Revista Médica Electrónica
Rev Méd Electrón
v. 47. 2025
ISSN: 1684-1824
Artículo de investigación

Influence of estrogens deficiency on body weight and glucose levels

Influencia de la deficiencia de estrógenos en el peso corporal y los niveles de glucosa

Ronald Alexis de-la-Cruz-Rodríguez[1*] https://orcid.org/0000-0001-6401-4936

Lizeth Susana Pacpac-Herrera[2] https://orcid.org/0009-0004-4146-5442

César Franco-Quino[1] https://orcid.org/0000-0003-1773-3019

Adrián Segundo Mallma-Medina[1] https://orcid.org/0000-0002-6121-9431

Eliberto Ruiz-Ramírez[1] https://orcid.org/0000-0002-5340-7168

Elías Ernesto Aguirre-Siancas[1] https://orcid.org/0000-0003-4713-5511

[1] Universidad Nacional Mayor de San Marcos. Lima, Peru.

[2] Universidad Peruana Cayetano Heredia. Lima, Peru.

[*] Corresponding author: ronaldalexisdelacruzrodriguez@gmail.com

ABSTRACT

Introduction: Estrogens deficiency, characteristic of menopause or surgical removal of the ovaries could be related to weight gain and altered glycaemia, but the physiological mechanisms are unknown, generating a scientific gap.

Objective: To assess the influence of estrogens deficiency on body weight and glucose levels.

Methods: Twelve, female, BALB/c mice were equally and randomly divided into two groups: sham surgery and ovariectomy. Mice in the ovariectomy group had their ovaries removed bilaterally, while those in the sham surgery group had their ovaries exposed without removal. Twelve weeks later the mice were sacrificed following the protocol. The weights of the mice were monitored one day before surgery and then monthly for three consecutive months. Preprandial and postprandial glucose levels were also measured before surgery and at 12 weeks after surgery.

Results: An increase in body weight was observed from the first month in favor of the ovariectomized group ($p<0.05$); also, preprandial and postprandial glucose levels were increased in the ovariectomized group.

Conclusion: Estrogens deficiency leads to increased body weight and altered postprandial and preprandial glucose levels in female mice.

Key words: glucose, blood glucose, body weight, ovariectomy, estrogens.

RESUMEN

Introducción: La deficiencia de estrógenos, característica de la menopausia o extirpación quirúrgica de los ovarios, podría estar relacionada con el aumento de peso y la alteración de la glicemia, pero los mecanismos fisiológicos son desconocidos, generando una brecha científica.

Objetivos: Evaluar la influencia de la deficiencia de estrógenos en el peso corporal y en los niveles de glucosa.

Métodos: Doce ratones hembra de la cepa BALB/c fueron divididos de forma aleatoria y equitativa en dos grupos: cirugía simulada y ovariectomía. A los ratones del grupo ovariectomía se les extirpó bilateralmente los ovarios, mientras que a los del grupo cirugía simulada se les expuso los ovarios sin ser removidos. Doce semanas después, los ratones fueron sacrificados siguiendo el protocolo. Se controlaron sus pesos un día antes de la cirugía y luego mensualmente durante tres meses consecutivos. También se midieron los niveles de glucosa preprandial y posprandial antes de la intervención quirúrgica y a las 12 semanas después de la cirugía.

Resultados: Se observó incremento de peso corporal a partir del primer mes a favor del grupo ovariectomizado ($p < 0,05$); asimismo, se incrementaron los niveles de glucosa preprandial y posprandial en el grupo ovariectomizado.

Conclusión: La deficiencia de estrógenos genera incremento de peso corporal y alteración de los niveles de glucosa posprandial y preprandial en ratones hembras.

Palabras clave: glucosa, glucemia, peso corporal, ovariectomía, estrógenos.

Recibed: 2025/03/03.

Acepted: 2025/09/06.

Reviewers: Silvio Faustino Soler-Cárdenas and Brian Zequeira-García.

