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# High-Fat Diets-Induced Metabolic Disorders to Study Molecular Mechanism of Hyperlipidemia in Rats

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## Abstract

Hyperlipidemia is a lipid metabolism disorder occurring due to consumption of a high-fat diet (HFD), which contributes to atherosclerosis and cardiovascular disease development. HFD causes metabolic problems in Rodentia animals like human metabolic abnormalities, making it a popular model for studying the signaling systems involved. Hyperlipidemia is a condition in which the body's cholesterol levels elevate. In recent years, several studies have investigated the relationship between HFD feeding and hyperlipidemia and signaling pathways involved in cholesterol homeostasis. However, this signaling mechanism in lipid metabolism has not been fully explained, so additional analysis is needed. The present study aimed to investigate the mechanism that occurs from hyperlipidemia due to HFD feeding. The method used is a literature review approach following the PRISMA scheme for selecting the primary literature, including identification, screening, eligibility test, and inclusion. Eleven articles included primary literature with credibility (H-index) of 20, 33, 71, 92, 93, 162, 180, 192, and 332 (six articles from Q1 journals and five from Q2 journals). Long-term administration of HFD directly affects lipid metabolism, including an increase in the concentration of total cholesterol, triglycerides, LDL, and a decrease in HDL concentration, followed by an increase in body weight. In addition, HFD also disrupts adipose tissue and insulin resistance. The conclusion of this study is that HFD can cause hyperlipidemia either directly or indirectly by inducing insulin resistance, which contributes to lipid metabolism disorders.

Keywords: high-fat diet, hyperlipidemia, atherosclerosis, insulin resistance

## 1. Introduction

Metabolic syndrome (MetS) is a group of metabolic abnormalities that include hypertension, obesity, insulin resistance, and hyperlipidemia that contribute to the development of atherosclerosis and cardiovascular disease (CVD) [1]. Hyperlipidemia is a common health problem in society due to various factors such as genetics, gender, diet or diet, age, obesity, sedentary lifestyle, smoking, alcohol intake, and high blood pressure [2]. Hyperlipidemia is characterized through elevated concentrations of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein-cholesterol (LDL-C), as properly as reduced concentrations of high-density lipoprotein-cholesterol (HDL-C). Hyperlipidemia is one of the main risk factor of coronary heart disease (CHD) [3].

Diet plays a vital position in regulating the concentration of lipids and lipoproteins in the blood. At the same time, a lifestyle with high-energy consumption, lack of physical activity, stress, and anxiety with a relatively frequent frequency are factors that cause the development of obesity, atherosclerosis, and CVD [3,4]. A high-fat diet (HFD) can trigger rodent metabolic disorders like in humans [5]. Metabolism disorders due to HFD feeding are considered more relevant than monogenic animal models (germline defect leptin production/signaling) because in humans, it rarely occurs. A widely used animal model for studying physiology, behavior, metabolic disorders, toxicology, and cardiovascular disease is the rat, especially the white rat (*Rattus norvegicus*) (6,7). Rats are an animal model of human disease that is more convenient and beneficial than other organisms (8). The advantages are small size, simplicity, low maintenance cost, and short life cycle. Rats are excellent model animals for biomedical research (7).

HFD is widely used to study signaling mechanisms of metabolic disorders and CVD. There is a relationship between high saturated fats or saturated acids intake with atherosclerosis and CHD [6]. Hyperlipidemia due to long-

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term feeding of HFD is a metabolic disorder that leads to an increase in LDL deposits in the circulatory system, leading to the potential to be atherogenic and contribute to the development of CVD (10,11). Previous studies showed that long-term HFD feeding could significantly increase the concentrations of TC, TG, LDL-C, and VLDL-C compared to the control group, while HDL-C decreased (12,13). In addition, HFD also causes weight gain (14), and 50-60% of overweight people tend to suffer from hyperlipidemia (10,15).

Based on the description above, this literature review study has three goals: (1) determine how the cellular mechanism of HFD increases the concentration of TC, TG, LDL-C, and VLDL-C, and decreases the concentration of HDL-C, (2) determine the effect of HFD on the functional physiology of the body, and (3) determine the time required to induce hyperlipidemia using HFD.

## 2. Research Method

This study belongs to the category of literature review with the format of semi-systematic. This research used to be carried out by evaluating and analyzing qualitative and quantitative facts from the primary literature that had been formerly selected. Data analysis used to be carried out by quantitative and descriptive methods.

In a literature review-based study, the primary literature becomes a main essential component as a source of data and discussion analysis. Therefore, proper determination of the primary literature is crucial to produce a good literature review-based study. The primary literature was searched through three article search sites, i.e., Google Scholar, National Center for Biotechnology Information (NCBI), and Elsevier's repository with the keywords "*Rattus norvegicus*", and "High Fat Diet", as well as implementing filers "year >2010" and "availability open access”. The search results obtained are then sorted according to relevance to the topics discussed, have high credibility, the necessary data, and parameters.

The sorting technique of primary literature candidates used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) method by identification, screening, eligibility, and inclusion (16,17). The process of searching and sorting the primary literature is presented in the flow chart in **Figure 1**. The primary literature obtained is 11 articles with credibility (H Index) 20, 33, 71, 92, 93, 162, 180, 192, and 332, which are from the journal Q1 has six articles, and Q2 journals have five articles. Eleven primary pieces of literatures can be seen in **Table 1**, and the variety of variables in the primary literature is shown in **Table 2.**

## 3. Results and discussion

### *3.1. High-Fat Diet-Induced Metabolism Disorder*

Diet is one of the factors that affect the concentration of cholesterol in the body. Other factors include genetics, little physical activity, stress, and anxiety with relatively frequent frequency. Especially high-fat diet (HFD) greatly contributes to the development of atherosclerosis, obesity, and coronary heart disease (CHD) (3,18).

