Clinical and Experimental Health Sciences

The Investigation of The Metabolic Effect of High Salt or Western Diet During Pregnancy and Lactation on Rat Dams and Postnatal Offspring Rats

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ABSTRACT

Objective: This study investigated the metabolic effect of maternal high-salt and western low-protein diets during pregnancy and lactation periods on rat dams and adult offspring.

Method: Female rat dams were divided into four groups and fed with a 1% high salt diet, a Western low-protein diet (high fat and sugar and low protein), or a 1% high salt/western low-protein combined diet (WS) during pregnancy and lactation. Afterward, 95 female and male offspring were divided into groups and fed with those diets until 18 weeks of age. The mothers' and offspring rats' body weights and chow intake were recorded periodically. At 18 weeks of age, blood samples were collected from the offspring. Their blood lipid profiles, leptin, and insulin levels were analyzed.

Results: Rat dams had similar weight changes during pregnancy and lactation. Rats exposed to the Western low-protein and WS diet during pregnancy, lactation, and/or postweaning had lower body weights than the control group. Male adult offspring from control dams and fed high salt were heavier and had higher LDL cholesterol than controls. However, rats from high salt dams and fed a high salt diet had lower body weights than the control group. Plasma insulin and leptin of male rats were not significantly different. Female offspring fed Western low-protein and WS diet in the fetal period or in early childhood had significantly low insulin. However, female rats exposed to Western low-protein and WS diets during pregnancy, lactation, and postweaning had similar insulin to control rats.

Conclusion: Maintaining the maternal diet after lactation prevents the detrimental effect of a low-protein diet on insulin levels. Anti-obesity mechanism may develop in offspring exposed to a high salt diet during the fetal period against salt intake in later life.
Keywords: Fetal period, fetal programming, high salt diet, insulin, leptin, western diet

1. INTRODUCTION

Fetal life is a critical developmental period characterized by rapid cell division. While the genes significantly affect fetal development, research shows that this development is affected by the environment, especially by how the mother is fed. Changes in maternal nutrition and endocrine status during the fetal period can result in developmental adaptations that permanently change the physiology and metabolism of the offspring. That is, nutrition during the fetal period may be related to metabolic, endocrine, and cardiovascular diseases in adult life (1).

Experimental studies have shown that the Western diet (high fat and high sugar) during pregnancy and lactation may have long-term effects on the offspring, such as high blood cholesterol, low insulin sensitivity, and liver damage (2,3). The lack of protein may exacerbate the detrimental effects of the Western diet (4).

Excessive sodium intake is related to obesity, low insulin sensitivity, cardiovascular diseases and mortality (5,6). Moreover, excessive sodium intake increases inflammation and is characterized by decreased renal function and hypertension (7). In experimental studies, high salt intake affects health negatively and increases body weight, blood insulin and glucose levels namely metabolic syndrome in rats (8). Excessive salt intake during the fetal period may adversely affect the fetus (9). High salt intake during pregnancy and lactation may also exacerbate the detrimental impact of the Western diet on the offspring (2).

According to the fetal programming theory, impaired fetal nutrition causes an adaptation, increasing the chance of survival of the fetus (10). Therefore, low-protein, high-fat, and high-salt diets during fetal and lactation periods may lead to an adaptation. Their detrimental effects may

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exacerbate or diminish with standard diet in adulthood (11, 12). Due to fetal adaptation, it is also unclear whether maintaining that impaired and unhealthy diet after weaning through adulthood is more detrimental or less harmful than the standard diet (13).

Therefore, this study investigated the metabolic effect of maternal high salt and western diet during pregnancy and lactation period on rat dams and adult offspring rats.

2. METHODS

2.1. Experimental Procedure

The experimental procedures were approved by the Ankara University Animal Experimentation Ethics Committee under protocol number 2018-17-114. The experiments were performed in the Animal Experimentation and Research Laboratory of Ankara University in accordance with relevant guidelines and regulations outlined by the ethics committee.

2.2. Animal and Experimental Design

Based on earlier studies, a power analysis was performed to determine the sample size (2). The results showed that a sample of 24 would be large enough to detect significant differences. The sample consisted of 28 female virgin Sprague Dawley rats. They were fed ad-libitum from weaning until week 12 and maintained at 20-21 °C, 50-60% humidity, and a 12 h light: 12 h darkness cycle. All female rats weighed 200-250 grams. Then, they were randomly assigned to four dietary groups and fed experimental diets ad-libitum for one week before pregnancy. Experimental groups were fed either (1) a Control (C, n = 8) standard rat chow, (2) a 1% NaCl rat chow, high salt diet (S, n = 7), (3) a 27% kcal from fat and 35% kcal from sucrose natural diet, Western low-protein diet (W, n =6), and (4) a 27% kcal from fat and 35% kcal from sucrose natural diet, +1% NaCl natural diet, Western low-protein + high Salt (WS, n = 7) ad-libitum throughout pregnancy and lactation. Female rats were mated with male rats. After pregnancy was detected, they were individually housed. Dams were maintained on their diets throughout pregnancy and lactation. Body weights and chows exposed to four experimental diets were weighed and recorded on the same day every week before pregnancy, during pregnancy (three weeks), and during lactation (three weeks). The baby rats were fed only breast milk until weaning. To ensure standardized nutrition until weaning, the offspring of mother rats with 8-13 pups in a litter were included in the study. The pups not included in the study were killed using 6-8% carbon monoxide in a closed container.

