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F0 Prenatal/Lactation Diets Varying in Saturated Fat and Long-Chain Polyunsaturated Fatty Acids Alters the Insulin Sensitivity of F1 Rats Fed a High Fat Western Diet Postweaning

Daniel C. Benyshek[1], Julie J. Kachinski[1], Hongbin Jin[2]

[1]Metabolism, Anthropometry and Nutrition Laboratory, University of Nevada, Las Vegas, Las Vegas, USA
[2]Department of Epidemiology and Biostatistics, University of Nevada, Las Vegas, Las Vegas, USA
Email: daniel.benyshek@unlv.edu

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Abstract

Previous research has shown that prenatal diets rich in specific nutrients (e.g. taurine, omega-3 fatty acids) may provide protective cardiometabolic effects for adult offspring. The purpose of the current study was to investigate the potential of a prenatal-lactation diet rich in omega-3 long-chain polyunsaturated fatty acids (omega-3 LC PUFAs) to improve metabolic function in offspring fed a high saturated fat "Western" diet postweaning. We compared growth and metabolic biomarkers of three groups of Sprague Dawley rat offspring all weaned to a high saturated fat "Western" (Western) diet, but whose mothers were fed one of three different diets during pregnancy-lactation: 1) omega-3 "PUFA"-rich (PUFA/Western); 2) control (Control/Western); and 3) high saturated fat "Western" (Western/Western). PUFA/Western offspring had significantly lower fasting insulin ($P < 0.01$) and HOMA-IR ($P < 0.01$), and lower mean plasma triglycerides than Western/ Western animals. Additionally, mean HOMA-IR, fasting plasma insulin, and triglycerides were 19%, 10% and 14% lower, respectively, than those of Control/Western animals, although these differences were not statistically significant. Western/Western adult offspring had the highest fasting plasma insulin, triglycerides, and insulin-resistance (HOMA-IR) of the three groups. Our results indicated that a maternal omega-3 PUFA-rich diet during pregnancy-lactation may provide modest protective metabolic effects for adult offspring, even when consuming a high energy and saturated fat diet.

Keywords

Developmental Origins, LC-PUFAs, Insulin Resistance, Animal Modelling

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1. Introduction

A large body of epidemiological and experimental animal research has shown that nutritional insults during pregnancy and lactation, including overnutrition, can deleteriously alter metabolic function in adult offspring [1]. Recent studies have also reported that prenatal diets rich in specific nutrients (e.g. taurine, Vitamin D, folic acid) may provide protection from disease in offspring [2]-[4], including cardiometabolic dysregulation in adulthood [5] [6]. Given the well-established cardiometabolic benefits associated with diets rich in long-chain polyunsaturated fatty acids (LC-PUFAs) [7]-[9], several experimental animal studies have investigated the effects of maternal prenatal/lactation diets varying in the content and ratios of omega-3 and omega-6 LC-PUFAs on bone growth/formation, systolic blood pressure, and levels of serum leptin, insulin, and triacylglycerols in neonatal offspring [10]-[12], as well as adult offspring weaned onto control diets [13]-[15]. These studies suggested that LC-PUFA diet content, and perhaps more importantly, more balanced omega-6 to omega-3 ratios, may be key dietary variables in the developmental programming of cardiometabolic function and bone growth in adult offspring.

The purpose of the current pilot study was to investigate the potential protective effect of a prenatal-lactation diet rich in omega-3 LC-PUFAs on metabolic function of adult offspring consuming a high saturated fat Western diet.