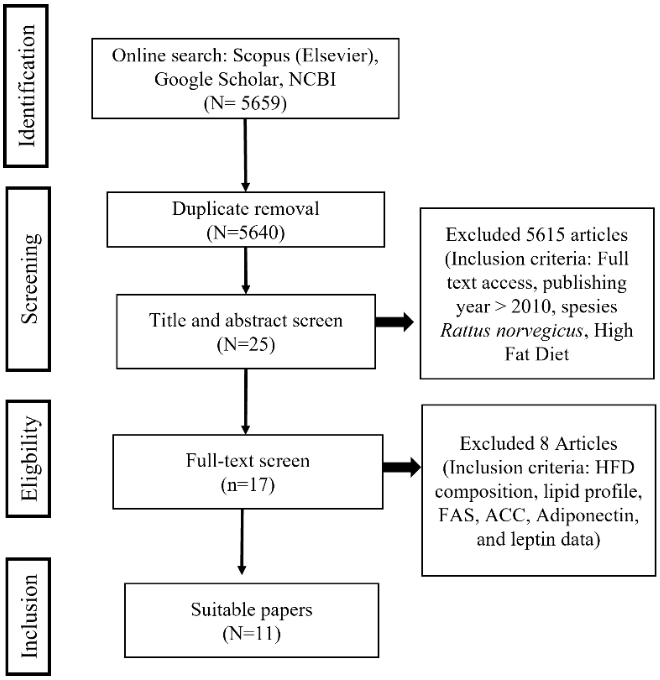


**Figure 1**. Flow charts of literature review PRISMA

HFD is metabolized in the liver and can accelerate *De Novo* lipogenesis and lipoprotein levels. HFD can also cause oxidative stress by increasing reactive oxygen species (ROS) and reducing antioxidant enzymes (19,20). In addition, HFD can induce obesity, hypertriglyceridemia, hyperlipidemia, hypertrophy, hepatic steatosis, insulin resistance, and beta-cell dysfunction in muscle and liver (9). Furthermore, the energy produced by HFD is higher than regular feed, thus contributing to strongly obesity (obesogenic is an external environmental factor that causes weight gain) (9,15,21).

According to Wang et al.(21), at the beginning of HFD administration, lipid profile parameters did not show any significant changes. This finding demonstrated that cholesterol has a regulatory feedback mechanism, indicating that extra fat in the body has no effect. Feedback regulation of cholesterol is a physiological process in humans and animals that adapts to changes in cholesterol concentrations from the diet to maintain cholesterol homeostasis in blood and peripheral tissues (22). The relationship between cholesterol absorption and biosynthesis is key in maintaining cholesterol homeostasis, which is a negative feedback mechanism. If there is an increase in cholesterol synthesis, the absorption of cholesterol decreases. Contrary, if there is an increase in cholesterol absorption, cholesterol synthesis will decrease (23). However, due to the long-term



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administration of HFD, the feedback regulation ability slowly decrease and is harmful to the body, especially to the heart and liver (24). Long-term HFD feeding can have a direct or indirect impact on lipid metabolism (9,25). HFD can also lead to insulin resistance, which disturbs glucose homeostasis and indirectly affects lipid metabolism disorders (26,27).

**Table 1.** Primary literature list

| No. | Year | Publication | Article Title | Pages | Authors | Journal |
|---|---|---|---|---|---|---|
| **1** | 2011 | BioMed Central Ltd. | Comparison of Dietary Control and Atorvastatin on High Fat Diet Induced Hepatic Steatosis and Hyperlipidemia in Rats | Vol. 10, Issues 23 | Ji, G., Zhao, X., Leng, L., Liu, P., & Jiang, Z. | Lipids in Health and Disease ISSN 1476511X **H-INDEX 71** **Q2** |
| **2.** | 2021 | Elsevier | Impact of protocatechuic acid on high fat diet-induced metabolic syndrome sequelae in rats | Vol. 907: 174257 | Nour, O.A., Ghoniem, H.A., Nader, M.A., Suddek, G.M. | European Journal of Pharmacology ISSN 00142999 **H-INDEX 180** **Q1** |
| **3.** | 2021 | Elsevier Ireland Ltd | Effective amelioration of hepatic inflammation and insulin response in high fat diet-fed rats via regulating AKT/mTOR signaling: Role of Lepidium sativum seed extracts. | Vol. 266:113439 | Abdulmalek, S.A., Fessal, M., El-Sayed, M. | Journal of Ethnopharmacology ISSN 03788741 **H-INDEX 192** **Q2** |
| **4** | 2013 | Elsevier BV | Metabolic features of rats resistant to a high-fat diet. | Volume 7, issue 4: e243-e250 | Akieda-Asai, S., Koda, S., Sugiyama, M., Hasegawa, K., Furuya, M., Miyazato, M., Date, Y. | Obesity Research and Clinical Practice ISSN 1871403X **H-INDEX 33** **Q2** |
| **5** | 2021 | Elsevier Ireland Ltd | Effects of Danhong injection on dyslipidemia and cholesterol metabolism in high-fat diets fed rats. | Vol. 274: 114058 | Du, H., Li, C., Wang, Z., He, Y., Wang, Y., Zhou, H., Wan, H., Yang, J., | Journal of Ethnopharmacology ISSN 03788741 **H-INDEX 192** **Q2** |
| **6** | 2020 | Elsevier BV | Potential mechanisms of improvement in body weight, metabolic profile, and liver metabolism by honey in rats on a high fat diet | Vol. 14: 100227 | Gohar, A., Shakeel, M., Atkinson, R.L., Haleem, D.J. | PharmaNutrition ISSN 22134344 **H-INDEX 20** **Q2** |
| **7** | 2021 | Elsevier Masson | Supplementation of cumin seed powder prevents oxidative stress, hyperlipidemia and non-alcoholic fatty liver in high fat diet fed rats. | Vol. 141: 111908 | Miah, P. Mohona, S.B.S., Rahman, Md.M., Subhan, N., Khan, F., Hossain, H., Sharker, S.Md. Alam, Md.A. | Biomedicine & Pharmacotherapy ISSN 07533322 **H-INDEX 92** **Q1** |
| **8** | 2019 | Hindawi Publishing Corporation | Antiobesity, Regulation of Lipid Metabolism, and Attenuation of Liver Oxidative Stress Effects of Hydroxy-α-sanshool Isolated from anthoxylum bungeanum on High-Fat Diet-Induced Hyperlipidemic Rats. | Vol. 2019: 5852494 | Wang, L., Fan, W., Zhang, M., Zhang, Q., Li, L., Wang, J., Zhu, L., Wei, D., Peng, W., & Wu, C. [2019]., 2019, 5852494 | Oxidative Medicine and Cellular Longevity ISSN 19420994 **H-INDEX 93** **Q1** |
| **9** | 2017 | Public Library of Science . | Resveratrol and caloric restriction prevent hepatic steatosis by regulating SIRT1-autophagy pathway and alleviating endoplasmic reticulum stress in high-fat diet-fed rats | Vol. 12, issue 8: e0183541 | Ding, S., Jiang, J., Zhang, G., Bu, Y., Zhang, G., & Zhao, X. | PLoS ONE ISSN 19326203 **H-INDEX 332** **Q1** |
| **10** | 2018 | MDPI Multidisciplinary Digital Publishing Institute | Regulatory Efficacy of the Polyunsaturated Fatty Acids from Microalgae Spirulina platensis on Lipid Metabolism and Gut Microbiota in High-Fat Diet Rats. | Vol. 19, issue 10: 3075 | Li, T. T., Liu, Y. Y., Wan, X. Z., Huang, Z. R., Liu, B., & Zhao, C | International journal of molecular sciences **H-INDEX 162** **Q1** |
| **11** | 2018 | MDPI Multidisciplinary Digital Publishing Institute | Regulatory Efficacy of Spirulina platensis Protease Hydrolyzate on Lipid Metabolism and Gut Microbiota in High-Fat Diet-Fed Rats. | Vol. 19, issue 12: 4023 | Hua, P., Yu, Z., Xiong, Y., Liu, B., & Zhao, L. | International journal of molecular sciences **H-INDEX 162** **Q1** |



