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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 High Fat Diet (HFD) induced obesity on the lipid profile in parent rats and their offspring.

Methodology: Twenty adult female rats were grouped into A and B which received NRC and HFD respectively for 16 weeks. Group B rats with BMI >0.50 g/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.

Results: 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: Offspring of obese HFD fed rats placed on NRC did not manifest the consequence of maternal obesity as depicted by their lipid profile.

Keywords: Obesity; High fat diet; Normal rat chow; Triglyceride; Cystatin c

Introduction

Obesity can be defined as an unbalance 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 [1]. 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 [2,3]. Assessment and prediction of obesity and obesity-related health risks has been approach by various anthropometric indices. These include BMI Waist-to-Hip Ratio (WHR) Waist Circumference (WC) and Waist-to-Height Ratio (WHtR) [4-7]. However there is no agreement on which index should be applied universally for defining 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) has been reported to contribute significantly to the pathophysiology of the insulin resistance syndrome but their phenotype varies distinctly between different studies in rodent models [9]. The disorders achieved by high-fat feeding resemble the human metabolic syndrome closely and this may extend to some cardiovascular complications [10]. The impact of a maternal high-fat diet in rodents throughout gestation shows epigenetic changes in the adipose tissue and liver of the offspring [11-13]. It has been reported by Li, et al. that "maternal consumption of a HFD is linked with increased weight gain hepatic hyperlipidemia 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 offspring's [12].

Materials and Methods

Animal care and management

The rats used for this study were obtained from the Animal House of the College of Health Sciences Obafemi Awolowo University Ile-Ife and were housed in plastic cages. The rats were kept under normal environmental conditions with natural light/dark cycle and allowed free access to clean water and Normal Rat Chow (NRC) and High Fat Diet (HFD) (Ace Feed PLC Osogbo Nigeria). They were allowed to acclimatize in the laboratory for two weeks before the commencement of the study. The experimental procedures adopted in this study were in strict compliance with Health Research Ethics Committee (HREC) College of Health Sciences Obafemi Awolowo University Ile-Ife Osun State Nigeria.

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 >0.50 g/cm^2 and Lee's index >0.300 g/cm in group 2 were considered fit for the obese group [14-17]. 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. Therefore the plasma was separated by centrifugation at 4℃ 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 48 and 12 months **(Table 1)**.

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	

Table 1: Study design.

Statistical analysis

The results obtained were expressed as Mean ± SEM. Significant differences between the sexes were determined using Student's one tail t-test. Age-related differences within the groups of rats were analysed using One-way Analysis of Variance (ANOVA). Post hoc test was done using the Student Neuman Keuls tests. Differences with probability values of $p<0.05$ were considered significant (Graph Pad Software Inc. CA USA).

Results

Nutritionists and feed manufacturers use a variety of qualitative and quantitative methods to assess the quality of feed ingredients including physical, chemical, and biological tests. Physical evaluation of feed ingredients often includes color, smell, and taste characteristics that are qualitative criteria. Chemical tests are quantitative and allow accurate estimation of energy and nutrient content as well as possible contaminants and toxic compounds. Biological evaluation of feed ingredients is the most definitive measure of the feeding value of an ingredient. Tabular content on feed formulation **(Table 2)**.

Description	**Quantity (gram)**	
	High fat diet	Normal rat chow
Maize white	1	13
Wheat bran	1.08	3.75
Fish Meal (72%)	__	1
Soya- Full Fat	18	__
Soya Beans Meal	__	3.25
Groundnut Cake	4	3
Salt	0.1	0.13
Vitamin C	0.1	0.13
Limestone	0.12	0.25
Di-calcium Phosphate (DCP)	0.6	0.5
TOTAL	25	25
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*
*=Quantitative values of lipid content in feed.		

Table 2: Result of proximate analysis of the high fat diet and normal rat chow.

Cholesterol, Triglyceride, LDL, HDL levels of parent rat after feeding NRC and HFD **(Table 3).**

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 3: Showing lipid profile of parent rats fed with NRC and HFD.

Below tables shows the various parameters of offspring of HFD and NRC fed rats at 4, 8 and 12 months period **(Tables 4-6)**.

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 4: Showing various parameters of offspring of HFD and NRC fed rats at 4 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 5: Showing various parameters of offspring of HFD and NRC fed rats at 8 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.		

Table 6: Showing various parameters of offspring of HFD and NRC fed rats at 12 months.

Discussion

The major contributor to multiple risk factors for diabetes hyperlipidemia hypertension and arteriosclerosis is the visceral body fat [18]. It has been demonstrated that obesity adversely affects plasma lipid profile by increasing the triglyceride cholesterol and LDL and decreasing HDL [19]. In this study the obese rats had increased cholesterol triglyceride and HDL levels when compared with non-obese rats. This is in agreement with the study of Khan, et al. who reported elevated level of cholesterol and triglyceride in obese rats [20]. Also Desai, et al. documented an increase in plasma cholesterol and no differences in plasma triglyceride of HFD fed rats when compared with the NRC fed rats [21]. Gregersen, et al. documented an increase in triglycerides concentration and no difference in cholesterol concentration in HFD fed rats at the age of 16 weeks when compared with rats fed with NRC. This report is in contrast with the result obtained in this study. 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. female mice were used [22].

The reported increased cholesterol and triglyceride levels in the study is in contrast with that of Uhegbu, et al. 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. soya bean oil supplement was used [23]. The increase in cholesterol in HFD fed rats when compared with non-obese rats is in agreement with the report obtained by Suliman who stated that HFD increases cholesterol levels [24]. 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 [25]. Mice fed with HFD developed increased levels of triglycerides oxidized low density lipoproteins free fatty acids and VLDL-cholesterol [26]. Hyperlipidemia is an elevation of lipids (fats) in the bloodstream. These lipids include cholesterol HDL, LDL and triglycerides. They are transported in the blood as part of large molecules called lipoproteins [18]. High cholesterol diet is regarded as an important factor in the development of cardiac diseases as it leads to the development of hyperlipidemia atherosclerosis and ischemic heart diseases [27,28]. The potential for Coronary Heart Disease (CHD) is increased in individuals with elevated concentrations of plasma Low-Density-Lipoprotein (LDL) cholesterol [28]. In this study no significant differences were observed in the plasma concentration of cholesterol in the offspring of HFD fed rats at 48 and 12 months of age when compared with their control counterparts. This is in consonance with You-Lin, et al. who documented no differences in the cholesterol level between the offspring of HFD fed rats and NRC fed rats for 6 months [29]. The report from this study is also supported by Khan, et al. [20]. This finding however disagrees with Desai, et al. 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. 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 [21]. 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. who also reported no difference in plasma triglyceride concentration in male offspring of control and HFD fed male parent at 8 months of age [30]. 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. 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 [29]. 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 may have resulted from additional demand of cholesterol by the cell beyond its normal 3-Hydroxyl-3-Methylglutaryl-CoA (HMGCoA) requirement. This result in 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 lead 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 [31].

Conclusion

The lipid profiles of the offspring of rats fed with HFD were significantly lower compared with their counterpart. This is in contrast to what was obtained in their parent lipid profile. 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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