INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Animal models in Metabolic Syndrome

Dr. Durga Devi Surya Kumar Verma*, Dr. Sugiram S.

JIPMER Puducherry.

ARTICLE INFO

Published: 03 Sept. 2025
Keywords:
criteria, elevated abdominal circumference, triglycerides, fasting glucose, blood pressure
DOI:
10.5281/zenodo.17047012

ABSTRACT

The first attempt to define metabolic syndrome is done in 1998 by WHO proposing a presence of insulin resistance, impaired glucose concentration essential component, along with at least two of the following parameters should be present, raised BP, hypertriglyceridemia and/or low HDL-cholesterol, obesity (as measured by waist/hip ratio or body mass index (BMI)), and microalbuminuria. The latest guideline of joint interim statement of IDF and AHA/NHLBL in 2009 simplifies definition stating presence of minimum any three of the following criteria, elevated abdominal circumference, triglycerides, fasting glucose, blood pressure and low HDL cholesterol. This joint definition is widely accepted by researcher. The metabolic syndrome is itself has interlinked diseases and condition involving genetic and environmental factor. Due to multifactorial condition establishment of appropriate experimental animal model mimicking the diseases state in human is crucial. This multifaceted effect of MetS has made researcher to put more effort in developing new intervention to reduce burden of disease worldwide. Various dietary models, genetic model, chemical model, drug induced model came into light to understand the diseases condition better. The major challenges to develop this model is expenses, as the metabolic syndrome animal model is quite expensive, it holds the researcher to experiment on primates and mammalian model which are like human. In this article we are going to see study procedure and outcome of zebrafish, rat, rabbit, canine, horse's animal model of MetS.

INTRODUCTION

Various international organizations has tried to define Metabolic Syndrome (MetS) proposing different criteria based on their understanding and observation. According to the World Health Organization (WHO), a diagnosis of MetS requires the presence of insulin resistance—evidenced by type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance—as one of the mandatory criterion to be called MetS, along with at least two of the following: abdominal obesity (waist-to-hip ratio >0.9 in men or >0.85 in

***Corresponding Author:** Dr. Durga Devi Surya Kumar Verma
Address: *JIPMER Puducherry.*
Email ✉: durgav1310@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

women, or BMI >30 kg/m²), elevated triglycerides (≥150 mg/dL) and/or low HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women), hypertension (≥140/90 mmHg), or microalbuminuria[1]. Similarly, the European Group for the Study of Insulin Resistance (EGIR, 1999) emphasizes insulin resistance, requiring hyperinsulinemia (fasting insulin >75th percentile) as mandatory criteria , in addition to at least two of the following: central obesity (waist circumference ≥94 cm in men or ≥80 cm in women), high triglycerides (≥150 mg/dL) and/or low HDL cholesterol (<39 mg/dL), hypertension (≥140/90 mmHg or on antihypertensive treatment), or elevated fasting glucose (≥110 mg/dL). American association of clinical Endocrinology (AACE, 2003) defines MetS by containing impaired glucose tolerance as a mandatory criteria , plus at least two of the following: BMI ≥25 kg/m², elevated triglycerides (≥150 mg/dL) and/or low HDL cholesterol, and hypertension (≥130/85 mmHg). In contrast, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI, 2004), building upon the revised NCEP: ATP III guidelines, proposes a simpler definition where any three or more of the following given criteria confirm the diagnosis: including abdominal obesity (waist circumference ≥102 cm in men or ≥88 cm in women), elevated triglycerides (≥150 mg/dL), low HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women), hypertension (≥130/85 mmHg), and elevated fasting glucose (≥100 mg/dL). This approach does not designate any single mandatory criterion, unlike some earlier definitions. International Diabetes Federation (IDF, 2005) defines central obesity (ethnicity specific waist circumference) as mandatory component (BMI>30kg/m^2), plus at least two of the following : elevated triglyceride (≥150mg/dl), low HDL cholesterol, Hypertension (≥130/85mmHg), elevated fasting glucose (≥100mg/dl). Joint Interim Statement by IDF and AHA/NHLBI in **2009** harmonizes previous definitions and simplifies the diagnosis by requiring any three of the following five criteria, with no mandatory component: elevated waist circumference (ethnic-specific), elevated triglycerides (≥150 mg/dL), low HDL cholesterol, elevated blood pressure (≥130/85 mmHg), and elevated fasting glucose (≥100 mg/dL).This definition is currently most widely accepted by researcher. As of 2022, the global prevalence of MetS ranges from 12.5% to 31.4% [2]. Metabolic syndrome leads to wide range of complication and serious health consequences as it is interconnected with other medical condition like , cardiovascular, endothelial dysfunction and dyslipidaemia. Insulin is a major contributor of MetS with worsening glucose intolerance. Numerous dietary studies has played a key role in balancing hormone , glucose metabolism, and lipid metabolic pathways[3]. Treatment of metabolic syndrome is multifaceted approach with lifestyle modification being the first strategy. Dietary changes such as adopting low calorie diet , Mediterranean-style or dash diet , combine with exercise lead to weight loss and significant improvement in insulin sensitivity. Pharmacological treatment required to treat specific component of MetS like metformin, statins, ACE inhibitor, appropriate for individual with morbid condition. Additional measures taken include cessation of smoking , limited alcohol intake, stress management, and maintain good sleep hygiene, this together with medical intervention helps in reducing the risk of complication and managing patient condition in Mets. MetS is a complex condition animal model of Mets simplifies in understanding a complex clusters of condition , these model help researcher in studying a interaction of various component overtime and allow depth knowledge of shared molecular mechanisms. Animal model make drug development process easy by screening new

compound and evaluating their long term safety. It also help in developing translational model that bring laboratory discoveries closer to clinical application . Despite their usefulness animal model of Mets face several challenges .one major limitation is that no single model fully replicated the complex cluster of condition like in human making it difficult to study the syndrome as a whole . Physiological differences between other species and human also limit the direct applicability of animal model finding to humans. Genetic model in most animal is monogenic while MetS is polygenic.

Table 1- Classification of MetS Model according to species.

Sl. No	Species	Name
1	Invertebrates	Zebra fish model
2	Rodent	Mouse model
3	Primate	Rabbit, Dog, Horses model
4	Genetic	Zebra fish, Rat, Horse ,Rabbit model

Table 2- Classification of MetS Model based on applied Intervention.