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**Table 2.** Primary literature variable variation

| Reference | HFD containing | Energy food | *Rattus norvegicus* strains | Initial Weight rats [g] | Condition | Method | Blood collected |
|---|---|---|---|---|---|---|---|
| Ji et al., 2011 | Casein (25.8 %), Cystine (0.3 %), Lodex (16%), Sucrose (9%), Solka Floc (6%), Lard (31%), Soybean oil (3 %), mineral (6%), vitamin (0.3 %). (Fat 60%, carbohydrate 20%, and protein 20%) | 5.21 Kcal/g | Male Sprague-Dawley | 180 – 220 | 12 h light-dark cycle at 22–26 °C | free access to water and feed | Abdominal aorta |
| Nour et al., 2021 | Normal Pellet Diet (365 G/Kg), Casein (300 G/ Kg), Beef Tallow (310 G/Kg) And Vitamins and Minerals Mix (60 G/Kg). (Fat 58%, Carbohydrate 17%, Protein 25%). | - | Male Sprague–Dawley | 150 –200 | 12 h light-dark cycle at 22 °C | free access to water and feed | Retro-orbital venous plexus |
| Abdul-malek et al., 2021 | Butter (310 g/kg), casein (253 g/kg), cholesterol (10 g/kg), vitamins (60 g/kg) and minerals, yeast powder (1.0 g/kg) and sodium chloride (1.0 g/kg). (58% fat, 17% carbohydrate, 25% protein). | - | Male Sprague-Dawley | 105 ± 15 | 12 h light-dark cycle at 22°C ± 2°C | free access to water and feed | retro-orbital venous plexus |
| Akieda-Asai,et al., 2013 | Casein (25.8 %], Cystine [0.3 %], Lodex (16%), Sucrose (9%), Solka Floc (6%), Lard (31%), Soybean oil (3 %), mineral (6%), vitamin (0.3 %). (Fat 60%, carbohydrate 20%, and protein 20%). | 5.2 kcal/g | Male Sprague-Dawley & Wistar | 150 -180 | - | free access to water and feed | - |
| Du et al., 2021 | Basic Feed (67.5%), Egg Yolk Powder (10%), Pig Fat (10%), Sucrose (10%), Cholesterol (2%), And Sodium Cholate 0.5%. | | Male Sprague-Dawley | 150 ± 20 | 12 h light-dark cycle at 22°C ± 2°C | free access to water and feed | Retro-orbital venous plexus |
| Gohar et al., 2020 | Casein (25.8 %), Cystine (0.3 %), Lodex 16%, Sucrose (9%), Solka Floc (6%), Lard (31%), Soybean oil (3 %), mineral (6%), vitamin (0.3 %). (Fat 60%, carbohydrate 20%, & protein 20%). | 5.2 kcal/g | Male Wistar | 120 –140 | 12 h light-dark cycle at ± 23°C | free access to water and feed | Heart |
| Miah et al., 2021 | Beef fat. The source of fat was local beef market | - | Male Wistar | 185 –200 | 12 h light-dark cycle at 22°C ± 3°C | free access to water and feed | Abdominal aorta |
| L. Wang et al., 2019 | Basic Feed (73%), Cholesterol (1.5%), Pig Fat (10%), Egg Yolk Powder (5%), Sucrose (10%), And Bile Salt (0.5%) | - | Male Wistar | 220 ± 20 | 12 h light-dark cycle at 22°C | free access to water and feed | Abdominal aorta |
| Ding et al., 2017 | Standard Chow (60%), Custard Powder (8%), Lard (12%), Sugar (12%), Peanut Podwer [6%], and Milk (1%). (Fat 41.26 %, Carbohydrates 39%, Protein 19.13%]. | 4.59 kcal/g | Male Wistar | 190 - 270 | 12 h light-dark cycle at 22°C - 23°C | free access to water and feed | Heart |
| T.T. Li et al., 2018 | Normal Diet (67%), Sugar (20%), Lard (10%), And Cholesterol (3%). | - | Male Wistar | + 200 | - | free access to water and feed | Heart |
| Hua et al., 2018 | Normal Diet (67%), Sugar (20%), Lard [10%], and Cholesterol (3%). | - | Male Wistar | 223 -227 | - | free access to water and feed | Heart |

### 3.2. *High Fat Diet Induces Lipid Metabolism Disorders*

Hyperlipidemia is a lipid metabolism disorder that causes an increase in the concentration of total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and a decrease in the concentration of high-density lipoprotein-cholesterol (HDL-C). Hyperlipidemia is the cause of CHD and other cardiovascular diseases (CVD) (3). As reported previously, it was shown that long-term or chronic administration of HFD in rats could induce a significant increase in TC, TG, LDL-C, and VLDL-C compared to the control group, while HDL-C decreased (13,28,29). Based on **Table 3**, lipid profile parameters showed no significant changes at the beginning of HFD treatment. This finding indicates that cholesterol has a regulatory feedback mechanism (21), which in the 2nd-week lipid profile and body weight did not change significantly, and the atherogenic index was low. However, from the fourth week to the eighth week, lipid profile parameters, namely TC, TG, and LDL increased, and HDL decreased compared



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to controls in each study. HFD feeding showed a significant increase in lipid profile from the fourth week, suggesting that the rats had hyperlipidemia.

