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

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Review Article

High-Fat Diet-Induced Obesity in Rodents: Dietary Composition, Adipose Remodeling and Metabolic Dysfunction: A Comprehensive Review

Hajera Begum, Dr. Koppala R. V. S. Chaitanya*, Bommu Vaishnavi, Mahadev Anitha

Department of Pharmacology, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana, India-500017.

ARTICLE INFO

Published: 7 Nov 2026
Keywords:
diet-induced obesity, high-fat diet, rodents, adipose tissue, insulin resistance, inflammation, reproducibility
DOI:
10.5281/zenodo.24034490

ABSTRACT

High-fat feeding is widely used to model diet-associated obesity and metabolic dysfunction in rodents, but "high-fat diet" does not describe a single reproducible exposure. The phenotype depends on the percentage of energy from fat, fatty-acid source, carbohydrate and protein composition, energy density, comparator diet, animal strain and substrain, sex, age, and exposure duration. These variables affect energy intake and expenditure as well as adiposity, glucose regulation, circulating lipids, liver pathology, and inflammatory readouts. Available comparative studies show that changing fat source can alter adipose distribution and metabolic outcomes even when diets are similarly fat-rich, while strain and sex can modify susceptibility and the time course of disease.[3,4,93] Consequently, body weight alone is an inadequate validation criterion. Robust studies should report exact diet composition and energy density, measure both food and energy intake, characterize body composition and tissue pathology, and prespecify metabolic endpoints. Rodent HFD models are useful for mechanistic experiments, but their controlled setting and biological heterogeneity limit direct extrapolation to human obesity.[1] This narrative review synthesizes the supplied outline and reference collection; it is not a protocol-driven systematic review.

INTRODUCTION

Obesity is a chronic metabolic condition characterized not only by excess fat mass but also by changes in adipose tissue function and metabolic regulation. Adipose tissue stores energy and releases endocrine signals, making its location, cellular composition, and secretory state relevant to systemic glucose and lipid

***Corresponding Author:** Dr. Koppala R. V. S. Chaitanya
Address: Department of Pharmacology, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana, India-500017
Email ✉: chaitukoppala.snvpmv@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.

homeostasis. Rodent models enable controlled manipulation of diet, age, and genetic background and permit tissue-level analysis that is difficult in human studies. Diet-induced obesity (DIO) is especially useful because it models environmental exposure without requiring a monogenic obesity mutation. Reviews of rodent obesity models describe HFD feeding as one of the most widely used approaches, while also emphasizing variation in model design and outcome severity. [6,7,10]

This review treats HFD as a defined experimental exposure rather than a standardized model category. The supplied reference spreadsheet includes review summaries and individual study abstracts, so the synthesis does not constitute exhaustive appraisal of all primary papers.

2. Principles of the HFD model

Dietary fat should be expressed as a proportion of total dietary energy (kcal%), not as a proportion by mass. Because fat supplies more energy per gram than carbohydrate or protein, a diet that is 45% of energy from fat is not equivalent to a diet containing 45% fat by weight. Rodent studies commonly use diets around 40 –60% energy from fat, but lower-fat formulations can also alter body composition or metabolism depending on the control diet and animal model. In one C57BL/6 substrain comparison, 60%-fat diets and a 42%-fat Western-style diet produced distinct strain-dependent responses.[93]

"HFD" also does not specify whether the diet is purified or based on conventional chow, whether sugar is added, or whether the comparator is composition-matched. These formulation differences can complicate attribution of observed effects to fat percentage alone; studies comparing purified and cafeteria-style diets note the latter's reduced control over nutrient composition.[5,30]

Model definition and intended inference

A useful way to describe an HFD experiment is to specify four linked elements: the exposure (what the animals ate), the biological context (which animals and under what conditions), the phenotype (what changed), and the inference (what the experiment can establish). This framing prevents a common interpretive leap: treating the observed phenotype as an intrinsic property of "the HFD model" rather than an outcome of a particular diet–animal combination. The same nominal fat percentage can be delivered with different fatty-acid mixtures, carbohydrate fractions, energy densities, and ingredients; those formulations need not induce equivalent responses. In a long-term rat study, total fat quantity influenced body weight and body composition more strongly than fat type during the initial feeding period, while fat type still affected later outcomes and subcutaneous distribution.[8]

The intended inference should be stated before choosing the diet. If the question concerns the effect of fat quantity, the design should hold fat source and other macronutrients as constant as possible while varying energy from fat. If the question concerns fat quality, diets should be matched for total energy and macronutrient composition while changing the oil or fatty-acid profile. If the objective is to model a Western dietary pattern, adding sugar or food choice may improve face validity for that exposure, but the causal contrast is then the overall dietary pattern rather than fat alone. A free-choice cafeteria diet deliberately models palatability and food variety, whereas a purified diet provides more control over macronutrient and micronutrient content.[5]

The comparator defines the contrast just as much as the experimental diet. A low-fat control that is not matched for protein, fiber, vitamins, minerals, and ingredient background can introduce alternative explanations. Conversely, a highly matched purified control may answer a narrower question than a conventional chow comparison. The manuscript should therefore state what the control represents and avoid describing it only as "normal diet" or "standard diet." If the control and experimental formulations come from different manufacturers or have different ingredient bases, those details are part of the causal interpretation, not peripheral technical information.

3. Dietary composition: fat, carbohydrate, and controls

3.1 Fat quantity and source

Fat quantity is only one dimension of the exposure. Lard, tallow, coconut oil, olive oil, and

polyunsaturated-fat-rich oils differ in fatty-acid composition and can produce divergent metabolic effects. In C57BL/6 mice fed 60%-fat diets for ten weeks, lard was associated with greater subcutaneous and visceral adipose accumulation, higher IL-6, and lower adiponectin than several plant-oil diets; insulin and leptin also varied by lipid source.[90] A separate study comparing dietary oils reported different weight gain and glucose responses across oils, demonstrating that glucose tolerance did not simply track total fat exposure or body weight.[103]

Fat quality can influence adipose tissue even after obesity is established. In male C57BL/6J mice switched from a lard-based HFD to isocaloric diets containing lard, coconut, olive, or fish oil, fish-oil feeding improved antioxidant potential and partly restored redox enzyme activity, while altering adipokines and the visceral-adipose metabolome.[3] This result supports distinguishing the effect of fat quality from the effect of excess dietary energy; it does not establish that one oil is universally protective across formulations, species, or disease endpoints. The fat sources discussed above and the evidence cited for each are summarized in Table 1.