At weaning (three weeks of age), male and female offspring of dams fed control diet were assigned to four experimental groups: (1) Control diet (CC, (M:6, F:6)), (2) high salt diet (CS, (M:6, F:6)), (3) Western low-protein diet (CW, (M:6, F:6)), and (4) Western low-protein and high salt diet (CWS, (M:6, F:6)).

Male and female offspring of dams fed 1% NaCl diet (high salt) were assigned to two experimental groups: (1) control diet (SC, (M:4, F:4)) and (2) high Salt diet (SS, (M:4, F:4)). Male and female offspring of dams fed Western low-protein diet were assigned to two experimental groups: (1) control diet (WC, (M:4, F:4)) and (2) Western low-protein diet (WW, (M:4, F:4)). Male and female offspring of dams fed Western low-protein and high salt diet were assigned to two experimental groups: (1) control diet (WSC, (M:4, F:4)) and (2) Western low-protein and high Salt diet (WSWS, (M:4, F:4)). The experimental design was illustrated in Figure 1.

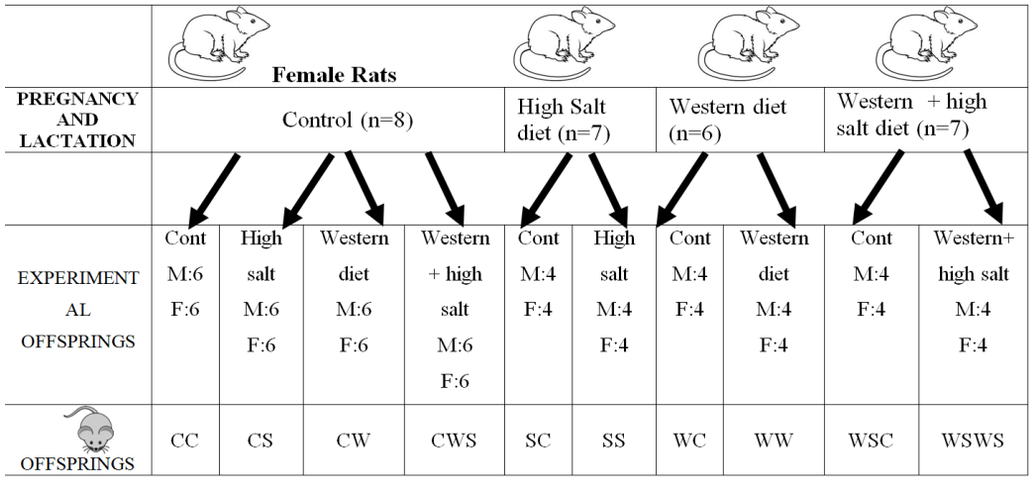

Figure 1. *The experimental design. M, Male; F, Female. CC, rats fed the control diet during pregnancy, lactation and postweaning periods; CS, rats fed the control diet during the pregnancy, lactation periods and high salt diet during postweaning period; CW, rats fed the control diet during the pregnancy, lactation periods and western low-protein diet during postweaning period; CWS, rats fed the control diet during the pregnancy, lactation periods and western low-protein and high salt diet during postweaning period; SS, rats fed the high salt diet during the pregnancy, lactation and postweaning periods; SC, rats fed the high salt diet during the pregnancy, lactation periods and control diet during postweaning period; WW, rats fed the western low-protein diet during the pregnancy, lactation and postweaning periods; WC, rats fed the western low-protein diet during the pregnancy, lactation periods and control diet during postweaning period; WSWS, rats fed the western low-protein and high salt diet during the pregnancy, lactation and postweaning periods; WSC, rats fed the western low-protein and high salt diet during the pregnancy, lactation periods and control diet during postweaning period.*

To assess gender differences, we examined both male and female offspring. After assigning experimental groups to prevent breeding, male and female offspring were housed separately. At 18 weeks of age, blood samples were collected and terminated under anesthesia after overnight fasting. The samples were stored at −20 °C until biochemical analysis.

2.3. Diet and Food Intake

This study used four natural rat chows (MBD animal feed/ Kocaeli). Since comparing the purified Western low-protein diet with the natural standard diet may lead to bias, we also used natural ingredients when preparing the Western low-protein diet. The compositions of chows were prepared based on previous studies (14, 15).

Control diet: Included standard rat chows. It was approx 70% carbohydrate, 18% protein, 12% fat per 100 kcal, 0 mg cholesterol and 0.5 g salt per 100g dry weight. The total energy was 35.5kcal/100g dry chow.

High salt model: Standard rat chow contains 0.2-0.5% NaCl. Therefore, a high salt diet is determined as 1%. It was approx 70% carbohydrate, 18% protein, 12% fat per 100 kcal, 0 mg cholesterol and 1 g salt per 100g dry weight. The total energy was 35.5kcal/100g dry chow.

Western low-protein diet: Consisted of natural ingredients. The composition was formed based on She et al. (14). It was approx 65% carbohydrate, 8% protein, 27% fat, 35% sucrose per 100 kcal, 94 mg cholesterol and 0.5g salt per 100g dry weight. The total energy was 42.3kcal/100g dry chow.

