

Effect of Cholesterol Enriched or Fatty-Acid Diets on Cholesterol and Lipid Levels in Young Wistar Rats

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Abstract

Nutritional intake is a fundamental determinant of health. It is well known that cholesterol rich diets can induce several pathological conditions but detailed mechanism underlying these remains unknown. Wistar rats, an animal strain widely used in the research have been employed to study the effects of dietary interventions due to their metabolic characteristics, which are closer to the human compared to mice. The effect of some components of the western diet, combined with cholesterol in the lipid profile have been studied, but the impact of only cholesterol or fatty-acid diets in such a profile has not been yet characterized. Here we measured the effect of 6 or 16 weeks of dietary intervention with cholesterol enriched diet (CED) or fatty-acid diet (FAD) on cholesterol, triglyceride levels, high density lipoproteins (HDL) and low density lipoproteins (LDL). We observed significant differences in body weight only in animals treated with CED or FAD from Week 9 onwards as compared to animals fed the control diet. There were no differences between animals fed with CED or FAD in cholesterol levels at any time point nevertheless, triglyceride levels were significantly increased as compared to control diet in animals under both diets at early time points. Finally, both CED and FAD induced a decrease in HDL as compared to control levels in treatments of more than 6 weeks, whereas LDL transiently increased in animals treated with FAD from 10 to 12 weeks, but after this period LDL levels returned to baseline, suggesting that young rats have a compensatory effect at least for the period of time analyzed here. Here we provide a temporal course on lipid profile of cholesterol, triglycerides, HDL and LDH in Wistar rats treated with CED and FAD diet that can be useful as reference for future studies.

Keywords

Cholesterol-Enriched Diet, Fatty-Acid Diet, Cholesterol, Triglycerides, Young Wistar Rat

1. Introduction

Obesity and metabolic syndrome are considered some of the risk factors contributing to the development of mental diseases and the mechanism underlying these effects is still not well understood. How diet can modulate mental health has become a trendy topic in the last few years, given its relevance. High cholesterol diets can produce hippocampal alterations in rats [1]. Elevated levels of cholesterol have been proposed as one of the mid-life risk factors for developing Alzheimer's disease [2]. It has been shown that hypercholesterolemia induced by diet can produce neuroinflammation accompanied by cognitive deficit as well as changes in the processing of amyloid precursor protein (APP) one of the markers associate to Alzheimer's disease in C57BL/6 mice [3]. In apolipoprotein E ϵ 3 and ϵ 4 knock-in mice 44 - 45 weeks of cholesterol enriched diet increases levels of brain cholesterol esters especially in APOE ϵ 4 knock-in mice [4]. Moreover it has been reported that dietary and metabolic factors are implicated in the damage of the blood brain barrier (BBB), which is a system of microvascular endothelial cells that protects the brain from toxic substances, limiting the entry of unwanted blood components [5]. Thus there could be a mechanistic link among Western diet consumption (high in saturated fatty acids), BBB impairment and learning and memory deficits, and possible the onset of a dementia [6] [7]. Furthermore, intake of saturated fatty-acid can induce cognitive deficits in rats. Whereas, it has been shown that feeding rats with fatty-acid diets (diet composed by 20% of fat) can affect its performance in learning and memory test. There is an association between the level of fatty-acid saturation and the learning capability, thus fatty acid saturation has a specific effect on the severity of the cognitive deficit in Rats, however the mechanism are not yet well understood [8] [9]. Additionally, it has been proposed that unsaturation of fatty-acid in the cell membrane is associate with an extended longevity [10]. Consume of high fat diets induces systematic metabolic changes in blood plasma, liver, and urine samples involving several metabolic pathways [11]. Diets combining high fat and cholesterol can also produce changes in lipid composition and enzyme metabolism [10]. Due to these important antecedents we wanted to compare in separate animal cohorts the effect of a cholesterol enriched diet (CED) or a fatty-acid diet (FAD) on the levels of cholesterol and lipids in a Wistar rat model since we considered important to establish physiological changes induced by diet that could precede the onset of dementias and other diseases related to dietary habits. Particularly we were interested in this animal model, due to its metabolic characteristics, which are closer to human than mouse [10] [11] [12]. Rats had a compatible metabolic rate of clearance, and are physiologically close to humans, whereas mice have faster metabolic rate of clearance than humans. Additionally the rat genome is much closer to human than mice, and this genetic closeness makes the rat model more appropriate to evaluate the effects of the diet and compare it to human being [12] [13] [14]. Another advantage of this animal strain is that prolonged times consuming high cholesterol diets does not promote arteriosclerosis, allowing longer periods of treatment [15] [16]. The aim of this study was to provide a base line of the effect of cholesterol enriched diet and fatty-acid diet on total cholesterol levels, triglycerides, HDL (or good cholesterol) and LDL (or bad cholesterol) in one of the most used rodent strains in order to provide an accurate reference for future studies on dietary interventions. Here we provide a temporal course lipid profile of cholesterol, triglycerides, HDL and LDH in Wistar rats treated with cholesterol enriched diet of fatty acids enriched diet that can be useful as reference for future studies.

