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Obesity and the Maternal Lipid Profile: Role of Diet in Epigenetic Transfer on the Offspring

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Abstract: Aim: investigate the implications of HFD induced obesity on the lipid profile in parent rats and their offspring. Methodology: Twenty adult female rats (100 - 150g) were grouped into A and B which received NRC and HFD respectively for 16 weeks. Group B rats with BMI >0.50g/cm^2 were considered obese. Adult male Wistar rats fed with NRC were introduced to each group, to ensure mating and pregnancy after feeding. The offspring produced by the rats in each group were divided into two groups of 20 rats each. They were fed with NRC for 12 months. The plasma obtained from the parent and offspring were analysed for lipid profile test. Result: The parent rats fed with HFD had higher Cholesterol, triglyceride and HDL compared with the rats fed with NRC. At 4 and 12 months, the offspring of HFD fed rats had lower triglyceride and LDL compared with offspring of NRC fed rats. The offspring of HFD fed rats had higher HDL compared with the offspring of NRC fed rats at 8 months. Conclusion: if offspring of obese HFD fed rats are placed on NRC throughout their life time, the consequence of maternal obesity on their lipid profile may notmanifest.

Keywords: Obesity, High Fat Diet, Normal Rat Chow, Triglyceride

1. Introduction

Obesity can be defined as an inbalance between energy intake and energy expended. It is the abnormal accumulation of fat in the adipose tissues, to the extent that health may be impaired. About 2.3 billion people aged 15 years and above are overweight, and over 700 million people worldwide are obese [29]. Overweight and obesity are major causes of type II diabetes, cardiovascular diseases, various cancers and other health problems, which can lead to morbidity and mortality [4, 9]. Various anthropometric indices like BMI, waist-to-hip ratio (WHR), waist circumference (WC), and waist-to-height ratio (WHtR) [10, 25, 28, 27] have been used to assess and predicts obesity and obesity-related health risks [10]. However, none of these indexes have been identified as the universal definition of obesity. Obesity is a complex disease often associated to hypertension, cardiovascular diseases, and metabolic disorders. The combination of these chronic diseases is called metabolic syndrome [8].

High fat diets (HFD) have been reported to contribute to the pathophysiology of the insulin resistance syndrome, but their phenotype varies distinctly between different studies in rodent models [5]. The disorders caused by high-fat feeding resemble the human metabolic syndrome, and this may extend to some cardiovascular complications [1]. The impact of a maternal high-fat diet in rodents throughout gestation shows epigenetic changes in the adipose tissue and liver of the offspring [22, 13, 15]. It has been reported by Li *et al* (2012) that "maternal consumption of a HFD is linked with increased weight gain, hepatic hyperlipidaemia, increased liver injury and hepatic expression of inflammatory markers in the offspring". Therefore, this study focuses on the impact of diet on the consequences of HFD-induced maternal obesity in the offsprings.

2. Materials and Methods

Metabolic cages constructed by Central Technological Laboratory and Workshops (CTLW), OAU, Ile-Ife were used for this study.

2.1. Animal Care and Management

The rats were purchased from the Animal House of the College of Health Sciences, Obafemi Awolowo University, Ile-Ife, and were housed in plastic cages for two week for the purpose of acclimatization under normal environmental conditions with natural light/dark cycle and with access to clean water and normal rat chow (NRC) and high fat diet (HFD) (Ace Feed PLC Osogbo, Nigeria). The experimental procedures adopted was in compliance with Health Research Ethics Committee (HREC), College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.

2.2. Experimental Design

Twenty adult female Wistar rats weighing 100 - 150 g were used for the first stage of the study. The rats were divided into 2 groups as follows; Group A, (the control) consisting of 10 rats were fed with (NRC) + water and group B consisting 10 rats were fed with (HFD) + water *ad-libitum* for 12 weeks to induced obesity.

Obesity was determined by calculating the body mass index and Lee's index. Body Mass Index (BMI)=[(weight in g) / (height in cm)^2].

Lee's index=[(weight in g) 0.33 / (height in cm)].

The weight of the rat was measured by using weighing balance while the length was measured from the tip of the nose to the anal region using meter rule. The rats that met the criteria for obesity as defined by a body mass index (BMI) of >0.50g/cm^2 [17] and Lee's index > 0.300g/cm [3, 2 and 14] in group 2 were considered fit for the obese group.

After the 16 weeks of feeding, adult male Wistar rats fed with NRC + water *ad-libitum* were introduced to each group, to ensure mating and pregnancy. The blood samples of the parents were collected into separate heparin bottle via retro-orbital puncture after weaning their offspring. The plasma was separated by centrifugation at 4°C using a Cold Centrifuge and then analysed lipid profile (triglyceride, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL)).

The offspring produced by the rats in each group of stage 1 were divided into two groups, each consisting 20 rats (10 males and 10 females) and used for the stage 2 of this study. They were fed with NRC + water *ad libitum* throughout the period of this experiment (12 months). Their blood and urine samples were analysed for the aforementioned substances at age 4, 8 and 12 months.