Table 1: Fat Sources Discussed in This Review and the Evidence Cited for Each.

Fat source	Principal fatty acids*	Evidence cited
Lard	Saturated and monounsaturated	In C57BL/6 mice on 60%-fat diets for 10 weeks, lard was associated with greater subcutaneous and visceral adipose accumulation, higher IL-6 and lower adiponectin than several plant-oil diets; insulin and leptin also varied by lipid source [90]. A lard-based HFD was the baseline diet before isocaloric oil substitution in established DIO [3].
Coconut oil	Saturated, with medium-chain fatty acids	One of four isocaloric diets (lard, coconut, olive, fish oil) given after a lard-based HFD in male C57BL/6J mice [3]; also compared with sunflower and extra virgin olive oil HFDs for immunometabolic effects in female mice [42]. Oil-specific outcomes are not detailed in the text.
Olive oil	Monounsaturated	Included in the isocaloric substitution study [3] and in the comparison with coconut and sunflower oil HFDs in female mice [42]. Oil-specific outcomes are not detailed in the text.
Fish oil	n-3 polyunsaturated	In established DIO, fish-oil feeding improved visceral-adipose antioxidant potential, partly restored redox enzyme activity and altered adipokines and the visceral-adipose metabolome [3]. High fructose intake blunted some hepatic lipid-lowering effects of a fish-oil-rich diet [89].
Other dietary oils	Variable	Weight gain and glucose responses differed across dietary oils in mice, and glucose tolerance did not simply track total fat exposure or body weight [103]. HFDs raised MCP-1 and PAI-1, while adipokine effects differed across oil types [97].
Hydrogenate d vegetable shortening	Saturated; trans fatty acids depend on the product	Compared with lard for HFD-induced obesity in rats [26]; outcomes are not summarized in the text.

*General classification of the predominant fatty acids; it is not derived from the cited studies. Abbreviations: DIO, diet-induced obesity; HFD, high-fat diet; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1.

3.2 Carbohydrate, protein, and comparator diet

Sucrose and fructose can add a second obesogenic and metabolically active exposure. A diet containing high fat plus fructose is therefore not equivalent to a fat-only challenge. In one mouse study, fructose blunted some hepatic lipid-lowering effects observed with a fish-oil-rich diet.[89] Protein source and amount, fiber, and micronutrient composition should likewise be matched or transparently reported. When experimental and control diets differ in several ingredients, observed effects cannot be attributed uniquely to dietary fat.

A purified low-fat control may be preferable when the goal is to isolate the effect of dietary fat, provided the diets are otherwise appropriately matched. Standard

chow serves as a pragmatic control; however, its compositional variability often leads to fluctuations in fiber and micronutrient levels.Alternatively, western-style or cafeteria diets more effectively emulate the palatability and diversity of food selection, yet they introduce further inconsistency regarding both formulation and consumption patterns.Such cafeteria feeding regimes are characterized by their capacity to induce substantial weight gain and metabolic dysregulation via access to highly palatable foods, a dynamic that inherently compromises the precise control over nutrient composition afforded by purified diets..[5] The main diet and comparator formats are compared in Table 2.

4. Energy density, intake, and energy balance

Food mass is not a sufficient measure of exposure when diets differ in energy density. Report the grams consumed and compute energy intake in kcal per animal, contextualized by body weight and feed efficiency.Empirical comparisons indicate that identical food masses may coincide with elevated caloric intake and enhanced feed efficiency when a high-fat diet is administered [85].Furthermore, increased adiposity may stem from heightened caloric consumption, altered energy expenditure, or a combination of both factors; consequently, food intake data alone fails to differentiate among these potential mechanisms. A 16-week investigation utilizing C57BL/6NCrjBgi mice revealed that while dietary consumption remained comparable between the high-fat and low-fat cohorts, the high-fat group exhibited significantly elevated caloric intake and superior feed efficiency.[85] Conversely, studies of rats fed different fat levels reported dose-related changes in energy intake, weight gain, fat mass, and metabolic markers, with obesity-prone animals showing positive energy balance and altered substrate use. [92] These findings illustrate why caloric intake and expenditure should be assessed separately where the mechanistic question concerns energy balance.

4.1 Energy intake, expenditure, and feed efficiency

A high percentage of energy from fat is not itself proof that an animal experienced greater total energy intake. Diet composition, palatability, and energy density can alter grams eaten and calories consumed in different directions. An animal may consume fewer grams of a dense diet yet receive more energy, or may compensate for a high-energy diet by reducing intake. The animal-level exposure is therefore the combination of food composition and actual consumption, not the diet formula in isolation.

Energy balance also includes expenditure. Thermogenesis, locomotor activity, body size, and substrate oxidation may influence whether a given energy intake is stored. The comparative rat–mouse study reported different compensatory energy-expenditure patterns between species and sexes, illustrating that identical diet access need not produce equivalent energy balance.[4] Where the research question requires a mechanistic explanation of weight gain, indirect calorimetry or activity measurements can be informative, but they should be interpreted in relation to body composition, feeding state, acclimation to measurement chambers, and timing. A single energy-expenditure estimate should not be treated as a complete explanation of chronic weight gain.

Feed efficiency can help describe conversion of ingested energy into body mass, but it is not a mechanistic endpoint by itself. It is influenced by the denominator chosen, body-size scaling, intestinal energy absorption, tissue composition of gained weight, and measurement error in food disappearance. Investigators should state the formula and report its component measures so the reader can interpret whether a high ratio arose from greater gain, lower measured intake, or both.