INTRODUCTION

Obesity and diabetes mellitus are two closely related chronic diseases, both of which have an impact on public health. Obesity is characterized by the presence of excessive adipose tissue in different parts of the body and diabetes mellitus is a disease in which the body generates decreased insulin production, increased glycaemia levels and insulin resistance.[1,2] These disorders may disproportionately affect different age groups, particularly women during the postmenopausal transition.[3]

The hypothalamus plays a key role in metabolism by activating neurons that control appetite.[4] Activation of estrogens receptor type α in hypothalamic proopiomelanocortin neurons inhibits appetite in experimental animals. In addition, the presence of estrogens would reduce the expression and activity of neuropeptide Y and ghrelin, both peptides with orexigenic effects.[5,6] Estrogens may also potentiate the action of leptin by increasing the expression and sensitivity of its receptors in the hypothalamus, thus inhibiting appetite.[7] This hormonal decrease alters energy homeostasis, increasing intra-abdominal fat.[8]

Estrogens may play a key role in regulating glucose levels, participate in insulin production, enable uptake of glucose levels from the gut and liver; modulate insulin sensitivity, and enhance insulin secretion by increasing pancreatic β-cell mass.[9,10] However, deficiency of this hormone induces a significant decrease in glucose transporters such as GLUT-1, GLUT-3 and GLUT-4.[11] In addition, parenteral estrogens treatment regulates fasting glucose levels in non-obese ovariectomized mice.[8,9]

Unfortunately, there are not many drugs available to treat these alterations. Because of increasing life expectancy, many women will spend half of their lives in an estrogens-deficient condition. It is unknown precisely how estrogens deficiency alters the molecular mechanisms that lead to imbalances in glucose levels and body weight. However, estrogens play a key role in energy balance and glucose homeostasis, which opens the door to new therapeutic applications for an increasingly large segment of the female population, yet the involvement of several factors, makes it difficult to combat these syndromes. The aim of the present study is to assess the influence of estrogens deficiency on body weight and glucose levels.

METHODOS

Study design: Experimental study carried out in the biotherium of the Faculty of Medicine of the Universidad Nacional Mayor de San Marcos (UNMSM).

Population and sample: There were used 12 mice of the BALB/c strain, 13 weeks old, from the INS. After a one-week ambience, they were randomly and equally divided into two groups: Sham surgery (SHAM) and ovariectomy (OVX).

Ovariectomy: Intraperitoneal injectable anesthesia was administered using ketamine (100mg/kg) and xylazine (10mg/kg). This combination was performed in order to maximize anesthetic effects and minimize adverse effects.[12]

Subsequently, the hair was trimmed and depilatory cream (Depile™) was applied to the dorsolateral regions, approximately in an area of 3cm x 3cm, followed by asepsis with iodopovidone. Lidocaine 2% was administered then subcutaneously at a superficial level in the working area. A 1cm skin incision was made over the skin, and then the dorsolateral abdominal muscles were cut to gain access to the peritoneal cavity. Once inside, the uterus and ovary were identified, surrounded by a considerable amount of adipose tissue. (Fig. 1)[13]

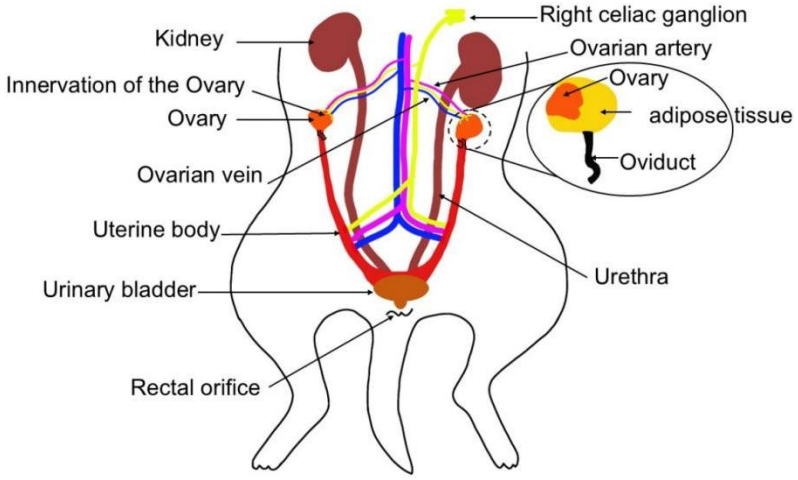

Fig. 1. Schematic representation of the mouse's internal anatomy, highlighting structures relevant to the experimental model.

