correlated with the blood glucose concentrations in ZDSD rats at 26 weeks of age (Hutter, 2019). Concentrations of KIM-1 are normally low in healthy persons, and it is therefore used as clinical biomarker for renal injury in human patients (van Timmeren et al., 2007). Osteopontin is upregulated in the glomeruli by macrophages, and lipocalin-2 is a marker for tubular damage (Kelly et al., 2002; Nielsen et al., 2012). The detection of these biomarkers for renal injury coincides with glomerulopathy of the kidneys from 33-week-old ZDSD rats, as determined by light and

electron microscopy that identified increased wall thickness, podocyte effacement and inflammation (Peterson et al., 2017).

Polyuria and albuminuria are well known in diabetes (de Zeeuw, 2007; Gluhovschi et al., 2016). High urinary albumin levels were found to be correlated with high blood glucose concentrations and kidney injury biomarkers in ZDSD rats (Hutter, 2019). Urinary albumin levels were higher in ZDSD rats between 26 and 33 weeks of age compared with SD rats (Peterson et al., 2017; Reinwald et al., 2009). Administration of the ACE inhibitor lisinopril to ZDSD rats prevented the development of albuminuria, and they showed a similar clinical response to humans, with reduced serum blood urea nitrogen and creatinine (Peterson et al., 2017; Schoolwerth et al., 2001). Given that ZDSD rats demonstrate hypertension, these effects were thought to be attributed to a reduction of hypertension-induced glomerular hyperfiltration by preferential efferent arteriole dilatation and improved renal blood flow (Peterson et al., 2017).

As early as 24 weeks of age, ZDSD rats demonstrate significantly increased urinary output compared with SD rats (Peterson et al., 2017). At 33 weeks of age, ZDSD rats demonstrate polyuria (203.2 ± 41.8 ml/day) compared with SD rats (16.2 ± 3.8 ml/day) (Reinwald et al., 2009). This is accompanied by an increase in fluid intake (Reinwald et al., 2009). In one study that separated ZDSD rats into upper and lower quartiles based on their blood glucose concentrations, the upper quartile demonstrated polydipsia (52.7 ml vs. 24.5 ml), and polyuria (34 ml vs. 11 ml) (Hutter, 2019).

3.3.6 | Neuropathy

Diabetic neuropathy arises from nerve or nervous system injury associated with long-term exposure to hyperglycaemia. The neuropathy can involve peripheral and autonomic nerves, and commonly, the optic nerve. Evidence for neuropathy in ZDSD rats (34 weeks of age) is based on the observation of thermal hypoalgesia responses; that is, animals take longer to withdraw their paw from a thermal stimulus (Davidson et al., 2014). Intra-epidermal nerve densities did not differ between ZDSD and SD rats, but there were fewer Langerhans cells in ZDSD rats (Davidson et al., 2014). These findings differ from studies with streptozotocin-diabetic SD rats but are similar to observations in T2D humans (Bilan et al., 2011; Tofovic et al., 2007). Zucker Diabetic-Sprague Dawley rats also demonstrate decreased corneal nerves and corneal sensitivity (Davidson et al., 2014). Regarding direct changes to the brain, white matter in the corpus callosum was atrophied and lymphocyte numbers were higher in the hypothalamus of diabetic compared with non-diabetic ZDSD rats (Mochida, 2009).

3.4 | Bone and skeleton

Type 2 diabetes is associated with skeletal fragility in humans. The leptin receptor missense mutation (*fa/fa*) is associated with congenital skeletal defects, which confounds the interpretation of the ZDF model. In this regard, the ZDSD rat is advantageous as a model (Fajardo et al., 2014; Reinwald et al., 2009). The rat skeleton is considered fully mature at 16 weeks of age (Hughes & Tanner, 1970); therefore, the ZDSD rat has been used to investigate skeletal fragility without the confounding effects of leptin-dependent mechanisms on bone formation (Takeda et al., 2002). Skeletal fragility and plasticity are increased and decreased, respectively, because it was observed that less force was required to induce femoral fractures in diabetic ZDSD rats, which showed fourfold the blood glucose and twofold the HbA1c levels of control animals (Gallant et al., 2013). Biomechanical testing of long and vertebral bones also revealed impaired cortical bone strength (as measured by yield force, failure load and stiffness) in ZDSD rats (Reinwald et al., 2009). Material strength of the cortical bone materials did not increase with ageing in ZDSD rats, whereas it strengthened in SD rats (Creecy et al., 2016). Longer exposure to T2D leads to increased decline in the material properties of bone (e.g., toughness and fracture toughness) (Creecy et al., 2016). Together, these studies characterize the ZDSD skeleton as having lower tolerances to withstand force and higher chance of fracture.