Animal model			
Diet induced model	**Genetic**	**Chemical**	**Drugs**
Diet induced Swiss albino mice model	Dahl S.Z-Lepr^fa (DS/obese) rats	Swiss albino mice model	Tadalafil rabbit model
Wistar rat diet comparison model	FAM17A gene risk allele model	Zebra fish intraperitoneal injection model	Tamoxifen rabbit model
C57BL/6J mice model	ApoE knockout (KO) rabbits model	Zebrafish streptozotocin model	
Arabian horse model	Watanabe heritable hyperlipidaemic (WHHL) rabbits model		
Mixed Horse model	Zebra fish genetic model		
New Zealand white rabbit model			
Wistar rabbit model			
Western diet induced dog model			
Beagle dog model			

Genetic model

Zebra fish strains to study skeletal muscle insulin resistance:

To study skeletal muscles insulin resistance Zebrafish were raised in an Aquatic Habitats system under a 14:10-hour light-dark cycle. Embryos were obtained through natural mating and raised at 28.5°C in an incubator with the same 14:10-hour light-dark cycle. Animals were staged by days post-fertilization (dpf) or by age in months. At 5 dpf, larvae were placed on a standard rearing diet and maintained according to established protocols until they reached the appropriate age. All zebrafish used in this study were maintained in the same genetic background. Establishment of Transgenic mice line: The Tol2 transposon system used to generate the Tg transgenic line . A 3.9 kb fragment of the Beta actin promoter used to derive expression of

dominant negative IGF-1 receptor. Initial analyses were conducted using two independent lines for each transgene, and similar results were observed. All reported findings were obtained from F2 or F3 generation fish.

Glucose Uptake: To evaluate the efficiency of glucose uptake in zebrafish skeletal muscle, a non-radioactive 2-deoxyglucose uptake assay was employed. Six month old trans genic fish line and their non transgenic sibling fasted overnight , anesthetized in ice water and injected intraperitoneally 0.5 mg of 2- deoxy glucose per gram body weight , with or without 0.0075U of bovine insulin/ gram of body weight. After injection fish were allowed to recover for 15 minutes and then euthanized in ice water immersion . skeletal muscles dissected from the posterior trunk, carefully separated from skin, major blood vessel and bones, snap -frozen in liquid nitrogen and stored a -80 °C until use. The muscles samples were solubilized in 10mM Tris buffer , sonicated and centrifuged to remove debris, total protein content was measured using a bio rad assay, and equal amounts of protein were used for glucose uptake analysis[9].

Dahl S.Z-Lepr fa (DS/obese) rats were developed by initially mating a male Zucker rat heterozygous for the *fa* allele of the *lepr* gene with a female Dahl/Jr Sea rat, followed by multiple rounds of backcrossing to produce a congenic strain. Genotyping of the *fa* locus was performed using PCR-RFLP, with a primer set designed to amplify a 111-bp region containing the *fa* mutation. The forward and reverse primer sequences were 5′-TATGGAAGTCACAGATGATGG-3′ and 5′-CTTACGATTGTAGAATTCTCTAA-3′, respectively. Digestion with the restriction enzyme MspI produced two fragments of 78 and 33 bp for the *fa* allele. In each generation , male rats carrying the fa allele selected for continued backcrossing, and after 8-12 generation , the final congenic strains was established under specific pathogen free condition. Breeding of heterozygous animals yielded offspring with three genotype , homozygous (fa/fa, +/+) and heterozygous (fa/+) in a ration of 1:2:1; only two phenotype observe (fa/fa) and lean (fa/+, +/+). DS/obese rats exhibited hyperphagia and developed central obesity starting at 5 weeks of age. Ten week old male DS/obese rat fed a standard laboratory chow diet containing 0.36% NaCl, with food and water ad libitum . At 18 week of age, rats were housed in metabolic cages for 4 hours , urine collection and blood samples were taken from the right carotid artery after overnight fasting . rat were euthanized by giving intraperitoneal sodium pentobarbital injection (50mg/kg body weight), and heart, liver, kidney, and both visceral and subcutaneous fats were collected. Age-matched male DS/obese rats served as control animals. Even when maintained on a normal diet, DS/obese rats developed obesity, hypertension, dyslipidaemia, insulin resistance, and type 2 diabetes mellitus. They also showed evidence of cardiac hypertrophy, along with renal and hepatic damage, contributing to premature death. These pathological features make the DS/obese rat a suitable and valuable model for studying metabolic syndrome (MetS) [10]. To study the Genetic association of Equine metabolic syndrome, hair sample were plucked from the mane of 20 ponies and stored in dark place at room temperature till analysis, age between 3-25 years, cohort can include wide variety of breed the ponies were of known metabolic status and history of diagnosis of laminitis and oral glucose test if there with in a three month period. Blood sample collected from each pony transferred for genomic sequencing analysis .Study conducted on FAM17A gene risk allele found to have no significant correlation with phenotype of ID and obesity in pony cohort [11]. In a study on metabolic

syndrome-associated genetics, ApoE knockout (KO) rabbits were generated using CRISPR-Cas9 endonucleases or the ZFN technique. Male heterozygous and homozygous ApoE knock out rabbit , aged 5-12 month compared with wild type New Zealand white rabbits and WHHL rabbits. To analyse plasma lipid profiles, including lipoprotein and apolipoprotein, blood sample collected from rabbits fed either normal diet and with cholesterol enriched diet 0.3% cholesterol, 3% soyabean oil for 2 weeks. To evaluate the effect of ApoE deficiency on aortic atherosclerosis, both WT and ApoE KO rabbits were fed the same cholesterol diet for 10 weeks. Rabbits had ad libitum access to food and water during this period. Blood samples were collected after a 16-hour fast for genetic diagnosis and lipid profiling at the end of 2 week, after a diagnosis result has shown that Homozygous ApoE KO rabbits exhibited mild hyperlipidaemia even on a chow diet, with plasma total cholesterol levels around 200 mg/dL—similar to those observed in patients with type III hyperlipoproteinemia, whose cholesterol levels typically range from 300 to 350 mg/dL. When challenged with a 0.3% cholesterol diet, ApoE KO rabbits developed more severe hypercholesterolemia. This was primarily due to the accumulation of endogenously derived remnant lipoproteins, supporting the critical role of ApoE in cholesterol metabolism, especially under high-fat dietary conditions. Interestingly , heterozygous loss of the ApoE gene did not significantly affect plasma lipid in ApoE KO rabbits [12]. A genetic study also conducted with the same for Watanabe Heritable Hyperlipidaemic (WHHL) rabbits, with three month old rabbit divided in to control (n-15) and high fat , high fructose diet (HFCD) group (n=14).The control group was fed a standard chow diet consisting of 17.3% protein, 3.9% vegetable fat, 13.6% fibre, 8.7% ash, 48.9% nitrogen-free extract, and 7.6% moisture by weight, with an approximate physiological fuel value of 2.997 Kcal/g. The WHHL rabbits in the control group consumed about 70-90g of chow diet daily. The HFHD group received the standard chow diet supplemented with 30% fructose and 10% coconut oil (91% saturated fatty acids by weight), which induced more pronounced insulin resistance compared to a diet containing fructose alone. Compared to the standard chow diet, the HFHD was rich in sugar and fat but provided less protein and fibre. To prevent excessive body weight gain in the HFHD group, we restricted their diet to approximately the same caloric intake as the control group for a duration of 8-16 weeks. Body weight and daily food consumption were monitored. Rabbits were housed into their individual cages at a temperature of 22-24 degree Celsius on a 12 hour light/ dark cycle . Plasma lipid and glucose metabolism weekly analysed, total cholesterol , triglycerides, HDL level determined using Wako assay kits. The plasma lipid level in HFHD Group were elevated , causing increase in VLDL concentration. The plasma lipid levels in the HFHD group were elevated, resulting in an increase in VLDL concentration. This increase in VLDL was due to delayed VLDL catabolism and a deficiency in the LDL receptor in the WHHL rabbits. Additionally, increased Nrf2 expression and low SOD1 expression in the liver suggested that the HFHD induced hepatic insulin resistance and subsequent steatosis. This occurred through enhanced fatty acid influx into the portal system and hepatic oxidative stress in the WHHL rabbits [13].