2. Methods

2.1. Animals and Treatments

We conducted all procedures in accordance with the Institutional Code of Practice for the Care of Experimental Animals and the experimental protocol was approved by Institutional Animal Ethical Committee (normativity NOM-062-ZOO-1999).

Male Wistar rats 12 weeks old at the beginning of the experiment ($n = 36$) were obtained from our Institutional animal facility. Animals were divided in two groups: the short ($n = 18$, feed for 6 weeks) and the long ($n = 18$, feed for 16) treatments groups. Rats were feed *ad libitum* for 6 or 16 weeks with cholesterol enriched pellets (Diet-Induced, Atherosclerosis/Hypercholesterolemia in Rodent Models, Diet 3, 40 kcal% Fat, 1.25% Cholesterol, 0% Cholic Acid; the Jackson Laboratory, D12108) or fatty-acid enriched pellets (Diet Induced Obesity (DIO) diet composition, 60 kcal% fat; the Jackson Laboratory D12492, Casein 200 g, 3 g L-cysteine) or Standard laboratory diet (26.8 kcal% protein, 16.7 kcal% fat, 56.4 kcal% carbohydrates, Formulab diet 5008) ($n = 6$ per group). Blood samples from all the groups were obtained weekly from the femoral vein to measure plasma lipids content during the 6 or 16 weeks of treatment. Body weight was registered weekly.

2.2. Lipid Measurements and Blood Samples Collection

The profiles measured were cholesterol, triglycerides, high density lipoproteins (HDL) and low density lipoproteins (LDL). Blood samples were obtained weekly from the femoral vein using heparinized capillary tubes in order to optimize the blood collection. To obtain blood samples animals were anesthetized with 5% isoflurane for induction and 3% for maintenance. Blood samples were stored in 1.5 ml eppendorf tubes. Lipid concentration was detected with test strips PTS that were read on a CardioChek analyzer (Polymer Technology systems, Inc.). A drop of blood per animal was analyzed and reported as mg/dL.

2.3. Statistical Analysis

Statistical analyses were carried out with GraphPad Prism software ver 5.0. A factorial analyses of variance (two way ANOVA) were used followed by Bonferroni post hoc test. Statistical significance is highlighted with an asterisk when $p \leq 0.05$; 2 asterisks when $p \leq 0.01$ or 3 asterisks when $p \leq 0.001$. All values are given as means \pm SEM, with an $n = 6$ in each condition.