5. Animal-related factors and exposure duration

5.1 Species, strain, substrain, sex, and age

Species and genetic background determine the magnitude and pattern of DIO. Sprague–Dawley and Wistar rats, and C57BL/6 mice, are common models, but none guarantees a uniform phenotype. Some Wistar substrains have been reported as relatively resistant to diet-induced obesity, whereas another comparative report described greater susceptibility in Wistar than Sprague –Dawley rats under its specific conditions.[79][91] This apparent inconsistency underscores the influence of substrain, protocol, and experimental context rather than supporting a universal ranking of rat strains.

Substrain differences also occur within C57BL/6-related mice. In a three-vendor comparison, groups gained similar total body weight on a 60%-fat diet yet differed in fat percentage and depot weights; responses to a fructose-containing Western diet varied more substantially.[93] Vendor, microbiome, acclimation, and husbandry should consequently be documented, particularly when reproducing published phenotypes.

Sex is a biological modifier, not merely a demographic descriptor. A comparative investigation into Sprague–Dawley rats and C57BL/6 mice revealed that interspecies variations significantly influence sex-specific disparities in weight accretion, adipose distribution, glucose tolerance, and energy expenditure. Specifically, female rats exhibited a delayed trajectory of weight gain alongside a reduced incidence of associated complications, in stark contrast to female mice, who demonstrated marked expansion of visceral fat.4] Many earlier obesity-model studies have relied predominantly on male rodents, limiting inference across sexes.[6] Both sexes should be included when relevant, with adequate power to estimate sex-by-diet interactions rather than treating sex as an unexamined covariate.

Age at diet initiation and developmental exposure can alter interpretation. Maternal diet during gestation and lactation, for example, affected offspring adiposity and glucose and lipid measures in a Wistar rat study, independently of post-weaning diet.[78] Reports should state age at arrival and at diet initiation, developmental stage, and any maternal or early-life exposure.

5.2 Duration and phenotype timing

Short (approximately 2–4 weeks), intermediate (6–12 weeks), and longer (>12 weeks) exposures answer different questions and should not be treated as interchangeable. Early changes may precede substantial weight gain; longer feeding can reveal sustained adiposity, insulin resistance, and organ pathology. A study of C57BL/6J mice reported age-dependent worsening of several metabolic and hepatic outcomes during longer HFD exposure.[82] Therefore, duration should be justified by the intended phenotype, and intermediate measurements can distinguish onset from progression. Table 3 summarizes the animal-related factors and exposure duration discussed above, and Table 4 lists the representative studies cited in this review.

Table 3: Animal-related Factors and Exposure Duration That Modify the HFD Phenotype.

Factor	Examples in cited studies	Reported or potential influence
Species	Rats and mice	Sex differences in weight gain, fat distribution, glucose tolerance and energy expenditure varied by species; compensatory energyexpenditure patterns differed between species and sexes.[4]
Strain and substrain	Sprague–Dawley and Wistar rats; C57BL/6related substrains	Some Wistar substrains were relatively resistant to DIO, whereas another comparison reported greater susceptibility in Wistar than Sprague–Dawley rats. C57BL/6 substrains from three vendors gained similar weight on a 60%-fat diet but differed in fat percentage and depot weights.[79,91,93]
Sex	Male and female rodents	Females showed delayed weight gain and fewer complications in rats, but pronounced visceral-fat expansion in mice. Earlier studies relied predominantly on males.[4,6]
Age and developmental history	Maternal diet during gestation and lactation	Maternal diet affected offspring adiposity and glucose and lipid measures in Wistar rats, independently of post-weaning diet.[78]
Vendor, microbiome, housing	Three-vendor comparison	Should be documented, particularly when reproducing published phenotypes.[93]
Duration of feeding	Short (about 2–4 weeks), intermediate (6–12 weeks), longer (>12 weeks)	Answers different questions; early changes may precede substantial weight gain, whereas longer feeding can reveal sustained adiposity, insulin resistance and organ pathology, including age-dependent worsening in C57BL/6J mice.[82]

Abbreviation: DIO, diet-induced obesity.

Table 4: Representative Rodent HFD Studies Cited in This Review.

Animals	Diet or comparison	Duration	Main findings as summarized in the text
Rats	Different amounts and composition of dietary fat	Long term	Fat quantity influenced body weight and composition more than fat type initially; fat type affected later outcomes and subcutaneous distribution.[8]
Sprague–Dawley rats	Different dietary fat levels	NS	Dose-related changes in energy intake, weight gain, fat mass and metabolic markers; obesity prone animals showed positive energy balance and altered substrate use.[92]
C57BL/6NCrjBgi mice	High-fat vs low-fat	16 weeks	Similar food intake, but greater caloric intake and feed efficiency on the high-fat diet.[85]
C57BL/6 mice	60% fat; lard vs several plant oils	10 weeks	Lard: greater subcutaneous and visceral adipose accumulation, higher IL-6, lower adiponectin; insulin and leptin varied by lipid source.[90]
Mice	HFDs with different dietary oils	NS	Weight gain and glucose responses differed across oils; glucose tolerance did not track total fat exposure or body weight.[103]

NS, not stated in the source summary available to the authors. Abbreviations: AMPK, AMP-activated protein kinase; DIO, diet-induced obesity; HFD, high-fat diet; IL-6, interleukin-6. .

6. Development and distribution of adiposity

A sustained positive energy balance promotes expansion of adipose depots, but body weight is an imperfect proxy for fat mass. Body composition measures and depot weights distinguish fat gain from changes in total body weight; comparative studies report diet-source-related differences in visceral and subcutaneous adipose accumulation.[90] Ectopic lipid accumulation and hepatic steatosis have also been reported in HFD-fed rodents.[82]

The distinction is experimentally consequential: different oil-based high-fat diets altered the relative accumulation of subcutaneous and visceral depots in mice, as well as adipokines and glucose-related measures.[90] Liver triglyceride accumulation and steatosis have also been reported after HFD exposure in rodents.[99] Thus a model should be validated using the tissue phenotype relevant to the hypothesis, not weight gain alone.