However, from the tenth week to the seventeenth week, the lipid profile tends to decrease, but bodyweight increases, which means the rat is still obese. This is possible because the lipid profile data were taken from different studies, so the use of feed composition, test reagents, and the formula for calculating the lipid profile is different, resulting in different results (13,30). However, in many studies, the lipid profile tends to increase over time with HFD administration. The highest lipid profile parameters in rats induced by hyperlipidemia using HFD occurred at the eighteenth week, indicated by very high TC, TG, and low HDL. The highest atherogenic index was 20.43, which indicates a very high atherogenic index. It is a powerful marker for predicting the risk of atherosclerosis, coronary artery disease, and cardiovascular disease (30,31). In addition, according to Kammar-Garcia et al. (32) it was reported that a high atherogenic index was correlated with a high prevalence of obesity and abdominal adiposity.

According to Han et al. (24), HFD feeding on rats caused a decrease in the amount of food consumption but still increased body weight. Energy from fat contributes to weight more than non-fat energy. Thermogenesis is the energy to digest, absorb, and store nutrients (33). Thermogenesis for fat is only 2-3%, while protein is 25-30%, and carbohydrates are 6-8%. Therefore, fat has a much higher energy efficiency of 97-98%, while protein is only 70-75%, and carbohydrates are 92-94%. This is what causes HFD to stimulate obesity by increasing energy uptake (18,34). **Table 3.** shows that feeding HFD can increase rat body weight. Individuals who are overweight have a 50-60% risk of developing hyperlipidemia (10).

### *3.3. HFD Induces Increase Free Fatty Acids (FFAs)*

One of the causes of lipid metabolism disorders is increased Free Fatty Acids (FFAs) in the blood (24,28,35). **Figure 2.** shows the increased levels of FFAs due to HFD feeding. FFAs are an energy substrate for the body by the oxidation of FFAs, especially for heart contraction. However, excessive levels of FFAs are one of the risk factors for CVD by increased levels of heart-type fatty acid-binding protein (H-FABP), causing changes in the morphology of the myocardium layer (24). Cardiomyocytes generate up to 70% of their energy requirements by the oxidation of FFAs. Nevertheless, in patients with coronary heart disease, levels of FFAs may lead to the severity of heart failure. FFAs have amphiphilic and detergent-like qualities, a persistent increase in their concentration can cause cardiac dysfunction, such as ion channel abnormalities, membrane integrity, and heart contraction interference (24,36).

Long-term feeding of HFD, which has a high content of saturated fatty acids (SFAs) may lead to a decrease in the levels of polyunsaturated fatty acids (PUFAs) in hepatocyte cells (37). PUFAs maintain cell membrane fluidity, inhibit inflammatory processes, reduce the secretion of proinflammatory cytokines by macrophages, maintain cardiac ventricular rhythm, improve vascular endothelial cell function, and reduce triglyceride synthesis in the liver (1,38). However, long-term HFD feeding can reduce PUFAs, especially in hepatocytes, causing oxidative stress and inflammatory conditions (37,39). These conditions make sterol regulatory element-binding protein (SREBP-1c) activation (9). This is a transcription factor that regulates genes that play a function withinside the synthesis and increases the absorption of FFAs, cholesterol and TG by stimulating the expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) proteins (40). It can be concluded that the administration of HFD can increase the expression of FAS and ACC proteins, as shown in **Figure 3.** ACC protein plays a role in inhibiting fatty acid transport to the mitochondria, and thereby fatty acids will be esterified into a large proportion of TG and stimulate *De Novo* lipogenesis (27).

Furthermore, TG is converted into VLDL. VLDL will then become LDL, resulting in an increase in LDL concentration followed by a decrease in HDL concentration (36). The hypothesis of the HFD mechanism that induces lipid metabolism disorders can be seen in **Figure 4.**

Lipolysis occurs in adipocyte cells in response to oxidative stress and inflammation, allowing more FFAs to be transported to the circulatory system (41). Increased levels of FFAs in the circulatory system, then FFAs will be sent to various tissues, especially to the heart and liver. In the liver, fatty acids will be esterified into TG under normal conditions and oxidized in the mitochondria (36). However, suppose fatty acid ranges are chronically high. In that case, the maximum of the fatty acids could be esterified into TG, which might also cause disrupting lipid metabolism characterized by the aid of using growth in LDL and a lower HDL (36,42).

### *3.4. High-Fat Diet-Induced Endoplasmic Reticulum (ER) Stress*

The content SFAs of HFD also causes endoplasmic reticulum (ER) stress (43). ER stress is due to the accumulation of protein misfolding because of SFAs. This may be detected with the aid of using the presence of protein kinase R-like endoplasmic reticulum kinase (PERK), endoribonuclease inositol-requiring kinase-1 (IRE1), and activation of transcription factor-6 (ATF-6) (27). In general, ER stress causes a decrease in the mRNA translation process, resulting in a reduction of protein synthesis. However, the



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transcription process usually continues, specifically in genes concerned with protein folding and protein degradation. ER stress causes inflammation through activation of IκB kinase-mediated by-activated IRE1 and c-JunN-terminal kinase (JNK) (44). Cell dysfunction due to ER stress by SFAs is found in various cell types and has different cellular mechanisms, such as macrophages and hepatocyte cells. In hepatocytes, ER stress stimulates the activation of X-Box Binding Proteins (XBP1s), thereby increasing *De Novo* lipogenesis in the liver, **Figure 4**. This causes an increase in the concentration of TG, VLDL, LDL, and a reduction in HDL (27). However, in macrophages, ER stress causes increased inflammation, mitochondrial dysfunction, and production of ROS, which interfere with insulin signaling in hepatocytes and skeletal muscle (44,45).