Body composition measured using dual-energy X-ray absorptiometry showed that ZDSD compared to SD rats had 3% lower bone mineral density, which was negatively correlated with HbA1c levels (Bhamb et al., 2019). Lean mass and bone mineral content was higher in ZDSD than SD rats (Hammond et al., 2013; Han et al., 2020). Likewise, the lumbar vertebra of diabetic ZDSD rats had significantly lower bone mineral content levels compared with non-diabetic ZDSD rats. Short or smaller femoral bones, even in the absence of lower bone mineral density levels, are at risk for requiring less energy to fail in bending (Reinwald et al., 2009). Micro-computed tomography analysis of femurs and lumbar vertebrae determined that the trabecular bone volume was decreased in diabetic ZDSD rats compared with SD rats (Creecy et al., 2016).

Zucker Diabetic-Sprague Dawley rats have been used in studies to investigate skeletal or bone treatments in humans. In one study, spinal fusion surgery performed, and less solid bony union found in ZDSD than in SD rats (Bhamb et al., 2019). Histological analysis revealed that less fibrocartilage and newly formed bone but greater fibrous tissue surrounding fusion segments were present in ZDSD rats (Bhamb et al., 2019). Treatments for skeletal fragility, such as raloxifene, a drug used to treat osteoporosis in postmenopausal women, lowered blood glucose concentrations in female ZDSD rats. Studies using atomic force microscopy, Raman (chemical composition) spectroscopy and the mechanical testing technique reference point indentation linked nanoscale morphology and the biophysical properties of bone, collagen and tendons to differences at microscale levels of organization in ZDSD rats (Gallant et al., 2013; Gonzalez et al., 2014; Hill Gallant et al., 2014). Advanced glycation end products have been proposed to form cross-links with collagen to slow turnover rates of collagen (Hammond et al., 2013; Reinwald et al., 2009). It was proposed that these advanced glycation end products might reduce energy dissipation and increase the brittleness of bone matrix, which could contribute to a higher chance of fracture (Creecy et al., 2016; Tang et al., 2007).

3.5 | Diabetes in University of California Davis type 2 diabetes mellitus rats

The University of California Davis type 2 diabetes mellitus (UCD-T2DM) rat is a close match to the ZDSD rat (Cummings et al., 2008). The background parent strains for the UCD-T2M rat are specifically described as lean ZDF homozygous wild-type (+/+) and obese insulin-resistant Crl;CD Sprague Dawley (Cummings et al., 2008). The stewardships differ between the ZDSD and UCD-T2M colonies, such that the ZDSD rat is available from a commercial supplier. No direct comparisons between these models have yet been made.

As was predicted (Peterson et al., 2015), the UCD-T2DM rat has many of the same characteristics as the ZDSD rat and is being used in translational preclinical diabetes research. Similar to the ZDSD rat, the UCD-T2DM rat also show a predominance for 2–3 months earlier onset of the development of diabetes in males vs. females. Studies with the UCD-T2DM rat have investigated feeding regular rodent chows [e.g., Purina 5012 (Cummings et al., 2008, 2011)] and other diets containing nutritional supplementation [e.g., safflower oil (Cummings et al., 2008), fish oil and eicosapentaenoic acid (Cummings, Stanhope, Graham, Griffen, et al., 2010) and fructose (Cummings, Stanhope, Graham, Evans, et al., 2010)], in addition to dietary restrictions and various chemicals (Green et al., 2017; Hung, Kanke, et al., 2019) and drugs (Agrawal et al., 2014; Cummings, Stanhope, Graham, Baskin, et al., 2010; Cummings et al., 2014; Guglielmino et al., 2012), including leptin, which normalized plasma glucose (Cummings et al., 2011). Surgical interventions for obesity, for example, gastric sleeve gastrectomy, ileal interposition and Roux-en-Y gastric bypass, have also been explored in the UCD-T2DM rat (Cummings, Strader, Stanhope, Graham, et al., 2010; Cummings et al., 2012; Cummings, Bettaieb, et al., 2013, Cummings, Graham, et al., 2013; Hansen et al., 2014; Hung et al., 2018; Hung, Napoli, et al., 2019), leading to evidence that, amongst other mechanisms, bile acids and changes in maternal weight contribute to the benefits of surgery in the experimental animals and, in some cases, even in the maternal offspring.