Western low-protein and high-salt diet: Constituted natural ingredients. It was approx 65% carbohydrate, 8% protein, 27% fat, 35% sucrose per 100 kcal, 94 mg cholesterol and 1 g salt per 100g dry weight. The total energy was 42.3kcal/100g dry chow.

2.4. Body Weight

Using a precision scale sensitive to 0.1 g, the rats were weighed every two weeks, from 4 weeks of age until 18 weeks of age. They were weighed in the early evening at the same hour. We did not weigh the rats every week to prevent rats from getting stressed.

2.5. Biochemical Analysis and ELISA Tests

After the experiment, the animals were sedated with Ketamine and Xylazine. Blood samples were collected through an intracardiac puncture after 12 hours of fasting. The sample was centrifuged to obtain the serum and stored at – 20°c. Biochemical variables were determined: fasting glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride.

Insulin and leptin analyses were performed in duplicate in plasma using the sandwich ELISA principle. The concentrations were determined using rat insulin and leptin ELISA kits (Elabscience, Texas, USA).

2.6. Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS, 21.0) at a significance level of < .05. Normality was tested using the Shapiro-Wilk and Levene tests. In rat dams, for the normally distributed groups, a One-Way Analysis of Variance (ANOVA) test was used. If there was a difference between the groups ($p<.05$), the LSD multiple comparison test was performed for post-hoc analysis. Where the assumption of normal distribution was met, but the assumption of homogeneity of variances was not met, the Welch Test was used. If there was a difference between the groups, the Games Howell Test was used for multiple comparisons. Where the normal distribution assumption was not met, the Kruskal-Wallis Test was performed. The Dunn Test was used for multiple comparisons.

In offspring, a two-way mixed ANOVA test was performed. If there was a difference between the groups, the LSD test was applied. Male and female groups were analyzed separately. We applied a logarithmic transform to normalize offspring energy intake. Since the normal distribution assumption was not met, the Kruskal-Wallis Test was performed to compare offspring blood glucose levels, and then, the Dunn Test was used for multiple comparisons. Mean ($\bar{X}$) and standard deviation (SD) values were given in all tables.

3. RESULTS

Body weight changes during pregnancy and lactation were not significantly different ($p>.05$) (Table 1). Dams fed a Western low-protein diet and a Western low-protein and high salt diet (WS) had significantly higher energy but lower protein intake than dams fed control and high salt diets during pregnancy ($p<.05$). During lactation, the energy intake of dams was not significantly different ($p>.05$) (Figure 2).

Table 1. *Body weight changes of rat dams during pregnancy and lactation and 2nd day weight of offspring (n= 6-8)*

	Control	High Salt Diet	Western low-protein Diet	Western low-protein and high salt diet	p
Weight Changes	**X̄±SD**	**X̄±SD**	**X̄±SD**	**X̄±SD**	
Weight gain during pregnancy (g)	113.75± 34.57	106.57± 21.56	107.0± 26.86	124.57± 32.93	.657+
Weight loss during lactation (g)	-20.875± 7.85	-9.86± 25.35	-11.83± 10.57	-10.29± 29.47	.329*
2nd days weight of offspring (g)	8.81±0.92	7.95±1.52	7.39±1.76	7.52±1.37	.226+

**Welch test; + One-way ANOVA test*

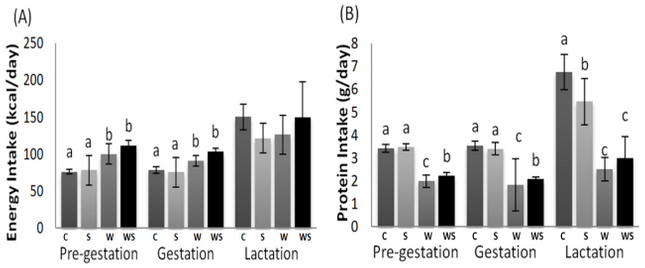

Figure 2. *Energy and Protein Intake of rat dams*
Energy intake of rat dams (n 6-8). (B) Protein intake of rat dams (n 6-8). Values are means, with standard errors represented by vertical bars. a,b,c Mean values with unlike letters were significantly different (p<0.05). C, dams fed the control diet; S, dams fed high salt diet; W, dams fed western low-protein diet, dams fed the western low-protein and high salt diet.

Male offspring groups did not significantly differ in energy intake in the second month. In the second month, female rats exposed to a Western low-protein diet during pregnancy, lactation, and postweaning periods consumed less energy than the CC (control) group (p<.05). In the fourth month, female rats from Western low-protein diet dams and fed a control diet consumed less energy than the control group (p<.05) (Supplementary Table 1). Both male and female adult rats exposed to the WS diet during pregnancy, lactation, and postweaning periods consumed the highest energy in the fourth month (Figure 3).