7. Adipose tissue remodeling

Adipose expansion involves enlargement of existing adipocytes (hypertrophy), recruitment and differentiation of new adipocytes (hyperplasia/adipogenesis), and remodeling of the extracellular matrix. Which process predominates can affect tissue oxygenation, immune-cell composition, and endocrine function. The supplied evidence includes studies reporting adipocyte hypertrophy and depot-specific accumulation, but does not provide consistent comparative measurements of adipogenesis, fibrosis, or tissue oxygenation across diet protocols.[12,14,50]

As adipose tissue expands, immune-cell recruitment and local inflammatory signaling may accompany metabolic dysfunction. Macrophage abundance and activation state are often discussed as components of obesity-associated inflammation, but a simple M1/M2 dichotomy may not capture the diversity of adipose immune states. Studies should report the assay, markers, tissue compartment, and cell-identification method rather than treating a cytokine change as direct proof of a specific macrophage phenotype. The reference set documents altered inflammatory cytokines and adipokines with different fat sources, but it does not support a single universal sequence from hypertrophy through hypoxia to inflammation.[42,97,90]

7.1 Adipocyte size, number, and tissue capacity

Adipose tissue can expand through hypertrophy of existing adipocytes, recruitment and differentiation of precursor cells, or a combination of both. Hypertrophy may be accompanied by altered lipid handling, mechanical stress, and changes in secretory behavior. Hyperplasia can increase storage capacity but depends on precursor availability, differentiation programs, and

depot-specific biology. Therefore, measuring total depot weight alone cannot determine which cellular process produced the expansion.

A rigorous adipose assessment combines depot mass with histology and, where possible, quantification of adipocyte size distributions. Reporting only a mean cell diameter can obscure a mixed population of small and very large adipocytes; methods should describe the number of animals, fields, and cells sampled, how fields were selected, and whether image analysis was blinded. If adipogenesis is central to the hypothesis, markers of progenitor populations or differentiation should be measured directly rather than inferred from adipocyte enlargement.

Extracellular matrix (ECM) remodeling is another important dimension. Collagen deposition and altered matrix organization can change tissue compliance and constrain healthy expansion. Yet a collagen stain or fibrosis-associated transcript is not by itself proof of functionally limiting fibrosis. Histologic scoring, biochemical collagen measurement, and functional or molecular correlates should be interpreted together. The supplied evidence set contains relatively limited harmonized ECM and adipocyte-progenitor data, so conclusions about the timing and causal role of fibrosis across HFD models remain less secure than conclusions about gross adiposity or selected circulating markers.

7.2 Vascularization, oxygenation, and tissue stress

As adipose depots enlarge, the relationship between tissue growth and vascular supply may influence local oxygen availability, nutrient delivery, and waste removal. Hypoxia-related responses are plausible mechanisms linking expansion to cellular stress, but their presence should be measured rather than presumed from obesity. A strong design can combine tissue oxygenation or hypoxia-response markers with vascular density, adipocyte size, inflammatory profiling, and metabolic function. Sampling location matters because central and peripheral regions of a depot may not be equivalent.

The distinction between local and systemic measurements is essential. Plasma cytokines integrate signals from multiple tissues and cell types; they cannot be assigned to adipose tissue without supporting evidence. Conversely, a tissue homogenate may obscure which cell population produced a signal. Flow cytometry, immunohistochemistry, single-cell approaches, or cell-specific assays can help localize the response, but each method has its own preparation and interpretation limitations. Cross-platform agreement strengthens an interpretation more than multiple measurements that share the same sample-preparation bias.

7.3 Adipokines and inter-organ communication

Leptin and adiponectin are commonly measured because they reflect aspects of adipose mass and function, but neither is a stand-alone diagnosis of metabolic health. Leptin generally rises with fat mass, yet concentration is affected by sex, species, depot, and leptin sensitivity. High leptin therefore may indicate increased adiposity without demonstrating effective signaling. Adiponectin often tracks more favorable insulin sensitivity, but changes in its concentration should be distinguished from changes in receptor signaling or functional response.

Comparisons of dietary fat sources report differences in leptin and adiponectin alongside changes in depot distribution and glucose-related measures.[3,90,97] Simultaneous measurement of circulating and depot-specific adipokines can help distinguish systemic availability from local expression or secretion, but assay matrices and normalization should be reported. Adipokine results become more informative when paired with body composition, insulin sensitivity measures, and tissue-level signaling.

Adipose tissue communicates with liver, skeletal muscle, pancreas, brain, and kidney through circulating substrates, hormones, cytokines, and neural pathways. HFD-related liver steatosis is one well-described endpoint in the supplied evidence; the relation between adipose dysfunction and hepatic lipid handling remains a mechanistic question that requires tissue-specific measurements.[82,99] A multi-organ panel can establish whether phenotypes co-occur, but causal direction requires longitudinal designs or selective interventions.

8. Molecular regulation and signaling

HFD-associated metabolic dysfunction involves interacting pathways in adipose tissue, liver, and muscle.

This section summarizes candidate regulators—including adipogenic factors PPARγ and C/EBPs, lipogenic regulators SREBP-1c, ACC and FAS, and fatty-acid binding protein FABP4—as a mechanistic framework; the supplied reference summaries do not provide a comparable, source-specific evaluation of every listed factor. Adipokine measurements demonstrate variation by dietary fat source and tissue compartment.[3,42,90,97]

AMP-activated protein kinase (AMPK) links cellular energy state to metabolic regulation. In rats fed HFD for 15 weeks, increased adiposity and hepatic triglycerides were accompanied by reduced hepatic AMPK and phosphorylated AMPK; the authors interpreted these findings in relation to hepatic steatosis.[99] This association is consistent with AMPK involvement but does not alone establish that altered AMPK activity caused the phenotype.