When fed the regular chow diet, the time to onset of diabetes in the male UCD-T2DM ranges from 4 months to >1 year and distributes according to body weight and weight gains at an earlier age. A common approach to address this challenge with the UCD-T2DM rat is to use body weight for selection of experimental animals, and to group animals by blood hyperglycaemia and duration of time for rats experiencing diabetes (e.g., <2 weeks, prediabetes; 2–3 weeks post-onset, recent diabetes; >3 months post-onset, long-term diabetes). In UCD-T2DM rats, fed or fasting blood glucose concentrations >200 mg/dl monitored by blood glucometer are commonly reported criteria for the time to onset of diabetes. Fed blood glucose concentrations >200 mg/dl coincide with fasted state hyperinsulinaemia and the beginning of a decline in fasting plasma insulin, 60% after 2 months and 75% after 4 months, in male UCD-T2D rats (Cummings et al., 2008). Elevated fasted plasma glucose >200 mg/dl lagged the detection of the elevated fed blood glucose levels by 2 months (Cummings et al., 2008). Levels of HbA1c >6% in combination with blood glucose concentrations have also been used as criteria to define diabetic groups for both male and females (Akther et al., 2021; Shaligram et al., 2020). Fasting HbA1c increased 2.25-fold (from 4 to 9%) in UCD-T2M rats fed regular diet from 2 to 6 months of age (Cummings, Stanhope, Graham, Baskin et al., 2010). Values of HbA1c in 6 months diabetic UCD-T2DM rats were 11.8%, versus 4.3% in age-matched obese SD rats (Fields et al., 2015). In a separate study using 2 months diabetic UCD-T2DM rats, HbA1c was lowered from 10.3 to 8.5% by treatment with leptin (Cummings et al., 2011). The characteristics of ITT and GTT in UCD-T2D rats are similar to those of ZDSD rats fed Purina 5008. Hyperinsulinaemic–euglycaemic clamp methods have not been used with the UCD-T2M rat. However, liver, skeletal muscle and adipose tissue of diabetic ZDSD rats showed decreased insulin signalling, as evidenced by decreased Akt phosphorylation (Cummings et al., 2011). In UCD-T2M rats, functional pancreatic islets, as evidenced by insulin-positive staining area, are reduced by 70% after the onset of diabetes (10–12 weeks) (Cummings et al., 2008; Rountree et al., 2013).

Studies conducted *ex vivo* with isolated blood vessels indicate that endothelial function with respect to vasodilator mechanisms is altered in the prediabetic and diabetic UCD-T2DM rats (Akther et al., 2021; Shaligram et al., 2020). In female and male UCD-T2DM rats, mesenteric arterial vasodilatation in response to the muscarinic agonist acetylcholine was reduced by 20 and 70%, respectively, in diabetic (6.7 to 8.5 weeks) compared with prediabetic groups (Shaligram et al., 2020). Mesenteric arterial vasodilatation was 24% less in male, but not in female, prediabetic UCD-T2DM rats compared with age- and sex-matched SD rats (Shaligram et al., 2020). In a subsequent *ex vivo* study looking at aortic endothelial function, it was found that acetylcholine-induced vasodilatations were 17% greater in UCD-T2DM males, but not females, compared with age- and sex-matched SD rats (Akther et al., 2021). Both studies also reported changes to vascular muscle contractility, as evidenced by increased sensitivity and/or increased efficacy of the α_1-adrenoceptor agonist phenylephrine (Akther et al., 2021; Shaligram et al., 2020). Together, the evidence suggests that the UCD-T2DM rat, like the ZDSD rat, is useful for investigating the progressive vascular dysfunction in prediabetes to diabetes.

Other similarities between the UCD-T2DM and ZDSD models of T2D include evidence of neuropathy and skeletal developmental defects. Neuropathies have been characterized by impaired vagal afferent pathways for sensing glucose in the gut of UCD-T2DM rats (Lee et al., 2012). Similar to studies with the ZDSD rat, the UCD-T2M rat exhibits evidence of skeletal fragility (Acevedo et al., 2018) and changes to intervertebral disc composition and biomechanical properties (Fields et al., 2015), which support these models for exploring management/therapy for lower back pain.