**Table 3**.Lipid Profile Concentration and Body Weight

| Reference | TC [mg/dL] | TG [mg/dL] | HDL [mg/dL] | LDL [mg/dL] | VLDL [mg/dL] | AI | Initial body weight [g] | Final body weight [g] | Duration of diet [weeks] |
|---|---|---|---|---|---|---|---|---|---|
| L. Wang et al., 2019 | 96.67 | 97.43 | 30.94 | 19.33 | 19.49 | 2.1 | 220 | 240 | 2 |
| T.T. Li et al., 2018 | 174.01 | 70.86 | 15.47 | 23.20 | 14.17 | 10.3 | 210 | 410 | 4 |
| Hua et al., 2018 | 154.68 | 115.15 | 11.60 | 23.20 | 23.03 | 12.3 | 224.28 | 418.53 | 4 |
| L. Wang et al., 2019 | 108.28 | 162.98 | 35.96 | 37.90 | 32.60 | 2.0 | 220 | 280 | 6 |
| Du et al., 2021 | 146.95 | 124.00 | 19.33 | 29.00 | 24.8 | 6.6 | 150 | 450 | 6 |
| Gohar et al., 2020 | 225 | 250 | 40 | 200 | 50 | 4.625 | 140 | 400 | 8 |
| Miah et al., 2021 | 300 | 225 | 25 | 250 | 45 | 11 | 71.71 | 377.65 | 8 |
| Akieda-Asai et al., 2013 | 50 | 60 | 20 | 18 | 12 | 1.5 | 180 | 580 | 10 |
| Adyab et al., 2019 | 62.6 | 38.97 | 46.79 | 7.73 | 7.79 | 0.3 | 237.17 | 476.5 | 10 |
| Nour et al., 2021 | 90.7 | 103.4 | 42.8 | 25.3 | 20.68 | 1.12 | 179.2 | 436.4 | 14 |
| Adyab et al., 2019 | 85.07 | 73.52 | 51.04 | 25.91 | 14.70 | 0.7 | 237.17 | 565.83 | 17 |
| Ding et al.,2017 | 81.21 | 115.15 | 29.00 | 25.14 | 23.03 | 1.8 | 190 | 620 | 18 |
| Abdulmalek et al., 2021 | 300 | 215 | 14 | 190 | 43 | 20.43 | 98 | 402 | 18 |
| Ji et al., 2011 | 168.60 | 80.60 | 32.10 | 147.72 | 16.12 | 4.25 | 220 | 542.14 | 20 |

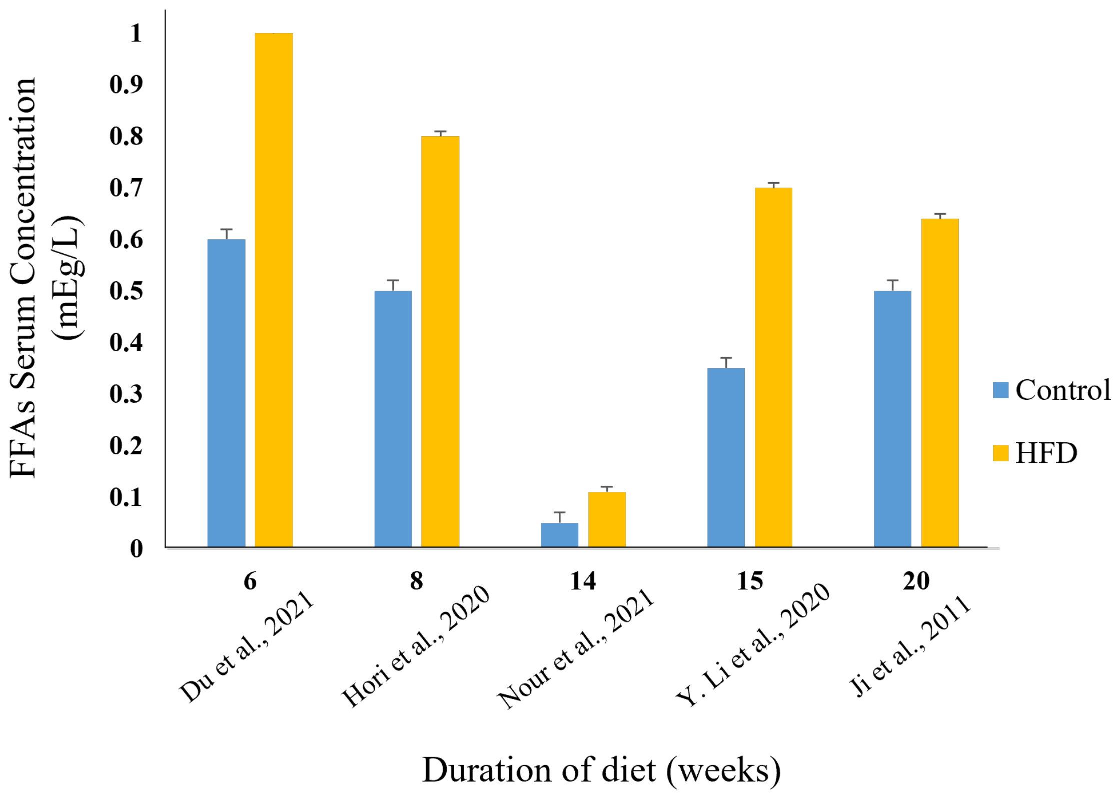


**Figure 2**. Free Fatty Acids Serum Concentration.



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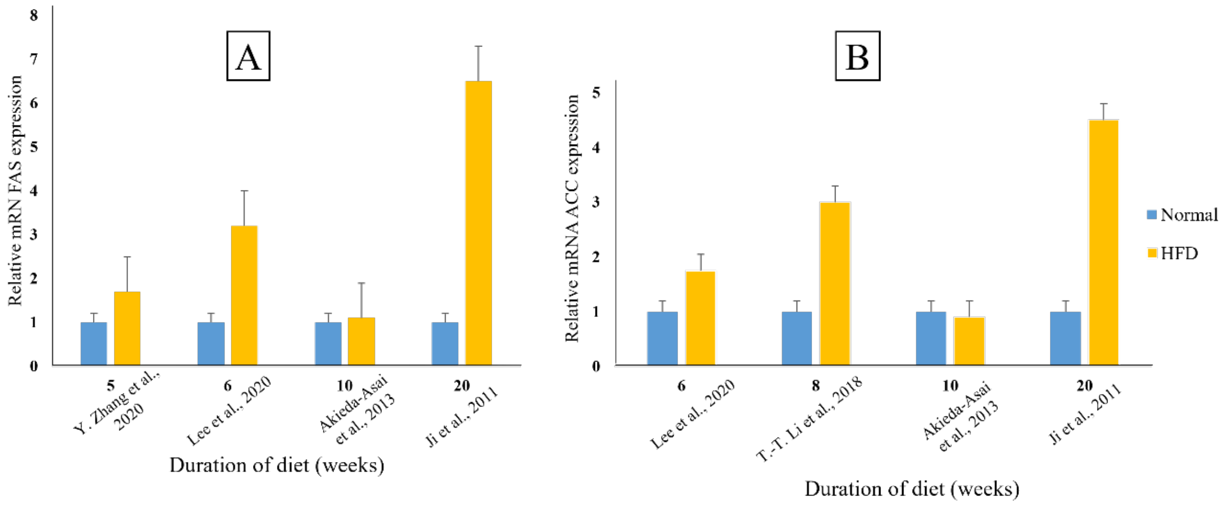