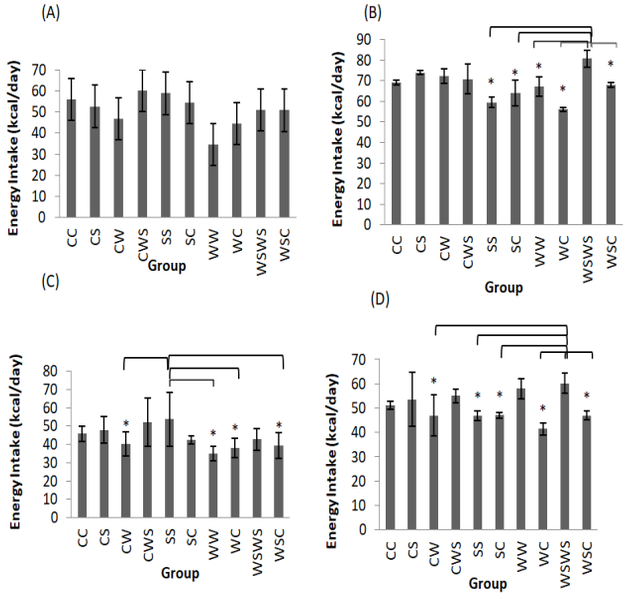

Figure 3. *Energy Intake of offspring*

*(A) Energy intake of males in the second month (n 4–6). (B) Energy intake of females in the second month (n 4–6). (C) Energy intake of males in the fourth month (n 4–6). (D) Energy intake of females in the fourth month (n 4–6). Values are means, with standard errors represented by vertical bars. CC, rats fed the control diet during pregnancy, lactation and postweaning periods; CS, rats fed the control diet during the pregnancy, lactation periods and high salt diet during postweaning period; CW, rats fed the control diet during the pregnancy, lactation periods and western low-protein diet during postweaning period; CWS, rats fed the control diet during the pregnancy, lactation periods and western low-protein and high salt diet during postweaning period; SS, rats fed the high salt diet during the pregnancy, lactation and postweaning periods; SC, rats fed the high salt diet during the pregnancy, lactation periods and control diet during postweaning period; WW, rats fed the western low-protein diet during the pregnancy, lactation and postweaning periods; WC, rats fed the western low-protein diet during the pregnancy, lactation periods and control diet during postweaning period; WSWS, rats fed the western low-protein and high salt diet during the pregnancy, lactation and postweaning periods; WSC, rats fed the western low-protein and high salt diet during the pregnancy, lactation periods and control diet during postweaning period. * displays significant difference*

For all months, offspring fed a Western low-protein diet consumed the least protein regardless of maternal diet. The offspring fed the WS diet come right after those groups in terms of consuming low-protein (Figure 3).

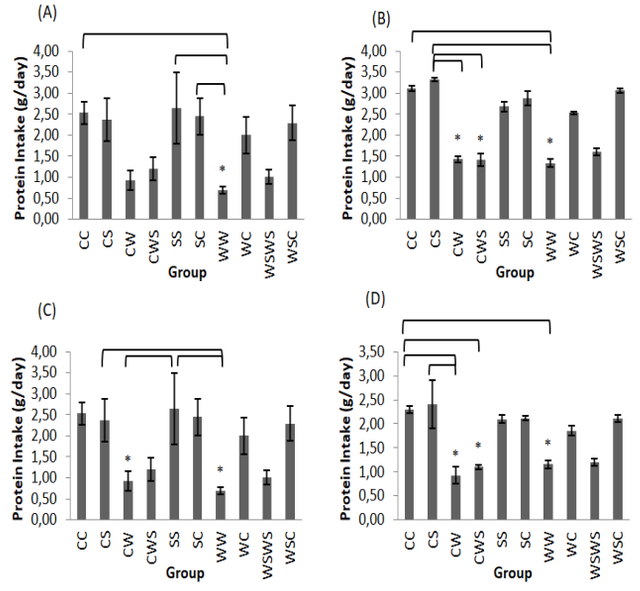

Figure 4. *Protein Intake of Offspring*

*(A) Energy intake of males in the second month (n 4–6). (B) Energy intake of females in the second month (n 4–6). (C) Energy intake of males in the fourth month (n 4–6). (D) Energy intake of females in thefourth month (n 4–6). Values are means, with standard errors represented by vertical bars. CC, rats fed the control diet during pregnancy, lactation and postweaning periods; CS, rats fed the control diet during the pregnancy, lactation periods and high salt diet during postweaning period; CW, rats fed the control diet during the pregnancy, lactation periods and western low-protein diet during postweaning period; CWS, rats fed the control diet during the pregnancy, lactation periods and western low-protein and high salt diet during postweaning period; SS, rats fed the high salt diet during the pregnancy, lactation and postweaning periods; SC, rats fed the high salt diet during the pregnancy, lactation periods and control diet during postweaning period; WW, rats fed the western low-protein diet during the pregnancy, lactation and postweaning periods; WC, rats fed the western low-protein diet during the pregnancy, lactation periods and control diet during postweaning period; WSWS, rats fed the western low-protein and high salt diet during the pregnancy, lactation and postweaning periods; WSC, rats fed the western low-protein and high salt diet during the pregnancy, lactation periods and control diet during postweaning period. * displays significant difference*