The table below summarizes stages 1 and 2 of this study;

Table 1. *Study Design.*

STAGE 1			
GROUP A (10 female rats)	(NRC) + water *ad-libitum* for 12 weeks and then mated with matured male rats.	GROUP B (10 female rats)	(HFD) + water *ad-libitum* for 12 weeks and then mated with matured male rats.
STAGE 2			
Offspring of rats in group A in stage 1 goes into STAGE 2		Offspring of rats in group B in stage 1 goes into STAGE 2	
Offspring of NRC (20 rats) (males and females)		Offspring of HFD (20 rats) (males and females)	
(NRC) + water *ad-libitum* for 4 months (NRC) + water *ad-libitum* for 8 months (NRC) + water *ad-libitum* for 12 months		(NRC) + water *ad-libitum* for 4 months (NRC) + water *ad-libitum* for 8 months (NRC) + water *ad-libitum* for 12 months	

2.3. Statistical Analysis

The results obtained were expressed as Mean ± SEM. Significant differences between the sexes were determined using Student's one tail t-test. Differences with probability values of $p < 0.05$ were considered significant (Graph Pad Software Inc., CA, USA).

3. Results

Feed Formulation

Table 2. *Result of Proximate Analysis of the High Fat Diet and Normal Rat Chow. DescriptionQuantity (gram).*

	High Fat Diet	**Normal Rat Chow**
Maize white	1.00	13.00
Wheat bran	1.08	3.75
Fish Meal (72%)		1.00
Soya- Full Fat	18.00	
Soya Beans Meal		3.25
Groundnut Cake	4.00	3.00
Salt	0.10	0.13
Vitamin C	0.10	0.13
Limestone	0.12	0.25
Di-calcium Phosphate (DCP)	0.60	0.50
TOTAL	25	25

Table 3. *Showing Lipid profile of Parent Rats Fed with NRC and HFD.*

Parents rats	NRC	HFD
Cholesterol (mg/dl)	167.7±8.13	204.5±7.75*
Triglyceride (mg/dl)	135.8±1.83	149.4±2.27*
HDL (mg/dl)	57.75±2.95	100.6±3.14*
LDL (mg/dl)	89.60±1.16	86.13±2.06

Values are expressed in mean ± SEM (n=5); $P< 0.05$, *=significant difference NRC versus HFD.

Table 4. *Showing various parameters of offspring of HFD and NRC Fed Rats at 4 months.*

Offspring rats	NRC	HFD
Cholesterol (mg/dl)	212.0±3.54	209.5±5.23
Triglyceride (mg/dl)	156.9±2.99	139.8±3.25*
HDL (mg/dl)	153.7±2.29	119.8±24.03
LDL (mg/dl)	70.78±2.68	57.42±1.85*

Values are expressed in mean ± SEM (n=5); $P< 0.05$, *=significant difference NRC versus HFD.

Table 5. *Showing various parameters of offspring of HFD and NRC Fed Rats at 8 months.*

Offspring rats	NRC	HFD
Cholesterol (mg/dl)	161.7±2.69	161.9±1.69
Triglyceride (mg/dl)	148.7±9.70	140.5±8.74
HDL (mg/dl)	39.71±3.61	50.12±2.32*
LDL (mg/dl)	62.84±3.63	64.15±3.69

Values are expressed in mean ± SEM (n=5); $P< 0.05$, *=significant difference NRC versus HFD.

Table 6. *Showing various parameters of offspring of HFD and NRC Fed Rats at12 months.*

Offspring rats	NRC	HFD
Cholesterol (mg/dl)	239.0±2.25	237.4±12.83
Triglyceride (mg/dl)	186.9±20.51	150.5±6.87*
HDL (mg/dl)	35.90±1.14	34.63±4.40
LDL (mg/dl)	142.7±3.45	107.3±11.82*

Values are expressed in mean ± SEM (n=5); $P< 0.05$, *=significant difference NRC versus HFD.

4. Discussion

4.1. Lipid Profile in the Parent Rats

Visceral body fat is majorly the risk factors for diabetes, hyperlipidemia, hypertension and arteriosclerosis [21]. It has been demonstrated that obesity adversely affects plasma lipid profile by increasing the triglyceride, cholesterol and LDL, and decreasing HDL [11]. In this study, obese rats had increased cholesterol, triglyceride and HDL levels when compared with non-obese rats. This supports the study of Khan *et al.* (2005) [12], who reported elevated level of cholesterol and triglyceride in obese rats. Also, Desai *et al.* (2014) [6] documented an increase in plasma cholesterol and no differences inplasma triglyceride of HFD fed rats when compared with the NRC fed rats. Gregersen *et al.* (2005) [7] documented an increase in triglycerides concentration and no difference in cholesterol concentration in HFD fed rats at the age of 16 weeks. This report is in contrast with the result obtained in this study, that is, significant increase in plasma cholesterol and triglyceride concentration in HFD fed rats. These differences may be attributed to the specie of the animals used by the two studies. In this present study female Wistar rats were used while in the study of Gregersen *et al.,* (2005) [7], female mice were used.