Chemical Induced

Study in metabolic syndrome model has shown that peripheral neuropathy a is a common complication of chronic diabetes and the most commonly characterized by sensory abnormalities. Approximately 20-30% patient of diabetes suffer from neuropathic pain .Various rodent models of MetS is been used to study

neuropathy and to evaluate potential therapies for the same[6]. Study conducted to investigate the impact of hypercholesterolemia on the functional status of acetylcholinesterase (AchE) , mitochondrial complexes and inflammation across four discrete brain region : cortex, striatum, hippocampus, and substantia nigra to understand its influence on brain function. Eight week old male Swiss albino mice , weighing 20-22g, used for this study. Animal were housed under standard laboratory conditions: temperature (24± 2 °C) , humidity (60 ± 5%), and a 12-hour light/dark cycle. During the whole experimental period , mice were kept individually in polypropylene cages with free access to food and water. All procedure were performed according to relevant guideline and regulations. Hypercholesterolemia was induced by providing with high cholesterol diet (HCD; 5% w/w cholesterol mixed with standard chow) for 12 week ad libitum. Control animals received a normal chow diet, while the experimental group continued on the HCD. To assess memory functions, mice were acclimatized to the testing apparatus without any objects 24 hours prior to testing. Short-term memory was evaluated on day 79 using the object location test, while long-term memory was assessed on day 84 using the object recognition test. Mice were sacrificed on day 84, following the completion of behavioural assessments. Serum cholesterol Level measure to confirm hypercholesterolemia the AchE activity and mitochondrial complexes were quantified using a spectrophotometer from four brain regions: the cortex, striatum, hippocampus, and midbrain. Blood Brain Barrier (BBB) permeability assessment is done by a subset of mice (n=5) anaesthetized and perfused with 10% glycerol. For glial fibrillary acidic protein (GFAP) immunoreactivity studies, mice anaesthetized and perfused with 4 % paraformaldehyde . Another subset of mice (n=5) sacrificed one hour after salicylic acid injection on the final day of treatment for analysis of hydroxyl radical level in the brain. Cholesterol homeostasis essential for life , cholesterol is a critical component of cellular membrane and myelin sheath of neuron. Disruption in this balance may contribute to development of Parkinson's diseases and exacerbate its symptoms and neuropathological features in animal model[14].

Zebrafish Maintenance and Experimental Design: Wild type(WT) Zebrafish (Danio rerio) maintained under standard laboratory conditions with 14-hour light and 10-hour dark cycle and at a constant temperature of 28.5 °C. Fish were fed twice daily with a combination of dry food and brine shrimp. Age-matched WT zebrafish (4–6 months old) with an equal gender ratio were used for all experiments. All procedures were conducted in accordance with the "Principles of Laboratory Animal Care. Fish were anaesthetised by immersing in a 1:1000 solution of 2-phenoxyethanol for 1-2 minutes. Intraperitoneal injection of insulin syringe with a 28.5 G needle used to administer 0.3 % streptozotocin prepared in 5mM citrate buffer (pH-5.0), at a dose of 350mg/kg body weight . The injected volume ranges from 70- 150 µL, depending on the weight of fish. Control fish were injected with an equivalent volume of citrate buffer. For direct caudal fin injections, the same STZ concentration was used, and the procedure was carried out using a Harvard Apparatus microinjector. Injection timing is detailed in the Results section. Following injection, fish were maintained at a temperature of 21–23 °C throughout the diabetes induction and maintenance phases. STZ injection resulted in a sustained increase in fasting blood glucose level (FBGLs) , effectively inducing hyperglycaemia. Adult zebra fish are known to regenerate multiple tissues including heart ,retina, spinal cord, pancreas, and fins. Among these , the caudal fin has become a widely used model for investigating

molecular mechanisms of regeneration due to its accessibility for amputation and relatively simple structure . Finding indicates the extent of sustained hyperglycaemia directly impacts the regenerative capacity of zebrafish. Furthermore, the degree of regenerative impairment correlates with the duration of hyperglycaemic exposure [15]. Adult male and female wild type zebrafish (danio rerio), aged 3-6 months, maintained under standard condition with a 14/10 hour light dark photo period and a temperature of 28+/- 1 degrees Celsius. The zebra fish fed daily with commercially available dry food. Animals were euthanized by rapid chilling on ice to induce lethal shock before spinal cord sectioning. Fish were deeply anaesthetized with 0.02% tricaine. To assess the impact of hyperglycaemia in zebrafish , animal subjected to either acute or chronic exposure to D-glucose , acute hyperglycaemia induced by intraperitoneal injection of D-glucose (2.5g/kg body weight) dissolved in 50 µL of phosphate buffered saline. Control fish for this group were injected with 50 µL of PBS. Chronic hyperglycaemia (CHG) was induced by supplementing fish water with 111 mM D-glucose over a 14-day period. The fish water was changed every two days. For both the acute and chronic hyperglycaemia models, control fish were rigorously maintained under the same conditions (light, temperature, and environment) as the treated fish [16] .

Drug induced MetS Model.

Another study conducted on male New Zealand White rabbits (weighing approximately 3 kg) housed individually under standard temperature and humidity regulated room with a 12-hour light/dark cycle. After one week acclimatization period , animal divided into groups; an untreated group (n-49) fed on a regular diet (RD), and a treated group (n-32) fed on a high fat diet , containing 0.5% cholesterol and 4% peanut oil for 12 weeks. Two additional group were fed with same HFD for 12 weeks and treated with tadalafil at a dose of 2mg/kg. Functional studies using corpora cavernosa strips were conducted to assess the biological efficacy of tadalafil treatment. The results demonstrated that tadalafil administration was biologically relevant, as it significantly reduced visceral adipose tissue accumulation [17]. In a similar study, instead of a standard control group, animals (n = 23) were fed a regular diet for 12 weeks, consisting of 12% water, 16.5% protein, 15.5% fibre, and 3.5% vegetable fat. A high-fat diet (HFD) group (n = 16) received a modified diet for 12 weeks, containing 4% peanut oil and 0.5% cholesterol. Compared to the regular diet, the HFD consisted of 12% water, 12.6% protein, 21.2% fibre, 6% vegetable fat, 0.5% animal fat, and Mucedola formulation. To evaluate the effect of tamoxifen (Tam) an additional group of animal receiving the similar HFD given Tam treatment (0.25 mg/kg/day , dissolved in drinking water) for 12 weeks. Blood sample for glucose ,total cholesterol , triglycerides testosterone and oestradiol analysis collected in the early morning following an overnight fasting, via the marginal ear vein at 12 week . at the end of the diet period , results showed that the HFD had a detrimental effect on epididymal sperm motility and morphonology.. At the end of the diet period, results showed that the HFD had a detrimental effect on epididymal sperm motility and morphology. Most sperm parameters were strongly associated with metabolic syndrome (MetS) features. The HFD induced fibrosis and inflammation which may impair testicular and epididymal function. Interestingly , it was found that tamoxifen did not appear to be an ideal treatment for MetS – associated reproductive dysfunction[18].