2. Materials and Methods

Male and female adult Sprague-Dawley breeders were obtained from Simonsen Laboratories, Inc. and housed in the University of Nevada, Las Vegas Animal Care Facility. Males and females were housed separately in plastic cages and were maintained on a control chow diet for 10 days while acclimatizing to the new environment (**Table 1**). On the 10th day female animals were randomly assigned to one of three test diets: PUFA, Western, or Control. The PUFA diet was custom formulated to model the "traditional" southwestern Alaskan Yup'ik Eskimo dietary intakes, a diet well known for its omega3/omega-6 balanced, high PUFA content [16]. The Western diet was formulated to model the highly processed, "fast food" diet associated with the global "nutritional transition" [17]. The Control diet was a standard rat chow (**Table 2**). Females were then placed on their assigned test diets; males consumed the same diet as their female cage-mates.

Females were maintained on their assigned diet for seven days. During this time, both food and water were supplied *ad libitum*. On day 17, males and females on the same diet were combined and transferred to larger

Table 1. Experimental Design.

F0 Generation	F1 Generation
Maternal Diets	**Post-weaning Diets**
PUFA	Western
Control	Western
Western	Western

Table 2. Diet Composition.

Component	Control	PUFA	Western
Calories provided by			
Protein	28.5%	30.3%	17.8%
Fat	13.5%	59.8%	29.8%
Carbohydrate	58.0%	10.0%	52.3%
P:S	1:1	2:1	0.5:1
Omega-6:Omega-3	6.5:1	1.5:1	9:1

plastic cages to begin breeding. Dams consuming the control diet were placed with a male breeder after the other two experimental dams became pregnant. Litters were standardized for size and sex within each prenatal diet group using cross-fostering and culling techniques when the pups were 10 days of age. Pups were fed their assigned postnatal diets at weaning (**Table 2**). Both food and water were supplied *ad libitum* throughout the study. Weights were recorded approximately every three days for 120 days. On the 120th day animals were fasted overnight. The following morning animals were restrained in a breathable tube, and lidocaine was applied to the end of the tail, approximately 1 cm in length. A small segment of the tail (~2mm) was excised using a surgical scalpel, and blood was collected by milking the tail. 100 µl of blood was collected in heparin coated capillary tubes for the glucose and blood lipid analyses, 600 µl was collected in non-heparin capillary tubes for insulin analysis. Blood collected for insulin analysis was spun at 4000 g at 4˚C. Plasma was removed and transferred to cryogenic vials and stored at −40˚C until insulin analysis was performed. The study was approved by the UNLV Institutional Animal Care and Use Committee (IACUC).

2.1. Experimental Diets

Experimental diets differed in macronutrient composition, fat sources, and ratios of polyunsaturated to saturated fatty acids (**Table 2**). The PUFA diet (Purina Testdiet, Greenfield, Indiana) differed slightly in mineral content for the breeders versus weanlings, but both contained the same percentages of macronutrients, 30% protein, 60% fat, and 10% carbohydrate (**Table 2**). The PUFA diet for breeders contained slightly more selenium, calcium, iron and zinc as recommended by the commercial vendor nutritionist. The sources of fat for the PUFA diet were fish and soybean oil (**Table 2**). A mix of corn, canola, soybean, safflower, coconut and fish oils, lard, beef tallow, milkfat, and cocoa butter made up the fat sources for the Western diet (Harlan Teklad Madison, Wisconsin). All diets contained a standardized AIN-93 vitamin and mineral mixture except for the noted modification mentioned above. Western diets were kept at 4˚C, Control diets at room temperature, and PUFA diets at −40˚C. At the beginning of each week, a week's allotment of PUFA chow was transferred to 4˚C refrigeration. To prevent excessive oxidation of the PUFA diet, animals were provided with fresh food every two days. Animals receiving the Western diet were supplied with fresh food every three days and animals consuming the Control diet had a constant supply of food.

2.2. Biomarker Analyses

Plasma glucose and blood lipid concentrations were measured using the Abaxis Blood Chemistry Analyzer. Glycosylated hemoglobin (HbA1c) was measured using the Bayer DCA 2000 Chemistry Analyzer. ZRT Laboratories in Beaverton, Oregon, analyzed insulin by ELISA.