3. Results

3.1. Outline

We observed significant differences in body weight only in animals treated with CED or FAD after 8 weeks as compared to animals fed with control diet. Interestingly there are no differences between the dietary treatments in cholesterol levels at any time point, probably due to the age of the animals, since they were young individuals and could compensate the effects of the diet. Nevertheless, triglyceride levels were significantly increased as compared to control diet in animals under both diets very early. Finally, both CED and FAD induced a decrease in HDL as compared to control levels in treatments of more than 6 weeks, whereas LDL transiently increased in animals treated with fatty acid diet from 10 to 12 weeks. Interestingly, after this period of time, levels of LDL went back to a normal range, reinforcing the idea that young animals can compensate the effects of CED and FAD at least for the period of time analyzed here. Interestingly there are no differences between the dietary treatments in cholesterol levels as was expected, suggesting that this strain has a particular lipid metabolism.

3.2. CED or FAD Diet Have an Effect on Body Weight Only after 9 Weeks of Treatment

Changes in body weight were registered weekly over 6 or 16 weeks of treatment in all rats from three dietary treatments. Normal growth related with age was observed in all groups. No changes in body weight were observed in animals treated with CED or FAD from 1 to 6 weeks as compared to control animals as shown in the **Figure 1(a)**, however, statistical differences were observed in animals that received the treatment for 16 weeks starting from Week 9 as seen in **Figure 1(b)**.

3.3. Neither Cholesterol Enriched Nor Fatty-Acid Diets Affect Total Cholesterol Levels but Both Dietary Treatments Increase Triglyceride Levels

Levels of cholesterol and triglycerides were measured every week for both, 6 and 16 weeks treatment groups. Neither 6 nor 16 weeks of CED or FAD affect the levels of cholesterol in plasma of young Wistar rats compared with animals under control diet as we show in **Figure 2(a)** and **Figure 2(b)**. All the groups maintained values of 100 mg/dl every week during the time of treatment. CED group reported a slight increase at the week 12 but thus was not statistically significant.

This is not the case with plasma triglyceride levels. CED induces a significant increase in triglyceride levels compared with the control diet starting at Week 2 as shown in **Figure 2(c)**. The increase is greater by Week 4 and it is sustained through the following weeks of treatment. Interestingly, the levels of triglyceride in the FAD group have a slight increase over 5 weeks compared with the control group but it shows a significant increase by the 6th week of treatment reaching the levels registered for CED group. This suggests that the effect of FAD on triglycerides is not immediate; however the accumulation of several weeks consuming this diet induces an increase in plasma triglyceride levels comparable to the animals that consumed CED.

After 16 weeks of dietary intervention as is observed with the 6 weeks treatment, CED induced a significant increase in triglyceride levels compared to the control from Week 2 onwards and this increase is maintained over

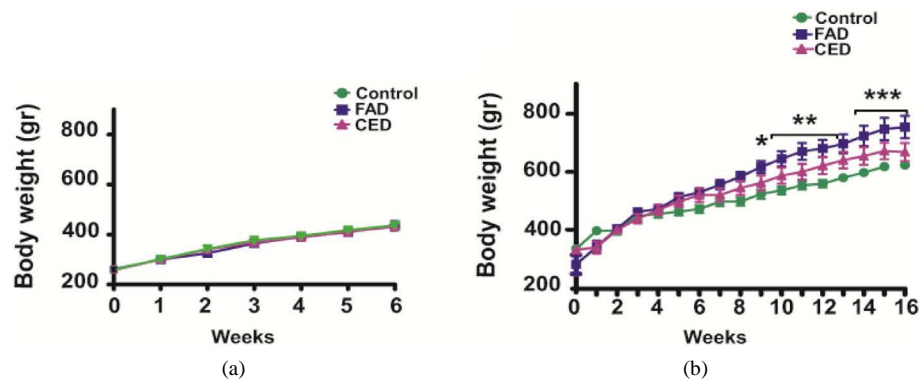


Figure 1. Changes on bodyweight induced by different type of diet. Body weight was measured weekly. No significant differences in body weight induced by diet were found within 6 weeks of treatment (a), whereas in 16 weeks treatment groups significant differences were found in bodyweight of rats treated with CED or FAD as compare to controls from 9 ($p \leq 0.05$), these differences increase between week 10 to 13 ($p \leq 0.01$) being more noticeable by Week 14-16 ($p \leq 0.001$) (b). N = 6 Wistar rats per treatment.