Diet induced MetS Model.

Rat model

The study conducted to investigate whether hypercholesterolemia causes psychomotor abnormalities in mice and alters their cortico-striatal biogenic amine neurotransmitters, with relevance to Parkinson's disease or not . Eight-week-old male **Swiss albino mice** (weighing 21–22 g) used, housed under standard laboratory conditions with a temperature of 24 ± 2°C, humidity of 60 ± 5%, and ad libitum access to food and water provided . A mice were acclimatized to environment 5-day before the start of the experiment, were divided into two groups: a control group fed a standard diet and a high-cholesterol diet group, which received a standard diet mixed with 5% cholesterol for 84 days. Behavioural tests, including the elevated plus maze, forced swim test, and gait and swim tests, performed on days 81, 82, and 83, respectively. After the 84-day treatment period, serum total cholesterol levels analysed and neurotransmitter content and immunoreactivity, assessed in discrete brain regions. The key findings of the study has revealed that a decrease in dopamine content and reduced tyrosine hydroxylase (TH) immunoreactivity in the striatum, as well as a depletion of serotonin content in the cortex of hypercholesterolemic mice. Mice also exhibited motor and depressive behaviours. It was also noted that while the body weight of the mice on the high-cholesterol diet did not change significantly during the 12-week dietary period, indicating the animals were not obese but the test results has proven that hypercholesterolemia still induced notable neurochemical and behavioural alterations [19]. Comparative intervention study was conducted to examine the diet induced metabolic syndrome using 16 male Wistar rats, aged 3 month and weighing 200-300g. the rat housed in Plexiglas cages (4 per cages) under standard laboratory condition with a 12 hours light /dark cycle . They were allowed a minimum of 7 days to acclimate new environment before the study began. Food and fresh drinking water were provided ad libitum for a period of 10 weeks. Rat were divided into 4 groups , each containing 4 animals (n=4). Group 1 Standard chow diet, group 2 fed on a High fat high cholesterol diet , group 3 fed on a high ft diet and group 4 on cafeteria diet. Weekly monitoring of blood glucose level were done and it was found that HF-HCD and CFD diet experienced increase of 32% and 53%, respectively. Serum biochemical parameters showed that urea levels were lower by 66%, 44%, and 70% in the HF-HCD, HFD, and CFD groups, respectively. Uric acid levels were higher in the HF-HCD and CFD groups by 44% and 102%, respectively. Total protein levels raised by 19%, 21% and 24% relative to HF-HCD, HFD and CFD, groups respectively while albumin level were raised by 61%, 70% and 59% . ALT and AST raised by 200% and 300% in al experimental groups. Additionally, bilirubin levels were elevated by 71%. Amylase activity was significantly lower in all diet groups, approximately 90% lower than in the control group. Body weight gain was 42% higher in the HFD group compared to the other groups. Antioxidant levels were significantly reduced in all fat diet groups [20]. A mouse model for diet induced obesity and relation of insulin resistance was done by using C57BL/6J mice aged 4-6 weeks housed under 12 hr light /dark cycle with ad libitum access to water were provided, control group diet fed with 10% kcal chow diet , while the experimental group received with 60% kcal fat diet , at the end of 16-24 week the blood glucose and insulin level measured[21].

Rabbit model

Diet regimen in normal rabbit 2% vegetable fat, 15% protein, 40-50% carbohydrates, and 15-25% fiber. In New Zealand generate typical plasma cholesterol range in the 30-65mg/dl. Mostly the duration of study in rabbit ranges from 8-36 week, most selected strain New Zealand white rabbit,

experiment begin 2-3 week after the acclimatization of animal. Monitoring of diet by giving restricted diet or ad libitum, in addition dietary modification has been controlled with genetic modification in some strain of rabbit animal studies [22]. Diet rich in fat widely used to induce obesity and MetS in experimental model, their ability to induce obesity has been demonstrated in ,promoting hyperglycemia, insulin resistance and dyslipidemia and increase in free fatty acid in blood. Only Male hybrid Flanders rabbit initially weighing 850g-1000g housed in a single cage in a humidity in a temperature controlled room with 12h light cycle. Housing rabbit singly in cage means moments restriction and sedentary lifestyle. They fed 100g/day of standard rabbit chow diet. After 1 week of acclimatization period they were randomly divided into two groups: one designated to remain lean (CD = 12),another group (HFD = 12). The lean group continued with the same normal diet, HFD group is given ad-libitum a standard rabbit chow supplemented with 18% fat, excess fat in the diet consists of corn oil 10% and lard 8%. Unsaturated to saturated ratio was 2.2+/-0.02. Experiment has been performed after the rabbit 6 week of dietary completion. Once the 6 week of dietary intervention food withdrawn for 12hrs and the rabbit were anesthetized directly measuring mean arterial pressure and heart rate in the carotid artery [23]. Sucrose is a disaccharide made of glucose and fructose. Upon ingestion both component get metabolized in the body. Phosphofructokinase enzyme in our body regulate glucose metabolism and its entry in glycolytic pathway is negatively managed .Fructose in turn bypasses this regulation and enter glycolysis continuously. As fructose is a favourable substrate for de novo lipogenesis, excess intake can lead to fat accumulation in the liver and adipose tissues. This characteristic make fructose significant dietary component for development of MetS in animal. Studies in rabbit has demonstrated a significant weight gain in experimental group compared to controls. Study conducted on 11 New Zealand male white rabbits, each weighing 4.39+/-0.14kg and aged 20-22 weeks at the start of experiment. The rabbit housed under controlled condition with a temperature of 20+/-0.15 degree Celsius and a relative humidity of 50±5% on a 12 hr light /dark cycle. The terminology chow and diet are used interchangeably .A high fat diet was prepared using a standard chow diet mixed with 10% hydrogenated coconut oil and 5% lard , providing an energy values of 3.7 kcal/g. Sucrose solution ranging from 5 to 15% prepared by dissolving appropriate amount of sucrose in sterilized water with a 15% solution yielding 0.6 kcal/mL .Animals were acclimatized for 4 weeks. The control group received 120g standard chow daily with ad libitum access to water. The MetS group fed 250g chow daily , beginning with a mixture of 50% control diet chow and 50% high fat chow , gradually increasing to 100% high fat chow by the end of acclimatization period. Simultaneously sucrose concentration increased from 5-15% in drinking water . throughout 28 week experimental period, the control group continued to receive 120g standard chow and water ad libitum. The MetS group received 250 g of high-fat chow and 15% sucrose solution as drinking water. The leftover chow and water were weighed daily to monitor consumption. Morphological assessments included weekly measurement of body weight and periodic evaluation of height, body length, and abdominal contour. Body mass index (BMI) was estimated before the experimental diet administration and again at weeks 14 and 28 in anesthetized animals. At the end of the experiment, blood pressure and fasting glucose levels were measured to evaluate metabolic changes [24].