2.3. Statistical Methods

Kruskal-Wallis tests were used to examine differences in body weight/BMI, HbA1c, fasting plasma glucose, HOMA-IR, fasting plasma insulin, and triglycerides among the three experimental diet groups. Levene's tests were performed to examine the homogeneity of variances. Bonferroni tests with Bonferroni correction and Dunnett's T3 tests were used in post-hoc analyses for variables with equal and unequal variances, respectively. For body weight data, given a larger sample size, one-way ANOVA tests were used to examine differences in body weight among pre-weaning pups after data normality was confirmed. Data were analyzed using SPSS version 21.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to detect potential outliers of which values were greater or less than mean ±1.65 standard deviations. The significance level was fixed at 0.05 for all statistical tests.

3. Results

Table 3 shows the details of the metabolic biomarkers for offspring of the three diet lines: PUFA/Western, Control/Western, and Western/Western.

3.1. Insulin

PUFA/Western offspring were significantly ($P < 0.01$) less insulin resistant (as measured by HOMA-IR) than Western/Western animals (**Figure 1**). The mean fasting plasma insulin of PUFA/Western animals was also significantly lower ($P < 0.01$) than Western/Western offspring. Compared to Control/Western animals, mean HOMA-

IR and fasting plasma insulin values were 19% and 10%, lower, respectively, for PUFA/Western animals. These differences were not statistically significant, however (**Figure 1**).

Table 3. Metabolic Markers for Male and Female Post-Weaning Rats by Experimental Diet.

Biomarker	PUFA/Western		Control/Western		Western/Western		P-value*	Post-hoc Test
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.		
BMI (g/cm^2)	4	0.60 ± 0.05	5	0.55 ± 0.03	3	0.60 ± 0.04	0.475	
Male	2	0.67 ± 0.00	2	0.61 ± 0.01	2	0.65 ± 0.01		
Female	2	0.53 ± 0.06	3	0.51 ± 0.02	1	0.52 ± 0.00		
HbA1c (%)	4	3.43 ± 0.05	5	3.22 ± 0.05	3	3.37 ± 0.03	0.052	
Male	2	3.50 ± 0.00	2	3.20 ± 0.00	2	3.40 ± 0.00		
Female	2	3.35 ± 0.05	3	3.23 ± 0.09	1	3.30 ± 0.00		
Glucose (mmol/L)	4	7.79 ± 0.17	5	8.78 ± 0.32	3	7.48 ± 0.27	**0.024**	C/W > W/W†
Male	2	8.08 ± 0.08	2	8.39 ± 0.28	2	7.75 ± 0.03		
Female	2	7.50 ± 0.00	3	9.04 ± 0.48	1	6.94 ± 0.00		
HOMA-IR	4	0.95 ± 0.07	5	1.17 ± 0.10	3	2.07 ± 0.20	**0.023**	W/W > P/W†
Male	2	1.04 ± 0.11	2	0.96 ± 0.03	2	2.27 ± 0.01		
Female	2	0.86 ± 0.00	3	1.32 ± 0.10	1	1.67 ± 0.00		
Insulin (pmol/L)	4	18.95 ± 1.12	5	20.95 ± 1.99	3	42.97 ± 2.76	**0.025**	W/W > P/W‡
Male	2	20.07 ± 2.25	2	17.82 ± 0.00	2	45.72 ± 0.42		
Female	2	17.82 ± 0.00	3	23.04 ± 2.78	1	37.47 ± 0.00		
Triglycerides (mmol/L)	4	0.66 ± 0.08	5	0.77 ± 0.08	3	0.83 ± 0.16	0.443	
Male	2	0.64 ± 0.12	2	0.83 ± 0.03	2	0.86 ± 0.28		
Female	2	0.68 ± 0.15	3	0.74 ± 0.13	1	0.76 ± 0.00		

*Kruskal-Wallis test; †Bonferroni test with Bonferroni correction; ‡Dunnett's T3 test.