Table 2. *Postnatal growth of male and female offspring*

		Body Weight (g)							
		4th week	6th week	8th week	10th week	12th week	14th week	16th week	18th week
SEX	Group	X̄±SD	X̄±SD	X̄±SD	X̄±SD	X̄±SD	X̄±SD	X̄±SD	X̄±SD
MALE	CC	73.3±16.3a	150.2±34.7a	203.8±36.1a	249.8±33.6a	297.8±35.3 b	335.0±36b	372.3±40.3b	386.2±42.9b
	CS	57.7±7.9bc	144.2±12.8ab	221.5±11.7 a	276.0±16.2a	331.7±17.7a	369.3±23.7a	408.0±30.1a	423.0±26.9a
	CW	57.8±4.4b	94.0±10.1 de	133.0±18.9 c	180.4±16.9c	221.8±22.6e	249.4±17.9e	282.0±23.2d	310.6±20.7d
	CWS	54.5±6.5bcd	112.7±17cd	167.8±28.5 b	212.5±29.9b	267.8±26.8cd	294.5±33.7 cd	323.7±33.7c	336.5±32.7cd
	SS	53.5±1.9bcd	114.3±8.3 cd	202.3±12.3 a	252.3±12.7a	284.0±17.1bc	306.0±17.9c	328.5±17.9c	340.8±20.8cd
	SC	55.8±2.2bcd	125.5±5.3bc	208.3±18.2a	260.0±23.7a	303.8±33.9ab	334.8±33.9 ab	347.0±39.4bc	366.3±37.4bc
	WW	29.3±3.7e	52.3±3.2g	87.5±5.9d	116.5±7.0d	163.5±8.4f	198.5±7.7f	193.3±26.2e	239.0±8.8e
	WC	31.3±1.9e	83.5±6.6ef	164.0±13.9b	210.8±13.4bc	245.8±13.4de	273.3±17.6 cde	303.3±15.8cd	320.3±22.9d
	WSWS	47.3±7.4d	94.8±15.9de	167.3±24.1b	207.5±25.8bc	259.0±31.4cd	295.5±36cd	328.5±40.9c	345.3±46.1cd
	WSC	46.3±2.4cd	115.8±8.6cd	205.3±14.5a	255.5±19.7a	310.3±18.8ab	347.8±20.4ab	385.0±22ab	406.8±25.5ab
FEMALE	CC	72.0±13.2a	122.3±16.7ab	167.8±13.3ab	202.8±16a	232.8±16.5a	247.3±17.9a	264.5±18.1a	269.3±15a
	CS	56.7±5.2bc	126.8±8.9a	168.0±16.1ab	201.0±16.8a	219.8±22.5ab	227.2±21.4ab	240.5±25.3ab	248.8±27.3ab
	CW	48.5±3.4de	78.2±6.1ef	106.3±8e	141.8±8.5d	172.3±8.5e	189.8±6.3cd	206.5±8.9cd	217.0±6.5cde
	CWS	47.8±7de	97.3±16.9cd	137.8±16.6cd	169.3±17.1bc	195.3±19.5cd	213.3±23.6bc	222.5±23.8bcd	227.3±22.8bcde
	SS	57.7±4.6b	121.3±4.9ab	175.0±5.2a	199.7±12.3a	215.3±20.6abc	228.3±15ab	245.0±13.5ab	249.7±10ab
	SC	53.0±3.6cd	111.8±6.9bc	159.3±9.2ab	187.3±9.2ab	204.3±8.9bc	213.3±8.2bc	228.0±13.8bc	233.0±12.9bcd
	WW	34.0±8fg	56.3±10.2g	88.0±13.8f	115.3±14.8e	154.5±22.2e	175.0±26.5d	223.0±12.6bcd	201.5±28.9e
	WC	31.8±4.3g	79.8±11.03ef	128.8±17.7d	156.5±23.8cd	172.0±27de	186.8±31.3cd	198.0±32.4d	206.3±31.6de
	WSWS	41.0±4.6efg	86.5±11de	135.8±18.3cd	165.0±22.9bc	198.3±27.7bcd	217.5±29.7b	232.8±26.8bc	238.5±23.9bc
	WSC	42.3±4.8ef	96.0±2.9cd	152.3±4.7bc	183.5±11.3ab	209.0±11.4abc	223.0±13.8ab	235.8±20.9b	242.8±27.8abc

C, control diet; S, high salt diet; W, western low-protein diet; WS, western low-protein and high salt diet; CC, rats fed the control diet during pregnancy, lactation and postweaning periods; CS, rats fed the control diet during the pregnancy, lactation periods and high salt diet during postweaning period; CW, rats fed the control diet during the pregnancy, lactation periods and western low-protein diet during postweaning period; CWS, rats fed the control diet during the pregnancy, lactation periods and western low-protein and high salt diet during postweaning period; SS, rats fed the high salt diet during the pregnancy, lactation and postweaning periods; SC, rats fed the high salt diet during the pregnancy, lactation periods and control diet during postweaning period; WW, rats fed the western low-protein diet during the pregnancy, lactation and postweaning periods; WC, rats fed the western low-protein diet during the pregnancy, lactation periods and control diet during postweaning period; WSWS, rats fed the western low-protein and high salt diet during the pregnancy, lactation and postweaning periods; WSC, rats fed the western low-protein and high salt diet during the pregnancy, lactation periods and control diet during postweaning period.

All male offsprings displayed weight gain over the weeks, all female offsprings displayed weight gain over the weeks except for 18th week ($p<.05$)

^{a,b} Mean values with unlike superscript letters were significantly different($p<.05$).