Once the ovaries are located, they are exteriorized and the artery, vein, ovarian nerve and distal uterine horn are ligated; then the ovaries are cut and removed (figure 1).[14] Finally, the internal and external tissue is sutured in planes with 5/0 resorbable thread. Once this procedure is completed, the same procedure is repeated on the other side. In the case of sham surgery, only the ovaries are exteriorized and returned to their original position. (Fig. 2)

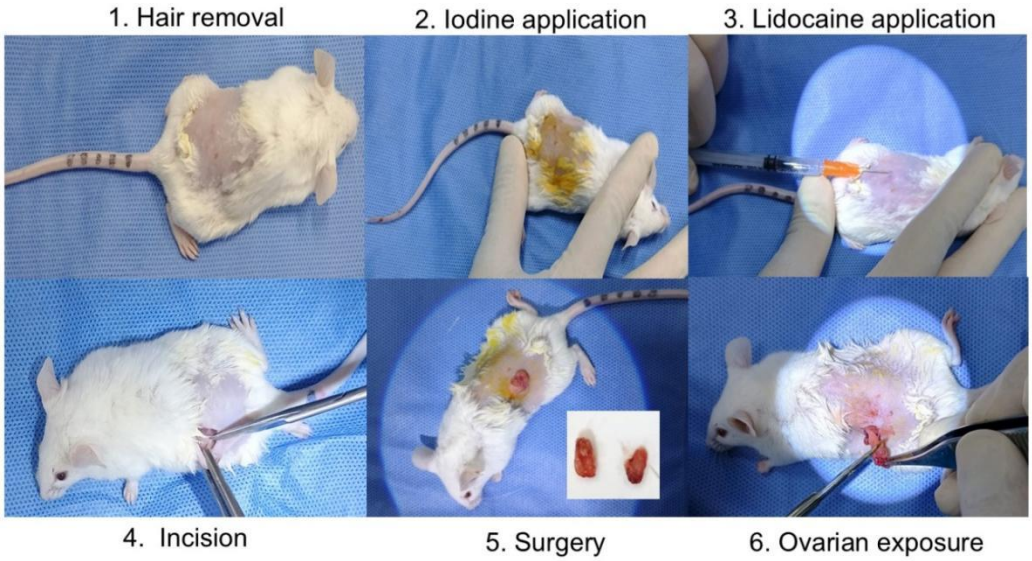

Fig. 2. Ovariectomy surgical procedure showing the key stages of the experimental approach.

Postoperative management: Topical rifocin was applied for 3 days (Rifamycin sv sodium salt 1g/100mL).[15] Paracetamol was administered orally for 3 days (Oral solution 100mg/mL, preparation consisted of mixing 1.4ml paracetamol with 300ml water).[16]

Weight control: Weight was measured on four occasions using an ADAM™ precision balance, UK. Measurements were taken before ovariectomy, at 1 month, at 2 months and at 3 months before the euthanasia of the animal.

Monitoring of glucose levels: Postprandial and preprandial glucose levels were assessed on four separate occasions with a glucometer (ACCU-CHECK™, China), before ovariectomy and at three months before euthanasia. To obtain the blood sample, the mouse was restrained and a cut was made at the tip of the tail and then squeezed from the base of the tail upwards to generate the drop of blood; the first drop was wiped with a gauze and the second drop was received on a test strip.[17,18]

Data analysis: Jamovi software version 2.3.28 was used. For data analysis, the Mann-Whitney U test, Welch's t-test, repeated measures Friedman test, and Wilcoxon signed-rank test were employed, considering a 95% confidence level. Additionally, the Durbin-Conover post hoc test was applied, and effect size was measured.