Canine Model

It was observed in human consumption that western diet is strongly associated with increasing central obesity , adipocyte hypertrophy, intestinal epithelial stemness, dyslipidaemia, and elevated blood pressure. These changes progress to metabolic dysfunction and contribute to development of type 2 diabetes mellitus and colorectal cancer. To study the effects of metabolic changes induced by a western diet , an animal canine model crossover design conducted on 10 dogs. The control diet (CON) was formulated based on human nutritional ranges and fibre recommendations, while the Western diet (WD) was designed according to parameters from the National Health and Nutrition Examination Survey dataset. Following each period (7–8 weeks), experimental parameters were measured. The mean body weight of dogs were 8.83kg for the control diet and 9.28kg for those receiving western diet. Fasting blood sample collected after 10 hrs showed significant differences in mean fasting bile acid, serum triglyceride and cholesterol levels demonstrating diet dependent alteration in lipid profiles. Additionally, systolic blood pressure was affected by diet. Histological analysis revealed diet-dependent changes in colonic epithelial villus height and the villus: crypt ratio, highlighting the impact of diet-induced changes. These findings suggest that this model effectively mirrors human Western diet-related diseases, making it a valuable tool for research [25]. The experiment conducted on 1-2 year old male beagles weighing 8.0kg to 10.5kg, maintained in standard environment with a 12 hour light/ dark cycle, temperature of $23.5 \pm 1°C$ and relative humidity of 60+/- 10%. The dogs has given ad libitum access to water. After two weeks, each beagle underwent a complete physical and nutritional examination, which included assessment of BMI and BCS, as well as imaging and blood tests. Eighteen **beagles** that met the healthy reference range based on physical and laboratory tests were randomly assigned to either a normal chow diet (n=9) or a metabolic overload group fed a high-fat diet (HFD) (n=9).The control (NC) dogs were fed a basal maintenance diet containing 3615 kcal/kg, while the HFD dogs received a customized diet rich in lipid, providing 4832 kcal/kg. During the study, physical examinations and blood sampling were performed every four weeks. All biological sample were collected and stored at -80 degree Celsius until analysis. Specifically , each animal received Intravenous glucose load 0.3g/kg body weight, with blood glucose level measure every 2minutes from 4-18 minutes. At 20 minutes , dog received 0.02U/kg body weight of Insulin IV , blood glucose level monitored repeatedly up to 3 hours.At week 24, dogs fed the HFD experienced a 60% increase in weight. BMI, subcutaneous fat, and body condition score (BCS) were measured simultaneously in HFD-fed and control dogs based on CT images. The HFD led to increased inflammatory cell counts, dyslipidaemia, and insulin resistance in the dogs. Urine analysis revealed 29 metabolites with lower levels in the HFD group. Among these, the top VIP metabolites included pyridoxal-5-phosphate, N-6-acetyl-L-cysteine, pyridoxal, and indoleacetic acid. Dogs on the HFD exhibited higher amounts of visceral and subcutaneous fat compared to control dogs, as observed through CT imaging at 24 weeks. A total of 132 metabolites (46 negative and 86 positive) showed significant differences between the groups, with 103 metabolites being higher in the HFD group. Plasma analysis explained 29.5% of the total variation in the levels of positive metabolites and 23.4% in the levels of negative metabolites[26]. Another study investigated alterations in the serum and urine metabolome in 12 lean and 16 spontaneously overweight dogs after 2 week continuous completion of their normal chow and High fat diet respectively and

reported lower plasma carnitine concentrations and lower postprandial urine taurine concentrations in overweight dogs than in lean dogs [27].

Equine model

The American college of veterinary internal medicine describe equine metabolic syndrome (EMS) increased fat deposition in throughout body or in specific location , abnormal insulinemic and glycemic response to a glucose test, laminitis that has developed without a recognized cause[28]. Equine metabolic syndrome is a challenging condition to manage in horse, cannot effectively metabolize dietary sugar due to reduced insulin sensitivity, and oxidative stress that's why they need to be fed with reduced sugar and starches [29]. Insulin in resistance in horse impaired cellular response to hormone insulin. This hormone is secreted by pancreas when blood sugar level is high , normally blood glucose level return to normal after two hours of meals, in horse with insulin resistance the cells of liver , muscles and adipose don't respond well to insulin[30]. Obesity though not the cause of the development of EMS but obesity is common in horse diagnosed with EMS, sometime they appear normal with general and regional fat deposition [28].

Diet Induced Weight Gain

This animal model is performed "To determine the effect of diet induced weight gain on glucose and insulin dynamic and plasma hormones and lipid concentration in horses". Thirteen Arabian or Arabian cross gelding horses aged 8-20 years of Initial mean body wight age 448kg was selected and horses were in moderate condition. Prior to study initiation all horses were maintained on Pasteur as a single group for >6 month, during the study period horses were maintained as a single group on a dry lot. The experimental protocol was approved by the Virginia tech institutional animal care committee. Experimental design- Longitudinal study design lasting 30 week all horses were concurrently exposed to protocol dietary treatment and sampling procedure. During period 1 (week 0 to 3) horses were maintained on a forage diet consisting of a mixed grass legume hay and fed 104% of their maintenance dietary requirement. During period 2 (week 4-7) horses were maintained at a high concentrate and hay diet and fed 110% of their maintenance dietary requirement . During period 3 (25- and 4 (week 8-24) horses were fed twice their dietary requirement,197 % of total dietary requirement which decreased to 179% during the last week of the period. During period 4 horses were fed on a mean of 193% of their maintenance which decreased to 183% during the final week of the period. During 5TH period horses maintained at obese diet fed with a mean of maintenance dietary requirement .Horses were fed three times daily 7am, 2pm, 7pm, and given 1 hour to consume each meal and unconsumed feed were weighed daily. Blood samples can collect between 7am and 9am, body weight measured the first day of each week and adiposity measurement evaluated biweekly. Horses were allocated into 3 group and subjected to insulin modified FSIGTT procedure on the first , second, third day of week 3, 24, 30 and regular FSIGTT on first, second, third day of weeks 7 and 16 correspond to last week of each period. Other accompanied study could also be performed like investigatory cytokine expression during diet induced obesity and individual and tissue biopsy test can also be done [31]. Diet induced weight gain In-vivo model was conducted to find the effect of diet induced obesity (haylage diet low in nonstructural carbohydrates) and Pasteur on blood pressure and serum cortisol and standardbred mares. studies in dog and humans have shown that weight gain and obesity even over a short period of time increase blood pressure, there is almost