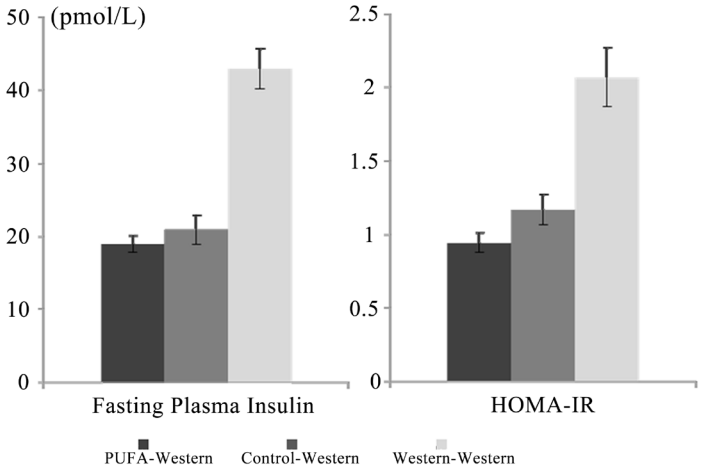

Figure 1. Fasting Plasma Insulin and Resistance as Measured by HOMA-IR at day 120.

3.2. Glucose

There were no significant differences in mean fasting plasma glucose between PUFA/Western animals and either Control/Western or Western/Western offspring. Mean fasting plasma glucose was significantly higher, however, among Control/Western animals than Western/Western offspring ($P < 0.01$). Longer-term, average blood glucose, as measured by HbA1c, varied minimally among the three groups, but was the highest among PUFA/Western animals, followed by Western/Western and Control/Western offspring.

3.3. Triglycerides

The mean plasma triglyceride value of PUFA/Western animals (0.66 mmol/L) was 20% lower than that of Western/Western offspring (0.83 mmol/L). Mean triglycerides of Control/Western (0.77 mmol/L) were intermediate to those of the PUFA/Western and Western/Western groups, although these differences did not reach a 0.05 P-value for statistical significance.

3.4. Body Weight

There were no significant differences in body weights on day 7 among offspring whose mother consumed the PUFA, Western, or Control diets during pregnancy-lactation. By day 21, offspring whose mothers were fed a PUFA diet during pregnancy and lactation were significantly ($P < 0.01$) heavier compared to offspring whose mother consumed either a Western or Control diet (**Table 4**). These results are inconsistent with other studies that have examined the effects of prenatal diets that are high in omega-3 LC-PUFAs on body weight. These studies have generally found offspring of mothers fed a prenatal-lactation diet high in omega-3 diet are lower in body weight compared to cohorts whose mothers consume a "mixed" omega-3/omega-6 diet or a high omega-6 diet [11] [14] [15]. This suggests that some other nutritional component of various PUFA-rich diets may be contributing to growth differences during the perinatal period in our study, or that there may be relatively narrow ranges of PUFA dietary intakes that differentially contribute to postnatal growth trajectories. Unsurprisingly, after weaning, Western/Western offspring maintained the highest body weights throughout the study, weighing an average of 58 grams more than Control/Western animals, and 32 grams more than PUFA/Western offspring on day 120 (**Table 5**). Differences in body weights after day 25, however, were not statistically significant.

Table 4. Body Weight in Grams for Pre-Weaning Rats by Maternal Diet.

Day	PUFA		Control		Western		P-value*	Post-hoc Test
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.		
7	15	16.80 ± 1.13	18	17.20 ± 0.19	18	16.44 ± 0.48	0.700	
21	15	54.31 ± 1.22	18	47.93 ± 0.61	18	51.64 ± 0.72	**0.000**	P > C, W > C†

*One-way ANOVA test; †Bonferroni test with Bonferroni correction.

Table 5. Body Weight in Grams for Post-Weaning Rats by Experimental Diet.