Ethical considerations: This research was approved by the ethics committee of the faculty of dentistry of the UNMSM (N°034-CEI-FO-2024).

RESULTS

The present study included 12 BALB/c mice, which were randomly divided into two groups: SHAM and Ovariectomy (OVX).

Body weight assessment

Body weight data assessed on four occasions are shown. A significant difference in body weight was observed from the first month of control, with an increase in favor of the OVX group ($p<0.05$). The values are detailed in table 1. Furthermore, intragroup weight measurements were analyzed to assess monthly variations over the course of the evaluation period. In image A (SHAM) there is a significant difference in relation to baseline weight (before oophorectomy) and the other months, except for the relationship between the first month and the third month. Image B shows a significant difference at all times, except between the second month and the third month. (Fig. 3)

Table 1. Intergroup body weight values evaluated at different periods

Weight (g)	Group	n	Mean	Median	SD	P value
Baseline	OVX	6	32,2	32,5	1,17	
	SHAM	6	31,7	31,5	1,21	0,502
1st month	OVX	6	40,7	40,5	1,86	
	SHAM	6	35,8	36,5	2,48	0,005
2nd month	OVX	6	46,5	45,5	3,78	
	SHAM	6	36,5	37,5	2,59	0,005
3rd month	OVX	6	48,8	48,5	1,47	
	SHAM	6	39,0	40,1	2,78	0,005

Mann-Whitney U ($p<0,05$), SD: Standard deviation and baseline: Before ovariectomy.

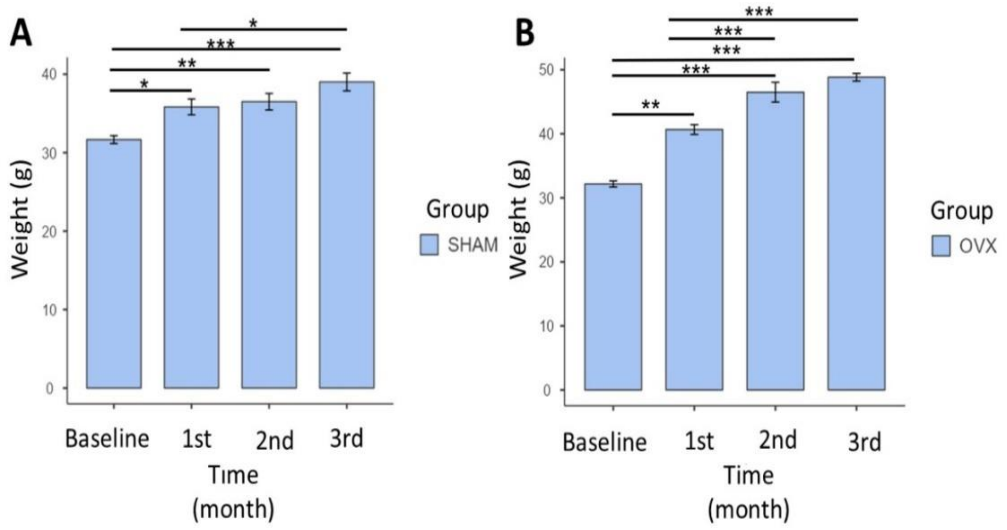

Fig. 3. Variations over the course of the evaluation period.

*p<0,05, **p<0,01 and ***p<0,001. The Friedman test was used, followed by the Durbin-Conover post hoc test.

Assessment of plasma glucose levels

Pre-prandial and post-prandial glucose levels measured in the OVX and SHAM groups are shown; a significant difference was observed in the third month, with an increase in favor of the OVX group (p<0.05), as shown in tables 2 and 3.