Table 3. *Blood parameters of adult offspring*

		Leptin (pg/mL)	Insulin (pg/mL)	Glucose (mg/dL)	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglyceride (mg/dL)
SEX	**Group**	**X̄±SD**	**X̄±SD**	**X̄±SD**	**X̄±SD**	**X̄±SD**	**X̄±SD**	**X̄±SD**
MALE	CC	721.49±54.13	2513.33±846.23	193.0±97.74ab	43.83±9.22	12.83±5.67a	58.3±12.43a	60.67±14.56
	CS	629.40±97.38	2941.67±335.58	270.5±122.97ab	54.83±15.11	22.33±7.34bc	66.42±17.7a	89.50±21.27
	CW	734.80±79.06	2400.14±457.76	131.2±16.75ab	47.2±3.83	13.80±1.92ad	68.48±8.83a	87.60±30.23
	CWS	668.20±129.69	2528.69±729.75	108.33±22.3b	55.67±7.71	21.83±4.79bcd	72.33±10.05a	80.0±12.02
	SS	588.04±48.09	2553.57±612.22	353.5 ±52.5a	58.75±10.24	21.50±5.26abcd	72.68±9.92a	88.50±18.16
	SC	626.86±55.12	2372.14±333.40	160.0 ±10.68ab	53.75±5.74	19.25±5.97abcd	72.43±5.87a	77.50±7.51
	WW	654.30±53.35	2139.29±365.57	155.25±19.91ab	53.5±8.96	14.50±7.42acd	87.6±9.96ab	81.50±33.43
	WC	679.72±29.31	3408.93±365.44	126.75±14.17ab	46.25±6.18	14.0±3.37acd	64.85±4.80a	114.25±40.43
	WSWS	617.84±29.62	2578.57±574.75	186.0 ±14.79ab	51.25±6.95	15.5±5.8acd	81.13±6.67b	64.75±10.11
	WSC	678.02±23.12	2620. 36±321.74	157.75±27.1ab	52.75±8.42	26.5±14.15d	63.83±21.29a	75.25±24.85
	p	.72**++**	.122+	**.003**++	.260+	**.035**+	**.038***	.179*
FEMALE	CC	839.08±111.52a	2713.45±597.30a	148.17±36.0abc	54.33±10.13ab	12.83±5.12ab	81.53±10.57a	117.67±43.44ab
	CS	747.94±166.32ab	2501.67±609.42ab	129.5±17.92bc	56.17±9.99ab	12.67±3.08ab	80.08±14.2ab	94.67±22.21ab
	CW	762.43±69.83a	1878.1±621.28cde	106.17±29.38c	44.5±4.28b	7.33±1.86c	83.62±8.44a	53.33±8.52b
	CWS	644.01±113.85ab	1871.55±368.82cde	125.33±27.08bc	55.17±8.52ab	12.0±3.90ab	82.48±8.12a	142.5±29.18a
	SS	690.28±106.83ab	1373.04±158.91e	147.25±24.49abc	59.75±14.5ab	12.75±4.99ab	80.78±5.12ab	159.0±83.32ab
	SC	665.28±48.58ab	2448.21±391.46abc	123.25±13.07bc	51.75±1.26b	9.0±2.16bc	86.63±6.68a	78.25±20.69ab
	WW	775.07±102.3ab	2334.29±518.84abc	113.67±3.06c	48.0±11.14ab	11.0±2.65abc	68.47±11.35b	153.33±58.53ab
	WC	628.71±53.03ab	2088.93±177.83bcd	115.5±5.07c	45.0±9.45ab	8.50±2.38bc	74.23±5.13ab	78.50±34.28ab
	WSWS	798.94±53.7a	2170.0±96.23abc	169.0±2.45a	64.5±0.41a	16.0±0.82a	109.05±1.18c	55.0±0.82b
	WSC	564.19±45.25b	1459.46±472.35de	160.25±8.77ab	51.25±4.99ab	11.75±3.77ab	86.2±1.52a	78.0±28.30ab
	p	**.002***	**.001**+	**<.001***	**<.001***	**.040+**	**<.001+**	**<.001***

**Welch test, +One way ANOVA test; ++ Kruskal-Wallis test; [a,b] Mean values with unlike superscript letters were significantly different(p<.05).*

C, control diet; S, high salt diet; W, western low-protein diet; WS, western low-protein and high salt diet; CC, rats fed the control diet during pregnancy, lactation and postweaning periods; CS, rats fed the control diet during the pregnancy, lactation periods and high salt diet during postweaning period; CW, rats fed the control diet during the pregnancy, lactation periods and western low-protein diet during postweaning period; CWS, rats fed the control diet during the pregnancy, lactation periods and western low-protein and high salt diet during postweaning period; SS, rats fed the high salt diet during the pregnancy, lactation and postweaning periods; SC, rats fed the high salt diet during the pregnancy, lactation periods and control diet during postweaning period; WW, rats fed the western low-protein diet during the pregnancy, lactation and postweaning periods; WC, rats fed the western low-protein diet during the pregnancy, lactation periods and control diet during postweaning period; WSWS, rats fed the western low-protein and high salt diet during the pregnancy, lactation and postweaning periods; WSC, rats fed the western low-protein and high salt diet during the pregnancy, lactation periods and control diet during postweaning perio

As shown in Table 2, among male offspring, the control group had the highest weight in the fourth week. Afterward, male offspring from control dams and fed high salt diet (CS) group gained more weight than the control group and had the highest weight in the twelfth and following weeks. The WSC group also gained more weight than the control offspring for all weeks and had the second highest weight among adult male rats from the 8th week on. The offspring fed the Western low-protein diet had significantly lower weight than the other groups ($p<.05$). Male WC offspring come right after those groups in terms of having low weight.