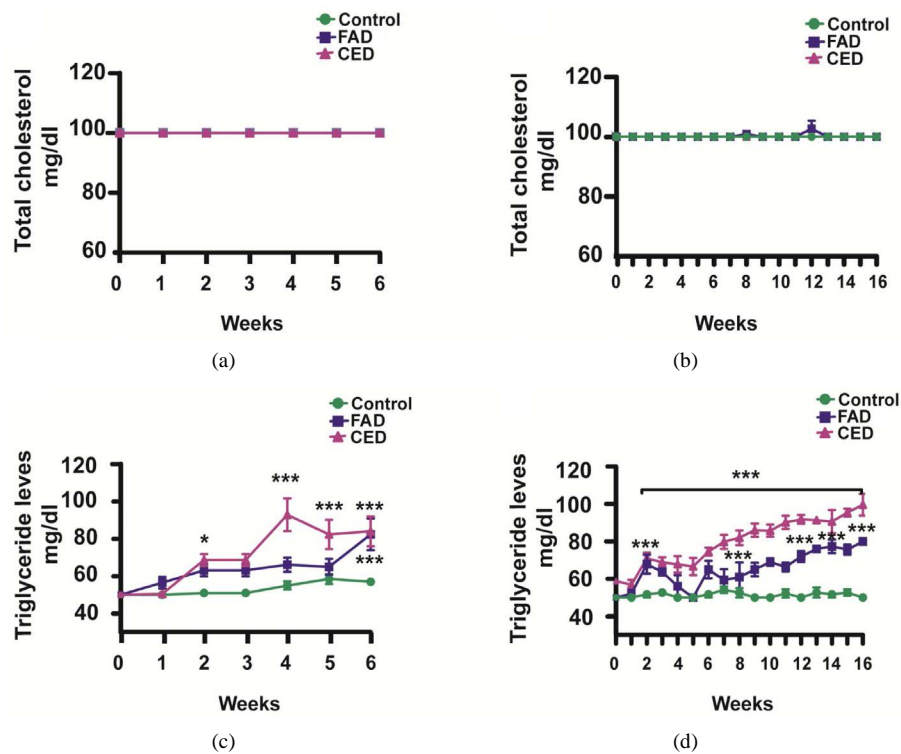


Figure 2. Effect of diet on cholesterol and triglyceride levels. Total cholesterol and triglyceride levels in animals treated with CED, FAD or control diet. Dietary treatments did not induce changes in total cholesterol levels at 1 to 6 (a) and 6 to 16 (b) weeks of dietary intervention (with CED or FAD). Cholesterol enriched diet induced an elevation on plasma triglycerides that starts as early as the 2nd week of treatment (c and d, $p \leq 0.05$). This increase is slower in FAD group however reaches the level of the cholesterol diet by the 6th week of treatment (c, $p \leq 0.001$) and these elevated levels are maintained over the weeks of treatment in the 16 weeks cohort (d, blue line). N = 6 Wistar rats per treatment.

the 16 weeks of treatment as is observed in **Figure 2(d)**. FAD shows a significant increase as well. It decreases reaching the control level by Week 5, increases again showing a significant increase compared with the control by Week 6. Such increase is maintained until the end of the treatment.

3.4. Cholesterol Enriched or Fatty-Acid Diets Differentially Regulate High and Low Density Lipoprotein.

Consuming 6 weeks of CED induces a significant decrease in the content of HDL by the 5th week compared with the control in **Figure 3(a)**. At this time point, there is as well a decrease in HDL levels observed in samples from animals treated with FAD but this is not significantly different from control diet samples shown in **Figure 3(a)**. Time points of the 6th to 16th week showed a significant decrease in HDL in both groups CED and FAD as compared to control diet in **Figure 3(b)**.