Insulin signaling through PI3K/Akt and GLUT4-dependent glucose transport is a candidate mechanistic axis for HFD studies. The supplied summaries report impaired glucose tolerance and altered insulin-related measures, but are heterogeneous in tissue, assay, and diet design; direct pathway claims therefore require measurements such as phosphorylation, transporter abundance or translocation, and tissue-specific function.[58,61,73]

NF-κB-associated inflammatory signaling and Nrf2-linked antioxidant responses are candidate pathways in HFD models. The supplied studies report cytokine, adipokine, and redox changes under selected diets, but do not establish a uniform causal pathway across protocols.[42,49,69,72]

9. Inflammation and oxidative stress

Obesity-associated inflammation is generally characterized as chronic and low grade, involving altered cytokines and immune-cell signals rather than the acute response to infection. In a C57BL/6 mouse study, lard-based HFD was associated with higher IL-6 and lower adiponectin than several alternative oil-based HFDs, and fat-source differences also affected insulin and leptin.[90] Other work in the supplied set found that high-fat diets could increase MCP-1 and PAI-1 while effects on adipokines differed across oil types.[97] These results caution against assuming that all high-fat diets produce identical inflammatory profiles.

Oxidative stress may reflect altered mitochondrial function, lipid overload, and changes in antioxidant defenses. Relevant experimental measurements can include reactive oxygen species, lipid-peroxidation products such as malondialdehyde, and antioxidant systems such as superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione. However, these markers are not interchangeable, and a single circulating marker does not establish tissue-specific oxidative injury. A study comparing fat sources in established DIO found improved visceral-adipose antioxidant potential with fish oil relative to lard, providing evidence that dietary fat quality can modify redox readouts.[3]

9.1 Immune-cell composition and inflammatory signaling

Adipose inflammation is often studied through macrophage abundance and cytokine expression. However, an increase in macrophage-associated transcripts can arise from more macrophages, altered expression per cell, changes in other immune cells, or shifts in adipocyte abundance within the sampled tissue. The frequently used M1/M2 labels are a simplification and should not substitute for explicit marker panels or functional characterization. Investigators should name the markers measured, whether they reflect cell identity or activation, and the method used to quantify them.

Chemokines such as MCP-1 can be measured in plasma or tissue, but concentration changes alone do not establish recruitment of a particular leukocyte population. To support recruitment, studies can quantify immune-cell abundance and phenotype in the relevant depot and connect those findings to chemokine expression. Similarly, TNF-α or IL-6 changes can be biologically relevant without demonstrating that either cytokine mediates insulin resistance. Causal mediation requires perturbation or temporal evidence, not only cross-sectional association.

Diet composition complicates interpretation because fatty acids can influence both adiposity and inflammatory signaling. The supplied studies report fat-source

differences in cytokine and adipokine profiles, and fish-oil substitution altered visceral-adipose redox and secretory measures in established DIO.[3,97] Such observations justify measuring diet composition precisely, but should not be generalized to every dose, species, or oil blend without replication.

10. Metabolic consequences

10.1 Glucose homeostasis and insulin resistance

HFD-induced glucose dysfunction should be characterized with complementary measures: fasting blood glucose (FBG), oral glucose tolerance testing (OGTT), insulin, and—where validated—HOMA-IR or HbA1c. These assays address different aspects of glucose homeostasis; HFD studies in the supplied set used glucose tolerance and insulin-related measures, demonstrating the value of multi-endpoint phenotyping.[61,82,85,98] Report fasting conditions, challenge dose, sampling schedule, and calculation method; no single endpoint should be treated as a synonym for insulin resistance.

HFD-associated glucose intolerance and hyperinsulinemia have been reported in both rats and mice, but the severity depends on diet, duration, and host background. A 12-week study reported impaired glucose tolerance and elevated glucose and insulin measures in animals fed 45% or 60%-fat diets compared with controls.[98] Another study found that the response to HFD differed across sexes and species, reinforcing that metabolic outcomes cannot be presumed from body weight alone.[4]

10.2 Dyslipidemia and hepatic outcomes

Dyslipidemia may include changes in triglycerides, total cholesterol, non-HDL cholesterol, and lipoprotein fractions. These endpoints should be reported separately because total cholesterol alone does not characterize lipoprotein distribution. Fat source can modify lipid outcomes: a study comparing oils reported that body-weight and glucose responses differed among groups, and the relationship between obesity and glucose tolerance was not reducible to a single fatty-acid measure.[103]

The liver is a frequent site of ectopic lipid deposition under obesogenic feeding. Histology and hepatic triglyceride measurements can identify steatosis, while serum ALT and AST can indicate hepatocellular injury in context; neither enzyme alone specifies the underlying pathology. Longer HFD exposure in C57BL/6J mice was associated with steatosis and subsequent inflammation alongside metabolic changes.[82] Renal changes, including albuminuria or histologic alterations, have also been reported in selected models, but should be measured directly rather than assumed to accompany every HFD phenotype.[20,82]

10.3 Glucose-test protocol and interpretation

Glucose tolerance tests are sensitive to fasting duration, time of day, route and dose of glucose, stress, prior handling, and sampling schedule. Longer fasting is not automatically better: prolonged fasting can alter glycogen stores, counter-regulatory hormones, and substrate use, potentially changing the apparent response. The test should specify whether glucose was administered orally or intraperitoneally, the dose basis, the fasting interval, sample time points, and whether the primary outcome is peak, return-to-baseline, or area under the curve.

An OGTT integrates intestinal absorption, incretin signaling, insulin secretion, and peripheral glucose disposal; it is not a direct measurement of insulin sensitivity alone. An insulin tolerance test assesses glucose lowering after insulin but is affected by baseline glucose, counter-regulation, insulin dose, and the floor effect. Fasting insulin and glucose can be useful descriptive measures, but HOMA-IR should be interpreted cautiously in rodents because the index was developed for a specific physiological and assay context. If the primary question is tissue-specific insulin action, a clamp or validated tissue-level approach may be more appropriate.

Longitudinal testing also requires attention to repeated-challenge effects. Repeated OGTTs can alter handling familiarity and may influence physiology; intervals and procedures should be standardized. If animals undergo multiple tests, the sequence, recovery period, and order of assays should be reported. Investigators should predefine the primary glycemic endpoint and avoid choosing among multiple time points after seeing which yields statistical significance.

10.4 Lipid and liver measurement

A lipid panel should identify whether triglycerides and cholesterol were measured in plasma or serum, whether samples were fasting, and how lipoprotein fractions were obtained. Rodent lipoprotein profiles differ from human profiles, so direct translation of a total-cholesterol value is limited. For liver phenotype, report organ weight, biochemical lipid content, histologic findings, and relevant enzymes separately. ALT and AST are indicators of injury in context, not specific diagnoses of steatosis or steatohepatitis.