linear relationship between BMI and BP. This relationship is existed in horse is not proven yet but hypertension and altered vascular function has reported in laminitic prone ponies. To study the same, study conducted on nine standard mares with an age of 16+/-3 years and a body weight of 497+/-15kg were included in the study. Body condition score (BCS) and Crest neck score at the study was 5.5+/-0.6. All horses were sedentary horses owned by the department of clinical science, Swedish university of agriculture. The horses were kept in box stall fed three time daily with a 7 hours daily turn out in small paddock and had no previous sign of laminitis and showed no sign of diseases on clinical examination on the CBC , before the start of the study, horses had ACTH secretion within normal reference range .Experimental design – prospective longitudinal study, during 2 month before the study horses kept on haylage diet with a low content of NSC (< 10% of dry matter) that fulfilled their 100% of daily dietary requirement. The haylage diet gradually increased with a goal to supply approximately 250% of the horse's daily energy requirement .During the weight gain (22week) the haylage diet given twice daily with rapeseed oil and chopped alfa alfa , the horses were then gradually adapted to 10hectar Pasteur, after one week of Pasteur acclimatization horses were kept on further four week on a Pasteur diet. Diet sample for analysis of NSC, energy, crude protein, nonstructural carbohydrates content and dry matter were collected three time during the stable and fourth day using Pasteur .Water and salt provided ad libitum throughout the study. The insulin sensitivity of each horses was determined before weight gain after weight gain (22 week) after 5 week of Pasteur using the euglycemic hyper insulinemic clamp method. Recording and blood sampling- Body weight recorded every week during the whole study using a portable electronic scale. Body condition score and CNS were determined by the same experienced person before and after 5,14,22 and 27 week by Henneke et.al [32] and Carter et.al [33] scale. Blood pressure measured in the morning 6:00 am at the Blood sample were collected in evacuated tube using vacutainer [34]. Comparison of two diagnostic test to detect insulin dysregulation in horses over a 6 month period during which participating horses must adhered to tailor-made ration prescription and a recommended amount of exercise. The age of the horse is 3-25 years of age without a known incidence of laminitis or previously established diagnosis of pituitary par intermedia dysfunction, horses should not be very lactating, pregnant, or actively ridden. 200 horses housed on private premises, majority of breeds are Dutch, German, Belgian warmbloods, mean weight 492 kg and body condition score range from 4-9 on 9 point scale. Study design- At the intake of consultation, horses visited to home premises during morning hours (8:00 am-11:00 am) by a veterinarian who determined morphometric measurement, blood sample were drawn for glucose and insulin concentration before the start of study and horses were not allowed to feed for 8 hours before sampling, water access freely allowed. Body weight with a set of scales designed for horses (All scales W-1500 Bos) and BCS determination is done Henneke scoring system, were horses 4-5 classified as lean, 6 moderate, 7-9 classified as obese. Heparinized blood sample for determination of insulin concentration and in sodium fluoride tube for glucose concentration estimation [35].

DISCUSSION

Metabolic syndrome (MetS) is a multi-component disorder characterized by the coexistence of multiple condition such as obesity , hypertension , dyslipidaemia and hyperlipidaemia . It is a major public health condition globally due to its strong correlation with cardiovascular diseases, type 2

diabetes, and neurodegenerative disorder. given its complexity it is difficult to replicate ideal MetS model resembling human physiology. Diet is a key environmental factor influencing MetS development and its impact hormonal balance , glucose metabolism and lipid pathways. The circadian regulation of metabolic genes highlights the role of feeding time, with studies showing that time restricted feeding can alleviated metabolic dysfunction. Among traditional model ,rats model are used widely due to their familiarity , tolerance for various diet and lower maintenance costs. The Dahl.S.Z-Lepr fa (DS/obese) rat model is highly relevant as it develop obesity, hypertension, insulin resistance , dyslipidaemia, and type 2 diabetes even on a normal diet. Same model can also be used to investigate the effects of hypercholesterolemia on brain functions, linking MetS to neurodegenerative disorder like Parkinson's. Thus providing utility for studying both metabolic and neurological outcome. Zebrafish (Danio rerio) is a valuable invertebrate model for studying metabolic syndrome due to their genetic similarity to humans, having transparent embryos, possessing rapid development, and ease of genetic manipulation in animal . Zebrafish are cost-effective as compare to other model, require minimal space, and support high-throughput screening. Zebrafish possess robust regenerative capabilities, including pancreatic and hepatic regeneration, making them ideal for studying the impact of metabolic dysfunction on tissue regeneration. Transgenic zebrafish models enable precise investigation of gene-diet interactions study by expressing metabolic disease-associated genes. Despite their physiological differences from mammals, zebrafish provide a more robust powerful platform for mechanistic studies and early-phase therapeutic screening in MetS research. Equine Metabolic Syndrome (EMS) involves regional or generalized adiposity, insulin dysregulation, and laminitis. These models closely mimic human metabolic responses, but it requires high maintenance costs and long study durations time (30–40 weeks) which limit their widespread use in experimental research. Rabbit models, particularly the New Zealand White rabbit, offer simplicity in dietary studies and moderate costs. Study durations typically range from 8 to 36 weeks. Though less similar to human metabolism compared to larger animals, rabbits are effective for exploring dyslipidaemia and atherosclerosis. MetS Experimentation model in rabbit has been succeeded as it allowed research protocol to be carried out with minimal staff, maintenance and resource also rabbit fed with high fat diet show hemodynamic and neurohumoral changes similar to observed in human as well as they possess high baseline plasma lipid transfer protein and low density lipoprotein (LDL), with so much similarities contribute to their usefulness as a translational model for a study of MetS and other atherosclerotic diseases. Despite so many similarities the rabbit has not been widely used in experimental protocol. "Canine models do not exhibit all components of metabolic syndrome (MetS), as the development of endothelial damage and fasting hyperglycaemia in dogs is questionable. Canine models are suitable for studying diet-induced obesity, dyslipidaemia, adipocyte hypertrophy, and elevated blood pressure. They offer physiological responses that are relevant to human MetS and are relatively easy to handle, though the associated costs remain high. In contrast, porcine models show high anatomical and physiological similarities to humans. However, their use is often limited because it needs a trained personnel , complex experimental procedures, and high maintenance costs, making them laborious and expensive to utilize." [8]. In this article, we had examine Zebra fish, rat, dog, rabbit, and horse models of metabolic syndrome (MetS) and their applications in various research studies.