Studies of the microbiome and metabolome of the UCD-T2DM rat (Mercer et al., 2020; Piccolo et al., 2016, 2018, 2021) indicate roles for gut microbiota in regulation of energy balance and metabolism, which is altered in the diabetic state. We note that these findings in UCD-T2DM rats would be particularly interesting to compare in the ZDSD

rat, because the drivers for the alterations in diabetic UCD-T2DM rats were not the diet or the environment (Piccolo et al., 2018).

3.6 | Diabetes in ZDF rats

Zucker Diabetic Fatty rats are a strain derived from inbreeding Zucker Fatty (ZF) rats, with subsequent selection for an obese and diabetic phenotype (Etgen & Oldham, 2000; Peterson et al., 1990; Phillips et al., 1996). The Zucker Fatty (ZF) rats are carriers of an *fa/fa* mutation (Phillips et al., 1996); they are obese, hypertriglyceraemic, hyperglycaemic and hyperinsulinaemic, but do not develop hyperglycaemia when fed a regular diet (Kleinert et al., 2018). In ZDF rats, a β-cell transcription defect is a heritable autosomal recessive characteristic that is independent of the *Lepr* mutation (Griffen et al., 2001). In lean ZDF rats, β-cell function is reduced but suffices to maintain normoglycaemia. For the time to onset of diabetes, significant differences between ZDSD and ZDF rats have been noted earlier in this review. Thorough reviews of the ZDF model have made detailed comparisons with other T2D models (Kleinert et al., 2018; Shiota & Printz, 2012). In the ZDF rat, insulin resistance and glucose uptake defects have been validated using precise methods and imaging modalities, including the hyperinsulinaemic–euglycaemic clamp and positron-emission tomography. Notably, hyperlipidaemia in ZDF (*fa/fa*) rats at 6–7 weeks (plasma triglycerides ~200 mg/dl) and 20 weeks (~500 mg/dl) are roughly twofold higher than reported in studies with the ZDSD (Peterson et al., 2015) and UCD-T2DM rats (Cummings et al., 2008; Cummings, Stanhope, Graham, Griffen, et al., 2010). Zucker Diabetic Fatty homozygous (*fa/fa*) rats are infertile, which presents another restriction on their use. Many of the complications of T2D arise early in the ZDF model (16–20 weeks), which constrains the time course for study of diabetes interventions without the presence of confounding co-morbidities (Shiota & Printz, 2012).

3.7 | Diet-induced obesity SD rats

A substrain of Crl;CD rat prone to developing diet-induced obesity (Levin et al., 1997) was used in the creation of the ZDSD rat (Peterson et al., 2015; Reinwald et al., 2009). It was selected because the adult onset of obesity and insulin resistance is polygenic in origin and persists for the entire lifespan (Levin et al., 1997). Rodent diet-induced obesity models are widely used for studying factors that lead to and regulate obesity; especially of interest are diets having high fat and energy (Kleinert et al., 2018). Like the ZDSD rat, sex differences, strain characteristics, such as genetic susceptibility, the composition and standardization of diets, and environmental factors in housing have an influence on the outcomes of research (Kleinert et al., 2018). The choice of diet-induced obesity model should be selected for the research objectives, given that the long period of time required to induce major pathologies of T2D can limit the usefulness, for example, for screening anti-diabetic compounds (Islam & Wilson, 2012).

4 | CONCLUSION

The increasing burden of T2D in humans and the need for new therapeutics make selection of preclinical research models of T2D essential to advancing translational research. The ZDSD rat develops a prediabetic state that progresses to overt diabetes with age, which can be accelerated in males with a HFD. There are sex-related biological differences in the ZDSD rat that have not been explored in detail; however, many well-known phenotypic and biochemical characteristics of human diabetes and its associated morbidities are replicated in the ZDSD rat.

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AUTHOR CONTRIBUTIONS

Conception and design of the work: J.J.M. formulated the idea for this review, and its overarching goal. Acquisition, analysis, or interpretation of data for the work: A.N.W. and J.J.M. collected and analysed data/evidence; all authors provided interpretations; J.J.M. supervised A.N.W. and J.C.; and funding was acquired by J.J.M. and G.M.F. Drafting of the work or revising it critically for important intellectual content: J.J.M. and A.N.W. wrote the original draft, reviewed and edited versions manuscript; J.C. and G.M.F. reviewed and edited drafts and provided critical commentary. All authors have approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and those who qualify for authorship are listed.

COMPETING INTERESTS

The authors are conducting research studies using ZDSD rats, some of which have been furnished gratis for evaluation from Charles River. These studies are not yet published. Neither Charles River nor funding agencies have provided input into the preparation of this review.

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