Histopathology benefits from blinded assessment and a stated scoring system. Steatosis, inflammation, ballooning, and fibrosis should not be collapsed into a single label when the study measured only one feature. Tissue sections should be sampled consistently across lobes and animals, with staining and imaging conditions held constant. If the question concerns progression, longitudinal or multiple-duration cohorts are needed; a single terminal time point cannot establish whether steatosis preceded inflammation. Kidney and other secondary phenotypes

Renal outcomes may be assessed through urinary albumin, the albumin-to-creatinine ratio, blood urea nitrogen, serum creatinine, or histopathological analysis, yet each metric possesses inherent constraints. Specifically, urine concentration fluctuates depending on hydration levels and the conditions under which samples are collected, while serum markers often fail to detect early stages of injury with sufficient sensitivity. Consequently, findings from high-fat diet (HFD) experiments must be contextualized by considering the subject's age, blood pressure, glucose status, and the duration of the intervention. It is crucial to recognize that such renal manifestations are not an inevitable consequence of every adiposity phenotype. Investigators evaluating secondary organs must delineate primary from exploratory endpoints within their analytical framework to mitigate the risk of spurious findings arising from unplanned multi-organ assessments. The credibility of a biologically coherent secondary phenotype is substantiated by replication, the presence of dose or duration responses, and the alignment between functional and structural metrics.

11. Experimental endpoints for model validation

Model validation should match the scientific question and combine organism-level, metabolic, and tissue-level measures. A practical core panel includes:

Table 5: Core Panel of Experimental Endpoints for Validating Rodent HFD Models.

Animals	Diet or comparison	Duration	Main findings as summarized in the text
Rats	Different amounts and composition of dietary fat	Long term	Fat quantity influenced body weight and composition more than fat type initially; fat type affected later outcomes and subcutaneous distribution.[8]
Sprague–Dawley rats	Different dietary fat levels	NS	Dose-related changes in energy intake, weight gain, fat mass and metabolic markers; obesityprone animals showed positive energy balance and altered substrate use.[92]
C57BL/6NCrjBgi mice	High-fat vs low-fat	16 weeks	Similar food intake, but greater caloric intake and feed efficiency on the high-fat diet.[85]
C57BL/6 mice	60% fat; lard vs several plant oils	10 weeks	Lard: greater subcutaneous and visceral adipose accumulation, higher IL-6, lower adiponectin; insulin and leptin varied by lipid source.[90]
Mice	HFDs with different dietary oils	NS	Weight gain and glucose responses differed across oils; glucose tolerance did not track total fat exposure or body weight.[103]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECM, extracellular matrix; FBG, fasting blood glucose; ITT, insulin tolerance test; OGTT, oral glucose tolerance test.

Table 5 describes candidate endpoints, not a requirement to measure every item in every experiment. Prespecify primary outcomes and report assay methods; reported rodent studies use combinations of intake,

glucose tolerance, tissue weights, serum chemistry, and histopathology.[82,85,98]

Distinguishing obesity induction from measured phenotype

Induction constitutes a procedural intervention, whereas obesity represents a quantifiable phenotype. Consequently, even when a protocol subjects animals to a diet typically employed to trigger obesity, the resultant degree and trajectory of adiposity may vary significantly across individuals. Therefore, investigators must establish success criteria prospectively—such as a statistically significant elevation in fat mass relative to concurrent controls, attainment of a specific body-composition threshold, or a composite metric integrating adiposity with metabolic parameters. While body-weight gain serves as a practical screening indicator, it fails to delineate whether the observed increase stems from augmented fat mass, lean tissue accretion, fluid retention, or organomegaly. The corpus of evidence presented herein underscores instances wherein body mass and metabolic phenotypes fail to exhibit a synchronized trajectory. A specific investigation into C57BL/6-related substrains revealed that, despite comparable total body weight accumulation under identical high-fat diet (HFD) regimens, significant disparities emerged regarding body fat percentage and depot-specific weights.[93] Conversely, a comparative study delineating sex-specific responses in rodents identified divergent patterns between rats and mice, characterized by distinct variations in visceral adiposity and glucose tolerance.[4] Such discrepancies compel the reevaluation of model validation protocols, suggesting that efficacy should be ascertained through metrics rigorously aligned with the target phenotype rather than relying exclusively on weight as a proxy for success. A critical distinction must be drawn between obesity and its associated complications, recognizing that while adiposity, impaired glucose handling, dyslipidemia, hepatic steatosis, and renal alterations are interconnected, they represent distinct outcomes. Certain experimental protocols may precipitate excessive adiposity without inducing significant glucose intolerance within the specified timeframe, whereas other studies might demonstrate disrupted glucose homeostasis prior to the emergence of substantial body weight discrepancies. Consequently, nomenclature should reflect the specific metrics observed; for instance, the designation «HFD-associated adiposity with impaired glucose tolerance» is more accurate than the blanket term «diabetic model» when formal diabetes criteria have not been established.

12. Sources of variability and reproducibility

Critical determinants of variability encompass fat percentage, fatty-acid provenance, sugar concentration, energy density, comparator formulation, feeding duration, species, strain and substrain, sex, age, vendor, microbiome composition, housing conditions, and individual susceptibility. Discrepancies in these parameters can profoundly influence both the magnitude of adiposity and the distribution of metabolic outcomes. Comparative analyses of C57BL/6 substrains and rat strain studies demonstrate that ostensibly identical dietary labels fail to guarantee equivalent phenotypic expressions. The inherent heterogeneity of individual responses undermines the validity of inferences drawn solely from aggregate data. Given the documented influence of specific bacterial strains and sex on physiological outcomes, researchers must report response distributions and establish prespecified thresholds for defining obesity or metabolic dysfunction, rather than relying exclusively on group means.[4,12,93] Furthermore, any exclusions predicated upon response characteristics must be rigorously prespecified and substantiated. **13. Standardization and reporting recommendations** To ensure scientific rigor, manuscripts must comprehensively report: (1) the manufacturer, catalog or formula identifier, and full ingredient composition; (2) the percentage of caloric intake derived from fat, carbohydrate, and protein; (3) the specific fat source alongside its fatty-acid profile, as well as the sugar source and quantity; (4) energy density and data regarding micronutrients and fiber content; (5) the composition of the control diet and the methodology employed to match it; (6) measured food intake and calculated caloric consumption; (7) detailed animal characteristics including species, strain or substrain, sex, age, vendor, and housing conditions; (8) protocols for acclimation and experimental duration; (9) the body-composition and metabolic criteria utilized to establish the disease model; and (10) precise