**Figure 3**. Relative mRNA (A) FAS and (B) ACC expression.

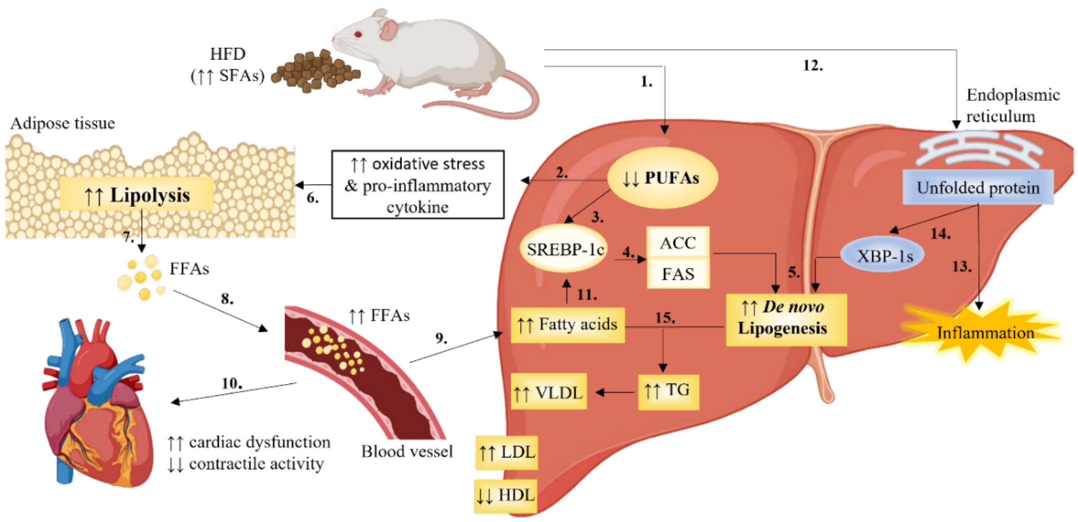


**Figure 4.** The hypothesized mechanism of HFD induces lipid metabolism disorders. HFD has a high content of SFAs (1), reducing PUFAs in hepatocytes, causing oxidative stress, proinflammatory conditions, and mitochondrial dysfunction in the liver (2). In addition, it activates the transcription factor SREBP-1 (3). SREBP-s stimulus proteins ACC and FAS (4). This induces an increase in *De Novo* lipogenesis (5). Oxidative stress conditions and pro-inflammatory cytokines induce increased lipolysis in adipocytes (6), leading to the secretion of FFAs (7) and more being transferred to the blood vessels (8). FFAs will be transferred to various tissues, especially to the liver (9) and heart (10). HFD causes stress on the ER (12), thereby inducing inflammation (13) and activation of XBP-1s (14). These factors increase the concentrations of TG, VLDL, LDL, and decrease HDL (15).

In macrophages, SFAs can directly induce inflammation extracellularly with the aid of activating the signaling of toll-like receptor-1/6 (TLR-1/6) and TLR-2, while intracellularly inflammation through the products of the metabolism of SFAs (44). Extracellularly, SFAs activate TLR-2 and TLR-1/6 signaling. This is the activation of IKK and NFkB, which lead to the production of pro-inflammatory cytokines (9,46). Intracellularly, metabolic products of SFAs contribute to the development of inflammation. SFAs are precursors of ceramides and sphingolipids, which are ceramides that contribute to inflammation and insulin resistance. Ceramide biosynthesis can be stimulated through TLR-4 signaling and



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may lead to insulin resistance by activating protein phosphatase-2A and PKC that inhibit Akt signaling (44). Ceramide can also activate inflammasomes to stimulate IL-1β secretion by macrophages causes inhibition of insulin signaling (47).

### *3.5. High-Fat Diet Induces Adipose Tissue Disorders*

HFD causes hypoxia in adipose tissue, thereby increasing adipocyte cell death (48). This stimulated the migration of M1 macrophages. M1 macrophages infiltrate adipose tissue and secrete many pro-inflammatory cytokines, including IL-6, IL-12, and tumor necrosis factor-α (TNF-α) (2,35,49). In addition to increasing the activity of M1 macrophages, HFD also decreases the activity of regulatory T cells and macrophages M2, both of which are anti-inflammatory cells (9). TNF-α is a pro-inflammatory cytokine usually produced via way of means of macrophages and stimulates the secretion of different pro-inflammatory cytokines. IL-6 may contribute to the development of vascular disease by increasing the ability of macrophages to degrade LDLox, whereas IL-12 contributes to pro-inflammatory cell differentiation and atherosclerotic stimulation (2,50). Pro-inflammatory cytokines result in insulin resistance by way of increasing the production of suppressors of cytokine signaling proteins (SOCS), which inhibit the signaling procedure via blocking off phosphorylation of tyrosine residues from the IRS so growing proteasomal degradation of the insulin receptor substrate (IRS) (9). The hypothesis of the HFD mechanism causing adipose tissue disorders is shown in **Figure 5.**

In addition, HFD also increases the adiposity properties of adipocyte cells (51). This causes dysfunctional adipose tissue, which results in a lower in adiponectin synthesis and an increase in leptin production. (13). **Figure 6 A.** shows that HFD can reduce adiponectin production. Adiponectin is a compound secreted by adipocytes cells that plays a vital position in regulating glycolipid metabolism and energy homeostasis. High adiponectin levels inhibit inflammation by reducing pro-inflammatory cytokines and increasing the expression of the anti-inflammatory cytokine IL-10 (2). Therefore, decreased adiponectin levels cause inflammatory conditions and lead to the severity of insulin resistance (2,10).