Table 2. Pre-prandial baseline and third month glucose levels

Glucose (mg/dL)	Group	n	Mean	Median	SD	p-value
Preprandial-baseline	OVX	6	99,83	100,00	2,64	0,747
	SHAM	6	99,33	98,50	2,73	
Preprandial-third month	OVX	6	140,83	134,50	23,91	0,005
	SHAM	6	96,50	97,50	6,09	

Mann-Whitney U test ($p<0.05$), SD: Standard deviation and baseline: before ovariectomy.

Table 3. Baseline and third month postprandial glucose levels

Glucose (mg/dL)	Group	n	Mean	Median	SD	P value
Postprandial-baseline	OVX	6	131	127,50	14,37	0,722
	SHAM	6	128,67	129	6,12	
Postprandial-third month	OVX	6	170,67	167,50	16,07	<0,001
	SHAM	6	130,5	132,50	7,06	

Levene's test 0.010 for baseline postprandial and 0.031 for third month postprandial. Variances are not equal. Welch's t-test ($p<0.05$). SD: Standard deviation and baseline: before ovariectomy.

Intra-group glucose levels were also assessed by comparing baseline preprandial values with those at month 3 and baseline postprandial values with those at month 3. This assessment was performed in both groups, with a significant difference in favor of the OVX group and an effect size of 1 in the OVX group ($p<0.05$). (Fig. 4)

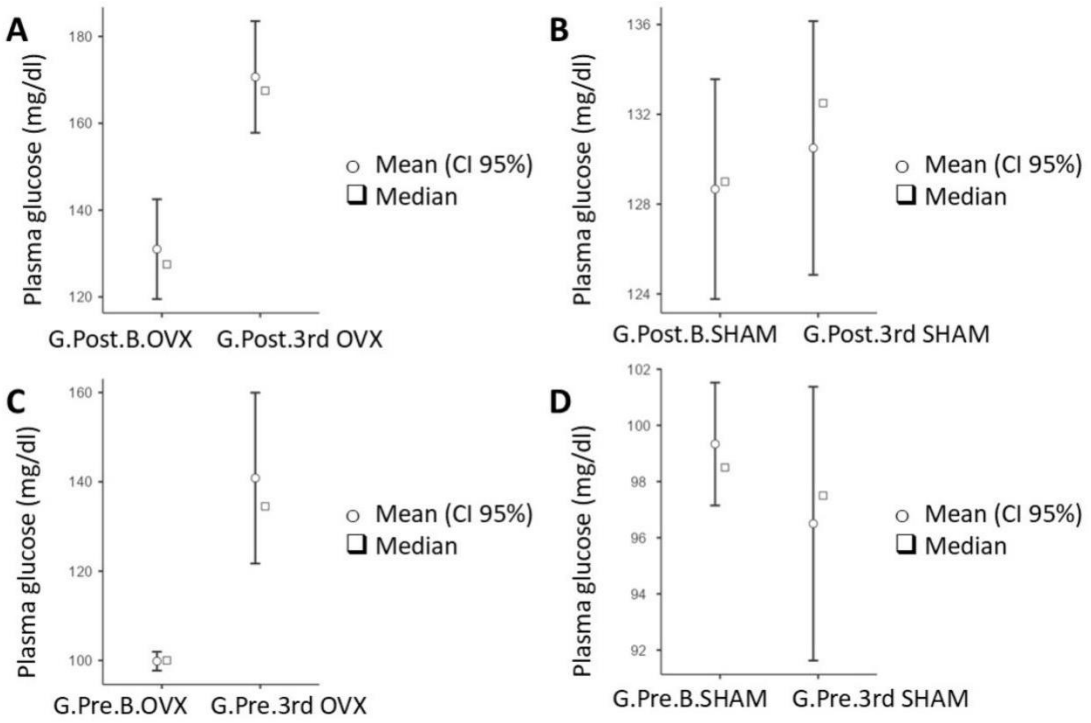

Fig. 4. Intra-group relationship.