timing, fasting conditions, analytical assays, and methodological approaches. This rigorous checklist is necessitated by documented variability in diet formulation and distinct responses observed across different strains and sexes.[4,10,30,93] A comprehensive review encompassing 110 comparative investigations into dietary-induced obesity (DIO) and dietary-induced metabolic dysfunction (DIMD) in rats revealed that less than half of these studies furnished complete details regarding diet composition and caloric consumption. [10] This finding underscores the imperative for explicit reporting to ensure reproducibility; however, the prevalence figure is contingent upon the specific corpus of literature examined and should not be indiscriminately extrapolated to other species or subsequent publication eras absent a more recent and extensive survey.

13.1 Experimental structure and allocation

Randomization should occur at the appropriate unit. If animals are individually housed and individually fed, the animal may be the experimental unit; if food exposure is delivered by cage, the cage may be the unit for intake-related outcomes. Treating multiple animals sharing one exposure unit as independent can underestimate uncertainty. Methods should state the experimental unit, allocation procedure, and whether litter, cage, or batch effects were addressed.

Control diet and HFD groups should be balanced for sex, age, and relevant baseline characteristics. For factorial questions, a design that includes diet and sex as explicit factors is preferable to separate analyses that cannot estimate interaction. If multiple HFD formulations are compared, randomization and housing should avoid confounding diet with room, rack, shipment, or assay batch. Blinding is feasible for many outcome assessments, including histology, image analysis, and biochemical processing, and should be described.

Sample size should be based on the primary endpoint and expected variability in the chosen strain and protocol. Pilot studies can estimate feasibility and variance but should not be used to justify arbitrary group sizes. Attrition, exclusions, and reasons for missing data should be reported by group. If nonresponse is expected, define in advance whether the study estimates the average effect of diet assignment or the effect among animals meeting a phenotype threshold; these are different questions.

13.2 Statistical analysis and transparent reporting

Repeated body-weight and intake measurements are longitudinal data. Analysis should account for within-animal correlation and time-by-diet effects rather than treating each observation as independent. Terminal outcomes can be modeled with relevant design factors, while covariate adjustment should be prespecified and biologically justified. Reporting only p-values hides the magnitude and precision of differences; provide effect estimates, uncertainty intervals, individual data where possible, and exact group sizes.

When many tissues, cytokines, genes, and time points are assessed, multiplicity becomes important. Separate confirmatory endpoints from exploratory profiling, apply appropriate correction or clearly label analyses as exploratory, and provide enough detail to reproduce data processing. For omics experiments, report normalization, filtering, batch correction, and validation procedures. A visually clear heat map does not replace a defined statistical model or independent validation.

Diet batches and shelf life deserve attention. Fatty-acid oxidation or degradation during storage may alter the exposure; manufacturers, catalog numbers, lot numbers, preparation, storage temperature, and time from preparation to use can be relevant, especially for oils rich in unsaturated fatty acids. Water supplements containing sugars should likewise be prepared and replaced consistently. These details can be particularly important when comparing fat quality or redox outcomes.

Practical reporting template

A concise methods description can follow this order:

1. **Animals:** species, strain/substrain, vendor, sex, age, developmental history, housing, acclimation, and ethics approval.
2. **Diet:** manufacturer, catalog and lot, kcal% and grams per kilogram of each macronutrient, fat source and fatty-acid profile, carbohydrate source, protein source, fiber and micronutrients, energy density, and storage conditions.

3. **Comparator:** complete formulation and rationale for its use; explicitly identify unmatched components.
4. **Exposure:** feeding duration, start age, ad libitum or pair-fed design, water supplements, food measurement method, spillage correction, and intake in both grams and calories.
5. **Phenotype definition:** prespecified criteria for adiposity and any metabolic complication; timing of all measurements.
6. **Endpoints:** test protocols, assay kits or platforms, tissue collection and processing, histology scoring, and blinding.
7. **Analysis:** experimental unit, randomization, sample-size rationale, primary outcome, statistical model, missing data, exclusions, and multiplicity handling.

This format allows another laboratory to determine whether a result is reproducible in its own setting and whether differences likely reflect diet composition, animal background, or analysis. It also makes negative findings interpretable: a null body-weight effect can coexist with altered depot distribution or glucose handling, and the report should make clear which outcomes were measured with sufficient precision.

14. Translational relevance and limitations

Rodent HFD studies report increased adiposity, impaired glucose regulation, dyslipidemia, and hepatic fat accumulation, enabling controlled mechanistic study and tissue sampling.[6,7,10] However, similarity on selected endpoints does not establish equivalence to human obesity across all disease features.

Translation is limited by controlled housing and diet access, genetic homogeneity in commonly used strains, species-specific physiology and lifespan, and differences between experimental diets and human dietary patterns. Even within rodents, sex, strain, and fat source alter outcomes. A review of translational validity notes that rodent diet-induced metabolic profiles do not fully replicate human obesity and type 2 diabetes, and identifies diet composition, duration, and controls as important sources of divergence.[1] Accordingly, these models are strongest for testing defined mechanisms under specified conditions, not for claiming that a single rodent diet reproduces the full human disease.

15. Future perspectives

Future studies should match exposure design to the biological question, include both sexes where feasible, account for strain and substrain, quantify caloric intake, and distinguish fat quantity from fat quality and sugar co-exposure. Sex- and substrain-dependent outcomes in comparative studies support these design priorities. [4,93] Longitudinal body-composition and metabolic measures can help establish the timing of phenotypic changes.