It was found that Minor dietary differences can significantly influence metabolic parameters and experimental outcomes. For example, lard, is a common component of rat diets, which has a more pronounced effect on adipose tissue compared to vegetable fat. Subtle modifications in the ratio of saturated to unsaturated fatty acids, as well as changes in the physical form of the diet, can lead to major variation in outcomes in diet-induced obesity (DIO) studies. That's why, careful preparation of the diet is a critical factor for achieving reliable study results and for determining whether germ-free mice are resistant or susceptible to DIO. All components of the experimental diet should be made from purified raw materials to ensure guaranteed nutrient composition and consistency across production batches [7]. A variety of mammalian genes exhibit daily fluctuations in expression levels, making circadian expression rhythms the largest known regulatory network in normal physiology. Cell-autonomous circadian clocks interact with the daily light-dark cycle and the feeding-fasting cycle to generate approximately 24-hour oscillations in gene function. The circadian expression of secreted molecules and signalling components transmits timing information between cells and tissues. These intracellular and intercellular rhythms optimize physiology by managing energy use and temporally segregating incompatible processes. Animal model of MetS studies have shown that disruption in circadian rhythms of animal increases the risk of metabolic diseases. While the Time-restricted feeding imposes a daily cycle of feeding and fasting without reducing caloric intake—helps maintain robust diurnal rhythms and can alleviate metabolic disorders.[4]. A wide Variety of animal models exists for studying metabolic syndrome, each is having their own unique strengths and limitations. Rats and zebrafish provide cost-effective, high-throughput options with varying degrees of physiological relevance, while larger animals like dogs and horses offer greater translational value but are more resource-intensive in terms of diet and cost ,MetS model has shown that while Incorporating both genetic and environmental factors, particularly dietary influences and circadian rhythms, plays a crucial for developing robust and translatable models of metabolic syndrome.

CONCLUSION.

Animal model in MetS give a good knowledge to understand the role in advancing our understanding of a complex and multifaceted diseases condition . These model has enable researcher to investigate and learned diseases overall pathophysiology. Each model offers unique strength and limitations in terms of physiological relevance , genetic similarity to human, cost, and ease of handling. Rodent model widely used due to their affordability established protocols and ability to replicate multiple MetS features. Large animal such as dogs and horses offer greater translational value due to their physiological resemblance to human. But this models as most costly and resource intensive. Even still so far no single animal model fully capture complexity of human MetS. Combined approach using multiple models may provide complete and comprehensive insight into diseases factor and provide better outcome in the development of effective prevention and treatment strategies.

REFERENCES

1. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med [Internet]. 2011 [cited 2025 May 24];9:48. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-9-48

2. Noubiap JJ, Nansseu JR, Lontchi-Yimagou E, Nkeck JR, Nyaga UF, Ngouo AT, et al. Geographic distribution of metabolic syndrome and its components in the general adult population: A meta-analysis of global data from 28 million individuals. Diabetes Res Clin Pract [Internet]. 2022 [cited 2025 May 22];188:109924. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822722007380
3. Wong SK, Chin KY, Suhaimi FH, Fairus A, Ima-Nirwana S. Animal models of metabolic syndrome: a review. Nutr Metab [Internet]. 2016 [cited 2025 May 13];13:65. Available from: http://nutritionandmetabolism.biomedcentral.com/articles/10.1186/s12986-016-0123-9
4. Panda S. Circadian physiology of metabolism. Science [Internet]. 2016 [cited 2025 May 5];354:1008–15. Available from: https://www.science.org/doi/10.1126/science.aah4967
5. Winick M, Noble A. CatelVlualrairouRseAspgoensse1/2in Rats during Malnutrition. 2018.
6. Jolivalt CG, Frizzi KE, Guernsey L, Marquez A, Ochoa J, Rodriguez M, et al. Peripheral Neuropathy in Mouse Models of Diabetes. Curr Protoc Mouse Biol [Internet]. 2016 [cited 2025 May 5];6:223–55. Available from: https://currentprotocols.onlinelibrary.wiley.com/doi/10.1002/cpmo.11
7. De Moura E Dias M, Dos Reis SA, Da Conceição LL, Sediyama CMNDO, Pereira SS, De Oliveira LL, et al. Diet-induced obesity in animal models: points to consider and influence on metabolic markers. Diabetol Metab Syndr [Internet]. 2021 [cited 2025 May 13];13:32. Available from: https://dmsjournal.biomedcentral.com/articles/10.1186/s13098-021-00647-2
8. Lozano WM, Arias-Mutis OJ, Calvo CJ, Chorro FJ, Zarzoso M. Diet-Induced Rabbit Models for the Study of Metabolic Syndrome. Animals [Internet]. 2019 [cited 2025 May 13];9:463. Available from: https://www.mdpi.com/2076-2615/9/7/463
9. Maddison LA, Joest KE, Kammeyer RM, Chen W. Skeletal muscle insulin resistance in zebrafish induces alterations in β-cell number and glucose tolerance in an age- and diet-dependent manner. Am J Physiol-Endocrinol Metab [Internet]. 2015 [cited 2025 May 26];308:E662–9. Available from: https://www.physiology.org/doi/10.1152/ajpendo.00441.2014
10. Hattori T, Murase T, Ohtake M, Inoue T, Tsukamoto H, Takatsu M, et al. Characterization of a new animal model of metabolic syndrome: the DahlS.Z-Leprfa/Leprfa rat. Nutr Diabetes [Internet]. 2011 [cited 2025 May 19];1:e1–e1. Available from: https://www.nature.com/articles/nutd20101
11. Cash CM, Fitzgerald DM, Spence RJ, De Laat MA. Preliminary analysis of the FAM174A gene suggests it lacks a strong association with equine metabolic syndrome in ponies. Domest Anim Endocrinol [Internet]. 2020 [cited 2025 May 13];72:106439. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0739724020300060
12. Niimi M, Yang D, Kitajima S, Ning B, Wang C, Li S, et al. ApoE knockout rabbits: A novel model for the study of human hyperlipidemia. Atherosclerosis [Internet]. 2016 [cited 2025 May 15];245:187–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S002191501530232X
13. Ning B, Wang X, Yu Y, Waqar AB, Yu Q, Koike T, et al. High-fructose and high-fat diet-induced insulin resistance enhances atherosclerosis in Watanabe heritable

hyperlipidemic rabbits. Nutr Metab [Internet]. 2015 [cited 2025 May 15];12:30. Available from: http://www.nutritionandmetabolism.com/content/12/1/30