Among female offspring, the control group had the highest weight for all weeks. Female offspring exposed to the Western low-protein diet during pregnancy, lactation, and postweaning periods had the lowest weight for all weeks, except for one week. The offspring from control dams and fed the Western low-protein diet (CW) had the second lowest weight till the twelfth week. After the twelfth week, the WC group had the second lowest weight. The rats fed WS diet come right after those groups in terms of having low weight. Since the weight gain of the offspring from high salt dams and fed control diet (SC) decreased over the weeks, they were among the low-weight rat groups after the 12th week (Table 2).

Regarding blood parameters, insulin levels of male offspring groups did not vary significantly ($p>.05$). Male rats exposed to the WS diet during pregnancy and lactation but fed the control diet had higher LDL cholesterol levels than the control group ($p<.05$). Triglyceride and total cholesterol levels of male offspring groups did not vary significantly ($p>.05$). The female control group had the highest leptin and insulin levels. The female WSC group had lower leptin and insulin levels than the control group ($p<.05$). The female offspring from control dams and fed Western low-protein and WS diet had lower insulin levels than the control group ($p<.05$). The female offspring exposed to high salt diet during pregnancy, lactation, and postweaning periods had higher triglyceride level than the control group but not significantly ($p>.05$) (Table 3).

4. DISCUSSION

Our results showed that body weight changes in rat dams fed the Western low protein diet and WS diet during pregnancy were not different from the control group (16, 17). In those studies, the daily energy intakes of dams fed the Western diet during pregnancy were not different from the control group. While our rats fed the Western low protein and WS diet during pregnancy consumed more energy than the control group, they gained similar weights. The protein content of our Western low-protein diet was 8.48%. However, the ideal protein intake in rats during growth, pregnancy, and lactation should be 12% of the dry raw material [National Research Council (NRC)] (18). If the protein is around 17-23%, the maximum growth will be supported by 95-100% (19). Therefore, the protein rate in the dry matter of the Western low-protein diet was below the required level. Brito et al. (20) stated that the weight gain of rats fed low-protein (5%) but high-fat and energy diet was lower than control dams. They reported that while energy and fat content were high, fat absorption might be impaired, thus preventing body weight gain. In lactation, similar to Merle et al. (17) and Alexandre-Gouabau et al. (16), weight changes in rats fed Western low-protein and WS diets were not different from control dams. The result may be caused by similar energy intake. The rat dams fed a high salt diet had similar energy intake and body weight change to the control dams (21, 22). While the reason is obscure (23), relatively short exposure time (pregnancy and lactation last six weeks) may have caused this result.

Both male and female offspring exposed to the Western low-protein diet during pregnancy and lactation had less weight than the control groups. A meta-analysis concluded that a maternal diet with a high protein/non-protein ratio leads to higher offspring weight. Postweaning diet had no effect on adolescent and adult weights (24). However, this result was inconsistent with our findings. The body weight of the offspring fed the control diet and having dams on the WS diet were similar to the control group. The offspring from dams on a Western low-protein diet and fed a control diet were lighter than the control group. Maternal high salt intake and a Western low-protein diet may have caused a change in appetite mechanisms. Coupe et al. (25) reported that orexigenic peptide mRNA expressions (NPY and AgRP) in the hypothalamus of offspring of dams fed a low-protein diet were higher than those from control dams. Increased orexigenic peptides cause hyperphagia and high energy intake, closing the weight gap. Our female offspring from dams on the WS diet and fed the control diet had lower leptin and insulin levels than the control group. Leptin reduces food intake and increases energy expenditure (26) Therefore, low leptin levels may be related to higher weight gain. Low insulin in the blood also leads to weight gain by increasing food intake and decreasing energy expenditure by stimulating orexigenic peptides, particularly NPY (27).

Adult male rats from control dams fed a high salt diet had higher weights than the control group. This result was consistent with human studies (28, 29). Salt improves food taste, thus increasing food consumption (29). However, most animal studies reported conflicting results (2, 30, 31). High salt diets in rat models are ≥4%, which is too much to reflect excessive salt consumption in humans (2, 32). The World Health Organization (WHO) and the American Dietary Guide recommend salt consumption to be less than 5 g/day (33). Salt consumption is 10-15 g/day in today's Western societies (34). An adult consumes an average of 1200 g of food daily (35). Salt intake constitutes 0.8%-1.2% of the total food consumption. One g salt in 100 g chow/diet better reflects the salt content in high salt diets. Our male rats fed the high salt diet gained weight regardless of energy and protein intake, as Ma et al. (36) found in humans. Excessive salt consumption, regardless of energy intake, causes more fat storage in the body (37). Chronic high salt intake leads to hyperinsulinemia, excessive secretion of insulin, an anabolic hormone, accelerates the conversion of glucose into lipids. Increased lipogenic activity causes adipocyte hypertrophy and increased body fat (37). Lanaspa et al. found hyperleptinemia

and leptin resistance in adolescent male rats fed with high salt water (1%) (8). Rats gained more weight than the control group by increasing food consumption and decreasing energy expenditure. Male rats from control dams and fed a high salt diet had neither higher leptin nor insulin levels than the control group. Decreased energy consumption or increased testosterone may be the key factor. Like Lanaspa et al. (8), we found higher LDL cholesterol and triglyceride levels than the control group. High body weight is associated with higher LDL cholesterol and triglyceride levels (38). However, we found that female rats from control dams and fed a high salt diet had similar weight, energy and protein intake, and blood parameters to the control group. Female rats handled a high salt diet better than males (39). Therefore, metabolic response to high salt diets may be gender specific.