Multi-tissue phenotyping can clarify whether changes in adipose tissue precede or accompany liver, muscle, or renal dysfunction. Molecular measurements should be paired with functional assays and interpreted within their tissue and time context. Genetically diverse models and cross-model replication may improve generalizability, while cafeteria or Western-style diets may be useful when palatability and dietary variety are central to the question—provided their reduced compositional control is acknowledged.[5][94] Evidence gaps and priorities for model development

Several evidence gaps limit broad conclusions. First, many entries in the supplied reference collection are abstracts or short summaries rather than full-text evaluations; exact methods, effect sizes, and risk of bias could not be assessed consistently. Second, direct comparisons of fat source, macronutrient matching, sex, substrain, and duration are not all conducted within the same factorial design. Cross-study comparisons therefore mix biological effects with differences in housing, feeding, assays, and control diets. Third, detailed adipose histology and cellular composition are less consistently reported than body weight and standard serum chemistry in the accessible summaries.

A useful next generation of studies would compare a limited set of well-characterized diets in a shared experimental framework. For example, a factorial design could separate fat quantity from fat source and sugar exposure while including both sexes in one or more representative strains. Such a design would require adequate power for interactions and careful control of energy density; the aim would not be to nominate a

universal diet, but to estimate which features reproducibly alter the phenotype. Replication across vendors or substrains would test transportability within rodents.

Standardized core outcomes could coexist with hypothesis-specific endpoints. A minimal panel might include food and calorie intake, body composition, at least one dynamic glucose test, fasting insulin or another specified insulin measure, serum lipids, and depot-specific adipose and liver histology. Additional assays—immune phenotyping, redox measurements, transcriptomics, or renal endpoints—should be selected to answer explicit mechanistic questions. Shared reporting standards and accessible diet formulations would make cross-study synthesis more reliable.

The translational goal should also be clarified. A model may be useful for studying nutrient sensing, adipocyte biology, or a particular organ complication without reproducing the epidemiology or full clinical heterogeneity of human obesity. Reviews of rodent DIO models emphasize both their experimental value and the need to account for differences from human metabolic disease. [1,6,7,10] Development should therefore prioritize fit-for-purpose validity: the model should reproduce the biological process relevant to the question, and conclusions should remain within that scope.

CONCLUSION

High-fat diet (HFD)-induced obesity does not constitute a monolithic, standardized entity; rather, adiposity and metabolic trajectories are modulated by a complex interplay of dietary composition, energy density, comparator controls, animal genetic background, sex, age, and experimental duration.[5] Consequently, weight gain in isolation is insufficient to confirm the complete phenotypic profile.To ensure greater interpretability of findings, rigorous protocols must encompass precise dietary documentation, accurate quantification of caloric intake, prespecified obesity criteria, and endpoints tailored to specific tissue types.While rodent models retain significant utility, their application demands that both the limitations of exposure and the boundaries of translational relevance be explicitly delineated.[10] Although high-fat feeding in rodent models represents a versatile experimental strategy, it constitutes a heterogeneous array of conditions rather than a singular standardized protocol. The interpretation of dietary fat percentage requires careful contextualization alongside fatty-acid composition, the nature of carbohydrate and protein sources, energy density, control formulation, actual caloric consumption, and the specific biological characteristics of the subjects. Adipose expansion and metabolic dysfunction manifest as multidimensional phenotypes; consequently, parameters such as body weight, fat mass, depot distribution, glucose regulation, lipid profiles, hepatic pathology, inflammatory signaling, and redox state may diverge significantly rather than exhibiting synchronous changes. Rigorous high-fat diet (HFD) investigations ensure reproducible exposure, establish the phenotype prior to experimental initiation, and assess outcomes across both tissue and organismal scales, thereby aligning causal assertions with experimental design. Variables such as sex, genetic strain, substrain, age, supplier, and duration must be regarded as critical determinants of the model rather than incidental variables.Enhanced reporting standards and cross-model replication will simultaneously advance reproducibility and translational potential, provided that the inherent limitation is acknowledged: no singular rodent HFD protocol can fully encapsulate the multifaceted complexity of human obesity.

Ethics Statement

Not applicable. This article is a narrative review of previously published literature and did not involve new experiments on animals or humans.

Data Availability Statement

No new data was created or analyzed in this study. All sources discussed are listed in the References.

Acknowledgments

None to Acknowledge

Conflicts of Interest

None

Abbreviations

The following abbreviations are used in this manuscript:

ACC, acetyl-CoA carboxylase; **ALT**, alanine aminotransferase; **AMPK**, AMP-activated protein kinase; **AST**, aspartate aminotransferase; **C/EBP**, CCAAT/enhancer-binding protein; **DIO**, diet-induced obesity; **ECM**, extracellular matrix; **FABP4**, fatty acid-binding protein 4; **FAS**, fatty acid synthase; **FBG**, fasting blood glucose; **GLUT4**, glucose transporter 4; **GSH**, reduced glutathione; **HbA1c**, glycated hemoglobin; **HDL**, high-density lipoprotein; **HFD**, high-fat diet; **HOMA-IR**, homeostatic model assessment of insulin resistance; **IL-6**, interleukin-6; **ITT**, insulin tolerance test; **MCP-1**, monocyte chemoattractant protein-1; **MDA**, malondialdehyde; **Nrf2**, nuclear factor erythroid 2-related factor 2; **OGTT**, oral glucose tolerance test; **PAI-1**, plasminogen activator inhibitor-1; **PI3K**, phosphoinositide 3-kinase; **PPARγ**, peroxisome proliferator-activated receptor gamma; **ROS**, reactive oxygen species; **SREBP-1c**, sterol regulatory element-binding protein 1c; **TNF-α**, tumor necrosis factor-alpha.

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HOW TO CITE: Hajera Begum, Dr. Koppala R. V. *S. Chaitanya*, Bommu Vaishnavi, Mahadev Anitha, High-Fat Diet-Induced Obesity in Rodents: Dietary Composition, Adipose Remodeling and Metabolic Dysfunction: A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 1527-1548. https://doi.org/10.5281/zenodo.24034490