Adiponectin can regulate fatty acid oxidation by activating the AMP-activated protein kinase (AMPK) signaling pathway. Adiponectin can protect liver tissue from lipid accumulation (52). Decreased adiponectin production causes an increase in cardiomyocyte cell apoptosis and interstitial fibrosis, thereby eliminating the contractile activity of the heart muscle leading to dysfunction and heart failure (53). In addition to affecting adiponectin, HFD also affects the concentration of leptin. HFD can growth the attention of leptin is shown in **Figure 6 B**. Leptin features as a law of power expenditure and appetite, will increase fatty acid oxidation, and decreases frame fats, and inhibits macrophages from secreting TNF-α, IL-6, and IL-12, thereby excessive leptin ranges motive multiplied subcutaneous fats deposits and obesity (54,55).

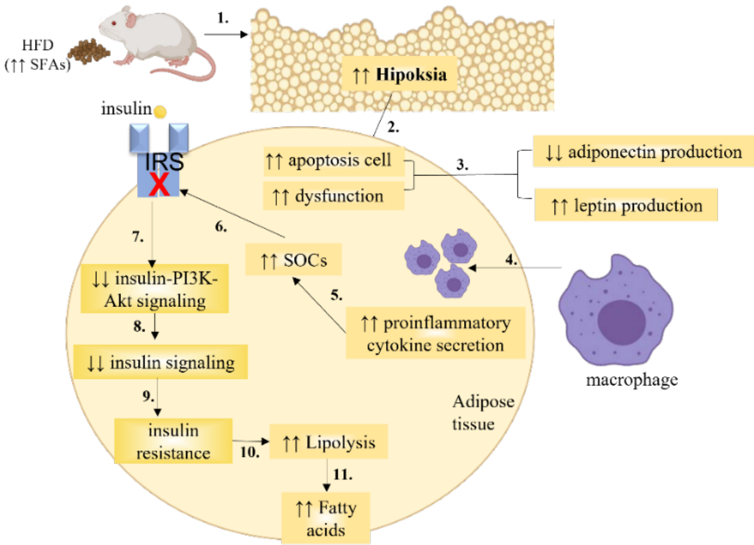


**Figure 5.** The hypothesized mechanism of HFD induces adipose tissue disorders. HFD can cause hypoxia (1.). Hypoxia stimulates apoptosis and dysfunction of adipocyte cells (2), thereby reducing adiponectin production followed by increased leptin production (3). This stimulates the migration of macrophages to adipose tissue (4). Macrophages secrete pro-inflammatory cytokines resulting in activation of SOCs (5). SOCs block IRS tyrosine residue phosphorylation (6), leading to



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decreased insulin-PI3K-Akt (7) and insulin signaling (8), resulting in insulin resistance (9). Insulin resistance results in increased lipolysis (10), and fatty acids (11).

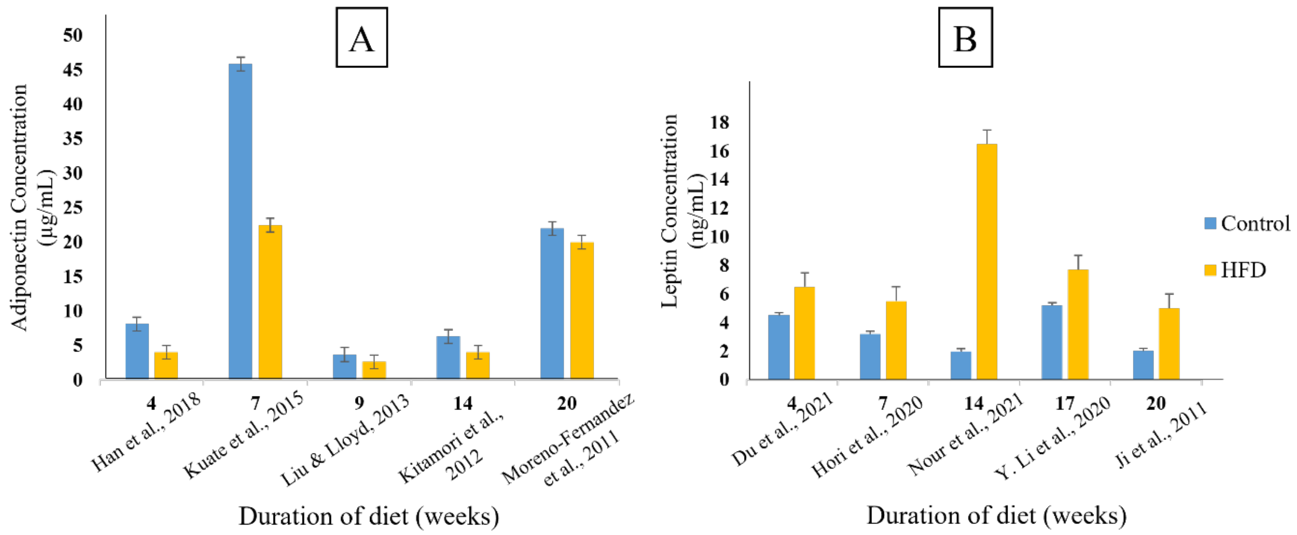


**Figure 6.** (A) Adiponectin and (B) Leptin Serum Concentration.

Adipose tissue is responsible for the development of insulin resistance (13). Insulin sensitive to adipose tissue will respond by storing TG through the differentiation of preadipocytes into adipocytes cells, thereby increasing uptake of fatty acids from the circulatory system and limiting the occurrence of lipolysis (27). However, in obese individuals, the amount of circulating lipids in the blood exceeds the capacity of adipose tissue for TG storage; thereby, fatty acids will accumulate in other tissues with limited lipid storage capacity, especially in the liver and skeletal muscle, and circulatory system (13). In adipose tissue, insulin plays a role in suppressing the lipolysis of TG to FFAs. However, due to the presence of insulin resistance, the process of inhibiting lipolysis did not occur, increasing the levels of FFAs and lipid deposits (27). Furthermore, there was an increase in the influx of FFAs to hepatocytes, as shown in **Figure 4.** This stimulates the synthesis and secretion of VLDL by the liver and in adipose tissue, which may lead to an increase in TG, VLDL, LDL, and a decrease in HDL (13).