We found rats from control dams fed a Western low protein diet and WS diet had lower body weights than the control group regardless of energy intake. Low protein intake during the developmental period leads to delayed growth. Postweaning low protein intake is associated with lifelong low offspring weights (40). Despite the low weight, we observed high LDL cholesterol levels in male rats fed Western low-protein and high-salt diets but not Western low-protein diets alone. A human study reported that the LDL/HDL ratio increases up to 12 g/day of salt consumption, reflecting our study's exact high salt model (41). While some researchers indicate that the relationship between salt intake and blood lipids is through hyperinsulinemia and insulin resistance, we found no difference in insulin levels (42). Impaired gut microbiota by a high salt diet may lead to high blood cholesterol. A high-salt diet affects gut health by altering gut microbiota composition. This alteration is characterized by a lack of diversity and increasing *Lachnospiraceae* and *Ruminococcus* but decreasing *Lactobacillus* group (43). *Lactobacillus* species, such as *L. acidophilus* ATCC 314, *L. bulgaricus* FTCC 0411, and L. *casei* MB3, are cholesterol-reducing bacteria, have rate-limiting 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and regulate bile salt hydrolase activity. Deficiency in that species may have caused high blood cholesterol levels (44).

Our female rats from control dams fed the Western low-protein diet (CW) and WS diet (CWS) had lower insulin levels than the control group. Our female rats from dams on the Western low-protein diet, and WS diet and fed the control diet (WC and WSC) had lower insulin levels than the control group. Low protein intake during the fetal period decreases vascularization of the pancreas and reduces the number of islets of Langerhans and β cells. The decrease in β cells causes insufficient insulin secretion (25, 40, 45). In the fetal period and early life/after weaning, pancreas islets, vascularization, and β cells are vulnerable to a low protein diet due to ongoing anatomical and functional growth (40). Rats from dams on high-fat diets have smaller islets size of Langerhans and lower insulin secretion (46). Insulin levels did not differ among male rats. Therefore, we concluded female rats are more vulnerable to low protein intake during critical development periods. We did not observe low insulin levels in female rats exposed to low protein during gestation, lactation, and postweaning periods (WW and WSWS), unlike Gosby et al. (45). This result reminds us of the Thrifty Phenotype Hypothesis, proposing a metabolic adaptation more advantageous if undernutrition sustains. If the postnatal environment supplies abundant nutrition, those individuals will be at increased risk of obesity and Type II Diabetes Mellitus (47). Considering the opposite results of Gosby et al. high fat and high sugar intake during all critical developmental periods may have affected fetal programming (45). While it is speculative, high fat and high sugar and low protein intake may have caused epigenetic modifications in female offspring.

Female rats from high salt dams and fed a control diet (SC) had lower body weight despite similar food intake. A study reported that the mice had lower body weight due to high energy expenditure despite similar food intake (48). Increased brown adipose tissue activity may have contributed to increased energy expenditure in offspring of high salt dams (49). Piecha et al. (50) reported that rats from high-salt dams had higher sodium excretion than the control group due to differences in intestinal absorption. Therefore, low nutrient absorption may be another reason for lower weight gain despite higher food intake (2). Other studies reported those results in male rats (49, 50). There should be more studies to investigate gender factors.

Male adult rats from high salt dams and fed high salt diet (SS) had lower energy intake and body weight than the control group in this study, like Piecha et al. (50). Since we did not find any study searching appetite mechanism in those rats and there was no difference in leptin and insulin levels, drawing a conclusion based on appetite could be speculative. The offspring of high salt dams had high sodium excretion due to low intestinal absorption. The high salt consumption after weaning may also have exacerbated sodium excretion and nutrient malabsorption because they produce more feces than other rats on low sodium diet (50).

5. CONCLUSION

Postweaning a high salt diet leads to higher body weight in male rats. However, a maternal high-salt diet prevents that detrimental effect. We also found regardless of energy, fat, and salt intake, low protein intake during critical developmental period (gestation, lactation, and early childhood) causes growth retardation and low adult body weight in rats. Also, female rats fed a low-protein diet in the fetal period or in early childhood were more vulnerable than male rats and had significantly low insulin levels. However female rats exposed to western low-protein and WS diet during pregnancy, lactation and postweaning periods had similar insulin levels to control group. Maintaining the maternal western low-protein diet after lactation prevents detrimental effect of low-protein diet on insulin levels. Exposure to high salt diet in fetal life may diminish obesity effect of high salt. Further research is needed to examine metabolic responses to maternal diet with respect of gender and fully define the mechanisms of the findings.

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Design of the study: MEÖ, NYA
Acquisition of data for the study: MEÖ
Analysis of data for the study: MEÖ
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