G= glucose, B= baseline (before ovariectomy), OVX= ovariectomy, SHAM= sham surgery, pre= preprandial and post= postprandial. The Wilcoxon test was applied.

DISCUSSION

Estrogens deficiency caused a significant increase in body weight over a three-month period in ovariectomized mice. The results are consistent with studies by other authors indicating that body weight increases with decreasing estrogens levels.[19,20] Studies in ovariectomized models indicate that weight gain is associated with estrogens loss and can be reversed by hormone replacement therapy.[15,21]

Weight gain would be influenced by low estrogens hormone levels, because the decrease modifies body fat metabolism, increases ghrelin levels and prevents leptin action. It could also be associated with the growth of adipose tissue, since it would increase the action of aromatase, which triggers a compensatory effect.[5] These results are therefore similar to clinical research correlating weight gain during the menopausal transition.[15,22]

This research demonstrated a significant increase in preprandial glucose levels over a three-month period in the ovariectomized group of mice. The preprandial baseline measurements show similarity to those measurements carried out by Kangudia Mbaya, et al.[23] Their results, in time, are consistent with research by other authors, indicating

that a decrease in estrogens in the body influences changes in glycaemia levels.[13,24,25] The changes in glycaemia could be associated with estrogens deficiency, which would reduce the passage of glucose transporters (GLUT1, GLUT3 and GLUT4), as well as limit insulin secretion and production; thereby, no significant difference in the study groups was evident when altering the estrogens receptors.[10,11,15] It could be due to the short evaluation time of six weeks as well as the variety of animal strain used for the research.[10]

The results of this investigation are similar to clinical research showing an association between estrogens depletion and high blood glucose levels in postmenopausal women.[26,27] Also in this analysis, postprandial glucose levels were assessed in relation to estrogens deficiency and a significant increase was found at 12 weeks. This increase in postprandial glucose levels could be explained by the low presence of estrogens, particularly estriol (E3), a key hormone that plays important roles in glucose metabolism. E3 may reduce the rate and magnitude of the rise in blood glucose after oral glucose administration by reducing intestinal glucose transport. In addition, E3 may be involved in the regulation of postprandial glucose levels in pregnant women. This was determined as pregnant women have 1,000 times more E3 than non-pregnant women at later stages and have lower postprandial glucose levels compared to healthy non-pregnant women.[15,28]

The strength of this study includes its clinical applicability, addressing the impact of estrogens deficiency on body weight and altered glucose levels, a common problem in postmenopausal women. This research could provide insight into the therapeutic and preventive role of estrogens, which could be applied in public health programs. Limitations of this study include limited financial resources, which prevent work on a large number of samples, and the use of more advanced techniques, which could have provided more accurate information. In conclusion, estrogens deficiency leads to altered pre- and postprandial glucose levels and weight gain over time in BALB/c mice. These findings underline the importance of addressing estrogens deficiency.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Ronald Alexis de-la-Cruz-Rodríguez: conceptualization, formal analysis, investigation, methodology, supervision, writing-original draft, writing-review and editing.

Lizeth Susana Pacpac-Herrera: formal analysis, investigation, methodology, supervision, writing-original draft, writing-review and editing.

César Franco-Quino: formal analysis, writing-review, editing, and investigation.

Adrián Segundo Mallma-Medina: writing-review, editing, writing-original draft, and investigation.

Eliberto Ruiz-Ramírez: writing-review, editing, conceptualization, and methodology.

Elías Ernesto Aguirre-Siancas: writing-review, editing, methodology, and supervision.

HOW TO CITED THIS ARTICLE

de-la-Cruz-Rodríguez RA, Pacpac-Herrera LS, Franco-Quino C, Mallma-Medina AS, Ruiz-Ramírez E, Aguirre-Siancas EE. Influence of estrogens deficiency on body weight and glucose levels. Rev Méd Electrón [Internet]. 2025. [cited: date of access];47:e6448. Available from: http://www.revmedicaelectronica.sld.cu/index.php/rme/article/view/6448/6353