Day	PUFA/Western		Control/Western		Western/Western		P-value*	Post-hoc Test
	N	Mean ± S.E.	N	Mean ± S.E.	N	Mean ± S.E.		
25	4	65.73 ± 5.44	5	63.36 ± 1.42	3	69.83 ± 4.83	0.594	
49	4	205.35 ± 27.27	5	192.76 ± 14.83	3	217.47 ± 26.23	0.635	
63	4	258.13 ± 39.74	5	242.26 ± 24.95	3	277.63 ± 42.37	0.807	
70	4	280.10 ± 44.22	5	256.76 ± 28.17	3	296.83 ± 45.07	0.724	
81	4	303.35 ± 49.25	5	277.38 ± 33.62	3	321.80 ± 45.95	0.538	
109	4	336.10 ± 57.03	5	304.62 ± 41.27	3	370.57 ± 42.75	0.457	
120	4	338.95 ± 57.70	5	313.22 ± 44.14	3	370.93 ± 48.41	0.695	

*Kruskal-Wallis test.

4. Discussion

4.1. Protective Metabolic Effects of an Omega-3 PUFA-Rich Maternal Diet during Pregnancy-Lactation

Previous experimental animal studies have shown diets rich in LC-PUFAs may play an important role in the developmental programming of growth and cardiometabolic function [13]-[15]. The current study investigated the potential of a high omega-3 LC-PUFA-rich diet during pregnancy and lactation to improve metabolic biomarkers among offspring consuming a high saturated fat Western diet postweaning in the context of the current global pandemic of obesity-related cardiometabolic disorders associated with the nutrition transition [17]. Our results provide the first evidence suggesting that a balanced omega-3/omega-6 PUFA-rich diet during pregnancy and lactation may provide some modest protection from metabolic dysregulation due to consumption of high saturated fat Western diets in adulthood that increasingly characterize global dietary patterns. Our results showed PUFA/Western offspring had significantly lower insulin resistance and fasting plasma insulin, and lower mean plasma triglycerides than Western/Western animals. Mean fasting plasma insulin, HOMA-IR, and triglycerides were also 10%, 19%, and 14% lower, respectively, than those of Control/Western animals, although these differences were not statistically significant. The fasting plasma glucose of Control/Western animals was 16% higher than Western/Western offspring. The lower mean average HbA1c glucose values of Control/Western animals, compared to Western/Western offspring, however, suggested the lower fasting glucose levels of Western/Western animals were of short duration, and likely the consequence of Western/Western fasting insulin values that were more than double those of Control/Western animals.

4.2. Broader Epidemiological and Public Health Implications

Our findings, showing a trend toward metabolic protection among offspring consuming an omega-3 PUFA-rich prenatal-lactation diet, and subsequently consuming a Western diet postweaning, are especially intriguing given that Yup'ik Alaskans, whose traditional diet is noted for its high omega-3 PUFA content, continue to have a low prevalence (3.3%) of type 2 diabetes [18], despite increasing levels of obesity and a shift to more store bought, and less locally-obtained foods [16]. This stands in sharp contrast to the high type 2 diabetes prevalence among many other Native North American groups [19], first recognized a half century ago following a similar dietary transition in many reservation communities [20]. The existing continuity with a traditional marine-based, omega-3 PUFA-rich diet among Yup'ik Alaskans has been offered as one explanation for what appears to be a protective effect against the development of type 2 diabetes [21] [22]. Consistent with this view, our study's results suggest that omega-3 PUFA-rich, metabolically protective diets may have a developmental component during pregnancy and lactation, and that such protective effects might be leveraged in future diabetes primary prevention programs.

5. Conclusion

The size of the current pilot study is an important limitation and our results should be interpreted with caution. Should our findings, which suggested that maternal prenatal-lactation diets rich in omega-3 PUFAs provide some metabolically protective effects for adult offspring, be confirmed by additional research, the public health potential of type 2 diabetes/metabolic syndrome primary prevention strategies based on this finding could be significant.

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