The reported increased cholesterol and triglyceride levels in the study is in contrast with that of Uhegbu *et al.* (2013) [24] who documented that soya bean oil supplement in feed decreased the levels of total cholesterol, triglyceride, LDL, and increase in HDL. This contradiction could have resulted from the differences in composition of the feed used in the two studies. In this study, soya full fat as a supplement was used, while in the study of Uhegbu *et al.* (2013) [24], soya bean oil supplement was used.

The increase in cholesterol in HFD fed rats when compared with non-obese rats is in agreement with the report obtained by Suliman (2008) [23], who stated that HFD increases cholesterol levels. The increased level of cholesterol may be due to overloads of cholesterol on the liver resulting to down regulation of LDL receptors which carry cholesterol, and then leading to recirculation of cholesterol in the blood [16]. Mice fed with HFD developed increased levels of triglycerides, oxidized low density lipoproteins, free fatty acids and VLDL-cholesterol [26].

4.2. Lipid Profile in the Offspring

Hyperlipidemia is the term used for an elevated lipid (cholesterol, HDL, LDL and triglycerides) in the bloodstream. Lipids are transported in the blood as part of large molecules called lipoproteins [21]. High cholesterol diet contributes to

the development of cardiac diseases and leads to the development of hyperlipidemia, atherosclerosis, and ischemic heart diseases [18 and 19]. The potential for coronary heart disease (CHD) is increased in individuals with elevated concentrations of plasma low-density-lipoprotein (LDL) cholesterol [18]. In this study, no significant differences were observed in the plasma concentration of cholesterol in the offspring of HFD fed rats at 4, 8 and 12 months of age when compared with their control counterparts. This is in consonance with You-Lin *et al* (2017) [31] who documented no differences in the cholesterol level between the offspring of HFD fed rats and NRC fed rats for 6 months. The report from this study is also supported by Khan *et al.,* (2013) [12]. This finding however disagrees with Desai *et al*. (2014) [6], who documented a reduction in plasma cholesterol in the offspring of HFD fed rats fed with NRC when compared with the offspring of NRC fed rats fed with NRC for 24 weeks. This difference could have arisen from the duration of exposure of the offspring to NRC.

The significant reduction in the plasma triglyceride concentration of the offspring of HFD fed rats at 4 and 12 months of age is an indication that the rats are less prone to cardiovascular diseases. This was supported by the report of Desai *et al.* (2014) [6], who documented a reduction in plasma triglyceride concentration in the offspring of HFD fed rats fed with NRC when compared with the offspring of NRC fed rats fed with NRC for 24 weeks. No significant differences were observed in the plasma concentration of triglyceride between the offspring of HFD fed rats and the NRC fed rats at 8 months of age. This is corroborated by Sabiha *et al (*2016) [20], who also reported no difference in plasma triglyceride concentration in male offspring of control and HFD fed fathers at 8 months of age. Also, no significant differences were observed in the plasma concentration of HDL of HFD fed rats at 4 and 12 months of age, while at 8 months of age, a significant increase in plasma concentration of HDL was recorded. The increase recorded at 8 months of age is contrary to You-Lin *et al.,* (2017) [31], who found no differences in HDL between the offspring of HFD fed rats and NRC fed rats that were fed with NRC for 6 months. This contradiction could be due to differences in the duration of the two experiments.

A significant decrease in the plasma concentration of LDL was recorded at 4 and 12 months of age in the offspring produced by HFD fed rats when compared with their control counterparts, while no difference was seen at 8 months of age. This could be due to the fact that the cells require additional cholesterol beyond its normal 3-Hydroxyl-3-methylglutaryl-CoA (HMGCoA) requirement. This would lead to the synthesis of the necessary LDL receptors by the cell to bind LDL particles in the bloodstream for delivery into the endosome, where conformational changes occurs to release the LDL to the lysosome for the hydrolysis of cholesterol esters in the LDL. The process reduces the level of LDL in the blood by mobilizing them into the cell where their function is needed. Hence, the decrease in the plasma concentrations of LDL at 4 and 12 months.

5. Conclusion

The lipid profiles of the offspring of rats fed with HFD were significantly lower compared with their counterpart. This was in contrast to what is obtained in their parent lipid profile. Also common to the offspring of both HFD and NRC fed rats at 8 and 12 months of age was the increase in the level of LDL in the blood. This is an indication that as the animals' increases in age, they are most liable to increase in the demand of cholesterol for the biosyntheses activities in their body.

It is concluded that if offspring of obese HFD fed rats are placed on NRC throughout their life time, the consequence of maternal obesity on their lipid profile may not manifest.

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