14. Paul R, Borah A. Global loss of acetylcholinesterase activity with mitochondrial complexes inhibition and inflammation in brain of hypercholesterolemic mice. Sci Rep [Internet]. 2017 [cited 2025 May 20];7:17922. Available from: https://www.nature.com/articles/s41598-017-17911-z
15. Olsen AS, Sarras MP, Intine RV. Limb regeneration is impaired in an adult zebrafish model of diabetes mellitus: Induced diabetes mellitus impairs limb regeneration. Wound Repair Regen [Internet]. 2010 [cited 2025 May 26];18:532–42. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1524-475X.2010.00613.x
16. Dorsemans A, Soulé S, Weger M, Bourdon E, Lefebvre d'Hellencourt C, Meilhac O, et al. Impaired constitutive and regenerative neurogenesis in adult hyperglycemic zebrafish. J Comp Neurol [Internet]. 2017 [cited 2025 May 26];525:442–58. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cne.24065
17. Maneschi E, Cellai I, Aversa A, Mello T, Filippi S, Comeglio P, et al. Tadalafil reduces visceral adipose tissue accumulation by promoting preadipocytes differentiation towards a metabolically healthy phenotype: Studies in rabbits. Mol Cell Endocrinol [Internet]. 2016 [cited 2025 May 15];424:50–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303720716300156
18. Marchiani S, Vignozzi L, Filippi S, Gurrieri B, Comeglio P, Morelli A, et al. Metabolic syndrome-associated sperm alterations in an experimental rabbit model: Relation with metabolic profile, testis and epididymis gene expression and effect of tamoxifen treatment. Mol Cell Endocrinol [Internet]. 2015 [cited 2025 May 15];401:12–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S030372071400344X
19. Paul R, Choudhury A, Chandra Boruah D, Devi R, Bhattacharya P, Choudhury MD, et al. Hypercholesterolemia causes psychomotor abnormalities in mice and alterations in cortico-striatal biogenic amine neurotransmitters: Relevance to Parkinson's disease. Neurochem Int [Internet]. 2017 [cited 2025 May 20];108:15–26. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0197018616302315
20. Petrova A, Simeonova R, Voycheva C, Savov Y, Marinov L, Balabanova V, et al. Metabolic syndrome: comparison of three diet-induced experimental models. Pharmacia [Internet]. 2023 [cited 2025 May 19];70:1539–48. Available from: https://pharmacia.pensoft.net/article/109965/
21. Singh R, Gholipourmalekabadi M, Shafikhani SH. Animal models for type 1 and type 2 diabetes: advantages and limitations. Front Endocrinol [Internet]. 2024 [cited 2025 May 19];15:1359685. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2024.1359685/full
22. Lozano WM, Arias-Mutis OJ, Calvo CJ, Chorro FJ, Zarzoso M. Diet-Induced Rabbit Models for the Study of Metabolic Syndrome. Animals [Internet]. 2019 [cited 2025 May 13];9:463. Available from: https://www.mdpi.com/2076-2615/9/7/463
23. Alarcon G, Roco J, Medina M, Medina A, Peral M, Jerez S. High fat diet-induced metabolically obese and normal weight rabbit model shows early vascular dysfunction:

mechanisms involved. Int J Obes [Internet]. 2018 [cited 2025 May 15];42:1535–43. Available from: https://www.nature.com/articles/s41366-018-0020-6

24. Arias-Mutis ÓJ, Genovés P, Calvo CJ, Díaz A, Parra G, Such-Miquel L, et al. An Experimental Model of Diet-Induced Metabolic Syndrome in Rabbit: Methodological Considerations, Development, and Assessment. J Vis Exp [Internet]. 2018 [cited 2025 May 15];57117. Available from: https://app.jove.com/t/57117
25. Iennarella-Servantez CA, Kathrani A, Sahoo D, Long E, Zdyrski C, Gabriel V, et al. 109 Diet-induced Clinical Responsiveness of Translational Dog Model for Human Western Diet (WD)-related Disease Research. J Anim Sci [Internet]. 2021 [cited 2025 May 19];99:58–9. Available from: https://academic.oup.com/jas/article/99/Supplement_3/58/6383872
26. Qu W, Chen Z, Hu X, Zou T, Huang Y, Zhang Y, et al. Profound Perturbation in the Metabolome of a Canine Obesity and Metabolic Disorder Model. Front Endocrinol [Internet]. 2022 [cited 2025 May 19];13:849060. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2022.849060/full
27. Söder J, Höglund K, Dicksved J, Hagman R, Eriksson Röhnisch H, Moazzami AA, et al. Plasma metabolomics reveals lower carnitine concentrations in overweight Labrador Retriever dogs. Acta Vet Scand [Internet]. 2019 [cited 2025 May 20];61:10. Available from: https://actavetscand.biomedcentral.com/articles/10.1186/s13028-019-0446-4
28. Frank N, Geor RJ, Bailey SR, Durham AE, Johnson PJ. Equine Metabolic Syndrome: Equine Metabolic Syndrome. J Vet Intern Med [Internet]. 2010 [cited 2025 May 13];24:467–75. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2010.0503.x
29. Kenéz Á, Warnken T, Feige K, Huber K. Lower plasma trans-4-hydroxyproline and methionine sulfoxide levels are associated with insulin dysregulation in horses. BMC Vet Res [Internet]. 2018 [cited 2025 May 13];14:146. Available from: https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-018-1479-z
30. Marycz K, Kornicka K, Szlapka-Kosarzewska J, Weiss C. Excessive Endoplasmic Reticulum Stress Correlates with Impaired Mitochondrial Dynamics, Mitophagy and Apoptosis, in Liver and Adipose Tissue, but Not in Muscles in EMS Horses. Int J Mol Sci [Internet]. 2018 [cited 2025 May 13];19:165. Available from: https://www.mdpi.com/1422-0067/19/1/165
31. Carter RA, McCutcheon LJ, George LA, Smith TL, Frank N, Geor RJ. Effects of diet-induced weight gain on insulin sensitivity and plasma hormone and lipid concentrations in horses. 2009;70.
32. Henneke DR, Potter GD, Kreider JL, Yeates BF. Relationship between condition score, physical measurements, and body fat percentage in mares. Equine Vet J [Internet]. 1983 [cited 2025 May 14];15:371–2. Available from: https://beva.onlinelibrary.wiley.com/doi/10.1111/j.2042-3306.1983.tb01826.x
33. Carter RA, Geor RJ, Burton Staniar W, Cubitt TA, Harris PA. Apparent adiposity assessed by standardised scoring systems and morphometric measurements in horses and ponies. Vet J [Internet]. 2009 [cited 2025 May 14];179:204–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S109002330800110X

34. Nostell K, Lindåse S, Winqvist E, Bröjer J. The effect of diet‐induced obesity and pasture on blood pressure and serum cortisol in Standardbred mares. Equine Vet J [Internet]. 2021 [cited 2025 May 13];53:542–8. Available from: https://beva.onlinelibrary.wiley.com/doi/10.1111/evj.13294
35. Van Den Wollenberg L, Vandendriessche V, Van Maanen K, Counotte GHM. Comparison of Two Diagnostic Methods to Detect Insulin Dysregulation in Horses Under Field Conditions. J Equine Vet Sci [Internet]. 2020 [cited 2025 May 13]; 88:102954. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0737080620300459.

HOW TO CITE: Dr. Durga Devi Surya Kumar Verma*, Dr. Sugiram S., Animal models in Metabolic Syndrome, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 347-364 https://doi.org/10.5281/zenodo.17047012