Levels of LDL are not affected by 6 weeks of FAD but CED induces a slight increase by the 4th week reaching significant differences by the 5th week of treatment but returns to control levels by Week 6 as shown in **Figure 3(c)**. Nonetheless at 10 weeks of treatment FAD induce an increase in the level of LDL, which is maintained until Week 12. Weeks 11 to 16 of FAD treatment showed a recovery of LDL levels, almost reaching the control diet values in **Figure 3(d)**. No significant levels of LDL were observed on animals treated with CED from Weeks 6 to 16 in **Figure 3(d)**.

4. Discussion

It has been demonstrated that diets rich in fat can represent a risk factor for developing mental diseases such as Alzheimer disease in humans, [2] and induce learning impairments in rats [8] [9]. To study the mechanism involved in such effect has importance for health.

Differences in rats body weight treated with CED or FAD as compared to control diet treated rodents were evident after 9 weeks of treatment, suggesting that only long term diet treatments can affect the corporal mass. Even when the information regarding changes on bodyweight after diets rich in fat or cholesterol is controversial

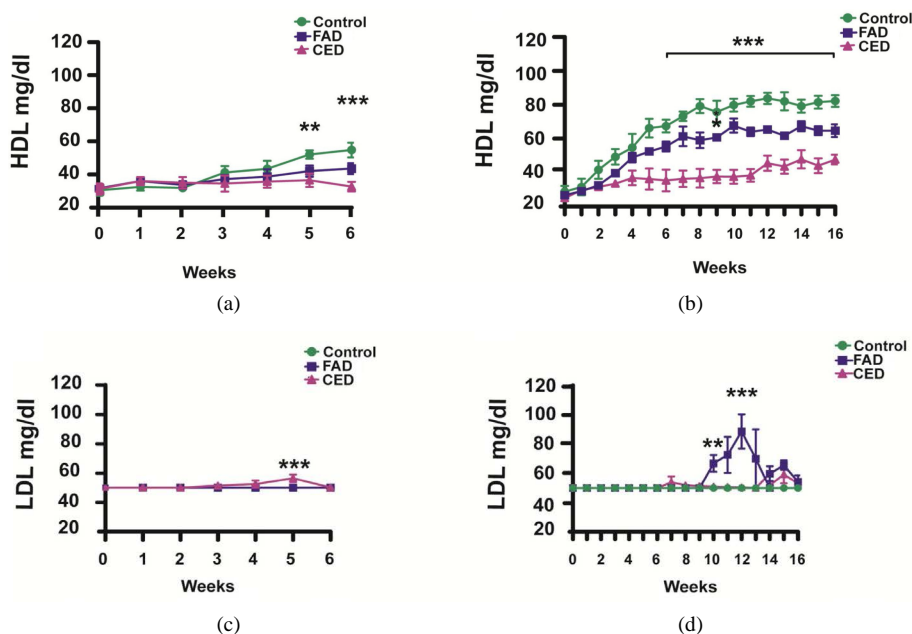


Figure 3. HDL and LDL plasma levels after dietary treatments. HDL and LDL plasma levels in animals treated with CED, FAD or control diet. Starting from 5th week CED induced a significant decrease in high density lipoproteins (HDL or good cholesterol) as compared to control levels (a, ** $p \leq 0.01$), such decrease is more significant by Week 6 (a, *** $p \leq 0.001$). This decrease was more evident at 6 to 16 weeks of treatment (b, *** $p \leq 0.001$) for the 16 weeks of treatment groups FAD induced a significant decrease at Week 7 (b, * $p \leq 0.05$). 6 weeks treatment groups showed a significant increase of low density lipoproteins (LDL or bad cholesterol) at 5 weeks of treatment with CED which decreases at level of control group by Week 6 (c, *** $p \leq 0.001$). For 16 weeks treatment groups there was a transiently increase in animals treated with fatty-acid diet from 10 (** $p \leq 0.01$) to 12 weeks (** $p \leq 0.001$), but after this period of time the levels of LDL were back to a normal range (d).