### *3.6. High-Fat Diet Induces Insulin Resistance*

Insulin is a hormone that plays a role in regulating glucose homeostasis in the body (56). Insulin binds to the insulin receptor (IR), resulting in phosphorylation of tyrosine residues on IRS1 and IRS2. This phosphorylation causes downstream phosphatidylinositol 3-kinase (PI3K) activity and the synthesis of triphosphorylated inositol (PIP3) in cell membranes. This stimulates activation of Akt (serine/threonine kinase) signaling and phosphoinositide-dependent kinase (PDK). Activation of Akt signaling leads to activation of the insulin signaling pathway and translocation of glucose transporter type 4 (GLUT4) to cell membranes for glucose uptake. In addition, the transcription factor SREBP-1c was activated for *De Novo* lipogenesis, S6K for protein synthesis, GSK3b for glycogen synthesis and inhibited phosphorylation of Forkhead Box O1 (FOXO1), thereby inhibiting gluconeogenesis (27,57).

Insulin resistance is a metabolic disease characterized via way of means of the lack of ability of insulin to stimulate the presence of glucose in goal tissues, which include the liver, adipose tissue, and skeletal muscle, resulting in systemic hyperglycemia (27). Hyperinsulinemia causes interference with gluconeogenesis, lipolysis in the liver and adipose tissue. Hyperinsulinemia is considered a cause of hypertension, dyslipidemia, and obesity. In general, insulin resistance occurs due to disturbances in insulin signaling pathways, namely insulin receptor substrate 1 (IRS-1), phosphatidylinositol 3-kinase (PI3K), and Protein Kinase B (Akt) pathways (13).

HFD feed for Rodentia animals is used to find out about insulin resistance at the molecular level and insulin signaling mechanisms. Insulin receptors are extensively dispensed in mammalian cells. However, the important sites of insulin action are hepatocytes, adipocytes, skeletal muscle, and neuronal cells. In the liver, insulin has the characteristic to inhibit gluconeogenesis and stimulate glycogen synthesis (56). In skeletal muscle cells, insulin signaling is associated with protein synthesis and glucose uptake. In contrast, in adipose tissue, insulin can inhibit lipolysis, induce glucose, and inhibit fatty acid uptake with the aid of GLUT4. In neuron cells, insulin activates satiety signals and locomotor (27).



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Long-term HFD feeding will increase the production of sn-1,2-diacylglycerol (DAGs) in the liver and muscle (48). The abundance of DAGs in liver tissue activates the calcium-independent "novel" isoform of the protein kinase C (PKC) family. In the liver, DAGs prompt PKC-ε, whereas in the muscle, it is PKC-θ. PKC activation causes phosphorylation of serine residues in the IRS, which inhibits phosphorylation of tyrosine residues by insulin stimulation, thereby decreasing insulin-PI3K-Akt signaling and inhibiting insulin signaling resulting in insulin resistance (9). In skeletal muscle cells, decreased insulin-PI3K-Akt signaling causes an impairing glucose absorption and reduction in GLUT-4 (58). The hypothesis of the HFD mechanism that induces insulin resistance can be seen in **Figure 7**.

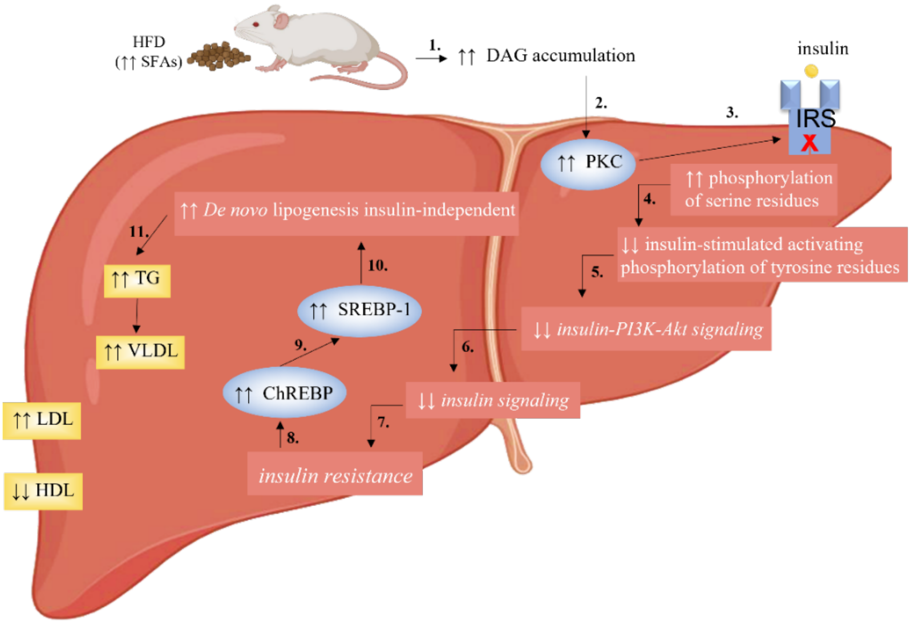


**Figure 7.** The HFD hypothesis induces insulin resistance. HFD induces the accumulation of DAG (1) in PKC-activated hepatocytes (2). PKC inhibits insulin-induced IRS via phosphorylation of serine residues (3), thereby inhibiting phosphorylation of tyrosine residues by insulin (4). This inhibits insulin-PI3K-Akt signaling (5) and decreases insulin signaling (6), resulting in insulin resistance (7). ChREBP activation (8) induces SREBP-1 (9), and *De Novo* insulin-independent lipogenesis occurs (10), thereby increasing the concentrations of TG, VLDL, LDL, and lowering HDL (11).

Under normal conditions, insulin stimulates lipogenesis in the liver (27). When insulin resistance occurs, there is a decrease in lipogenesis. However, this reduction in lipogenesis only occurred in animal models with genetic defects in hepatic insulin resistance (hepatic insulin receptor ablation) (59). If genetically normal, insulin resistance contributes to increased hepatic lipogenesis and hepatic steatosis in the liver (60,61). It occurs when chronic nutrient overload, especially carbohydrates (glucose and fructose), causes activation of carbohydrate response element-binding protein (ChREBP) and SREBP-1C, thereby activating signaling pathways of insulin-independent lipogenesis, and cells can produce TG (27,62).

## 4. Conclusion

HFD can cause hyperlipidemia either directly or indirectly. HFD induces hyperlipidemia directly by increasing the production of TG in the liver, thereby increasing TC and LDL-C and lowering HDL-C. HFD causes adipose tissue disorders and insulin resistance, thereby indirectly impacting lipid metabolism disorders. In addition, HFD also causes obesity, where individuals with obesity tend to experience hyperlipidemia. HFD can induce hyperlipidemia after administration of HFD for four weeks.

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