our findings accord with what was previously reported in rats that received three types of diet: high in fat and sucrose, high in fat and glucose, or a standard laboratory diet. This type of diet did not induce changes in body weight but learning impairments were found in rats fed with high fat and glucose [17]. As well, another study done with high fat diet showed significant differences in bodyweight of rats after 83 days (about 12 weeks) but they detected an increase in triglycerides, total cholesterol and other markers in serum, similar to our cholesterol or fatty-acid enriched diet. As well, no divergences between the weight gains were found, similar to our 6 week treatment [11]. A study done with C57BL/6 mice showed that a high fat/cholesterol diet did not induce changes in body weight, on the other hand a study done with APOE ϵ 3 and ϵ 4 KI mice who received a diet composed of 10% fat, 0.75% cholesterol showed lower bodyweight compared with the control. The authors attributed this to the fact that this type of diet induces a decrease in testosterone, which is crucial in muscle building. Possibly this lower body weight of animals fed with such diet 44 - 45 weeks could be due a decrease in muscle mass [4]. A recent study done with Sprague Dawley rats fed 7 days with high-fat-and-fructose reported that such diet induced obesity and several hippocampal alterations such as decreased insulin signaling, diminishment of hippocampal weight, as well as a reduction in dendritic arborization and number of dendritic spines, as well as a decrease in microtubule-associated protein 2 (MAP-2) and decreased synaptophysin content in the CA1 region accompanied for an increase in tau phosphorylation and number of reactive astrocytes [1].

With our dietary interventions we also observed differences in the lipid profiles. An interesting finding is that both dietary interventions (CED and FAD) did not change the levels of cholesterol but it does affect plasma levels of triglyceride. This finding does not agree with the data reported for the mouse model of obesity in which C57BL/6 mice were fed for 14 days with a high fat diet. With such conditions there was no change in serum triglyceride but there was an increase in serum cholesterol levels [18]. As well, a high fat and cholesterol diet induced elevated level of total serum cholesterol in control and APOE ϵ 4 mice [4]. All this divergences can be due the use of different species, strains, diet composition, time of treatment, age and sex of the individuals. Our study is the first so far to examine a lipid profile of Wistar rats treated with cholesterol enriched or fatty-acid diet. Interestingly, in our experimental model the main changes were observed in the levels of triglycerides, HDL and LDL after the 6th week (from the 6th to the 16th week). This time period coincides with the time interval where the significant increase in body weight was observed. While FAD promotes a non-significant decrease in HDL at 5 to 6 weeks, from the 6th week to 16th weeks HDL showed a statistically significant decrease. The observed increase in LDL induced by FAD at 10 to 12 weeks of treatment does not last for long, since at 14 to 16 weeks of treatment they reach control levels suggesting a compensatory mechanism of these young rats in agreement to our results that show no changes in total cholesterol with any of the treatments (neither CED nor FAD). This might be similar to what can happen in some human individuals with a higher capacity of adaptation to unhealthy diets at shorter time points [19] [20].

Triglycerides help to enable the bidirectional transference of adipose fat and blood glucose from the liver. High levels of triglycerides in the bloodstream have been linked to atherosclerosis and the risk of heart disease and stroke. It is considered as a risk the inverse relationship between the levels of triglycerides and HDL, thus our results show a sustained decrease in the levels of HDL (more evident from 6 to 16 weeks) that correlates with an increase in triglycerides level in both dietary treatments: CED and FAD. Even when changes in LDL were not very dramatic we could speculate that the animals were at risk of forming lipid deposits and developing a disease at later time points if this diet would continue.

First we can conclude that even before bodyweight is affected by diet, functional metabolic effects can be detected. It has a big biological relevance since our and previous results show that diet can induce functional affectations even before a noticeable change happens, in this case bodyweight. We can also conclude that the rat animal model is a good experimental system to study the effect of CED and FAD to follow the progression of lipid profile changes that could be associated with disease. This study can provide a baseline lipid profile after high cholesterol or fatty-acid diet in a commonly used animal model, Wistar rat. A future direction must be to carry out a more detailed study on the physiological and cognitive effects produced by the consumption of these diets. The present study can serve as reference for further studies.

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