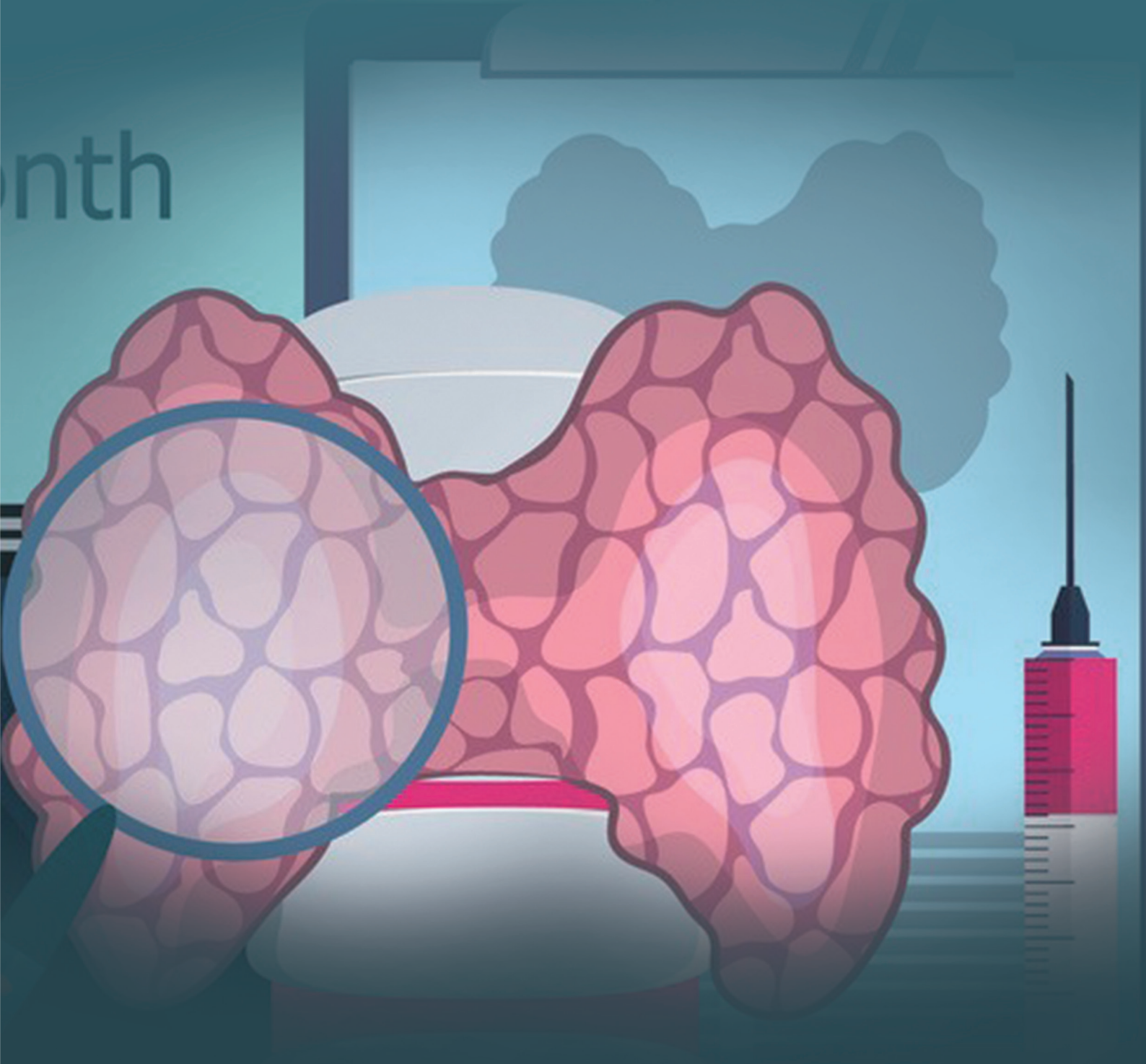
BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research

Volume 4 · Issue 2 · July 2022 · ISSN 2630-5224(Online)



Volume 4 Issue 2 • July 2022 • ISSN 2630-5224 (Online)

Journal of Endocrinology Research

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Volume 4 | Issue 2 | July 2022 | Page1-30
Journal of Endocrinology Research

Contents

Articles

1 **Histopathological Characteristics of Folliculo-stellate Cells in Pituitary Glands of Wild Type, Obese and High-fat Diet Induced Mice**
José Filipe Melo Gonçalo Borrecho Noelia Martínez-Sánchez Francisco Tortosa

10 **Do Endocrinopathies Differ in Most Prevalent Hemoglobinopathy of Middle East: Beta-thalassemia?**
Salma Ahi Mohsen Adelpour Bahareh Haghdoost Ali Jaberi

Mini Review

17 **Evaluating the Effect of Irisin on Obesity-Concerning Physical Activity**
Onur Oral Pınar Tatlibal Evangelia Stavropoulou

Review

21 **Cortisol Response in Breast Cancer: The Role of Physical Activity and Exercise**
Margarida Marinho Sílvia Rocha-Rodrigues

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Histopathological Characteristics of Folliculo-stellate Cells in Pituitary Glands of Wild Type, Obese and High-fat Diet Induced Mice

José Filipe Melo[1] Gonçalo Borrecho[2] Noelia Martínez-Sánchez[3] Francisco Tortosa[1,2*]

1. Instituto de Anatomia Patológica, Faculdade de Medicina, Universidade de Lisboa, Lisbon, 1649-028, Portugal
2. Center for Interdisciplinary Research Egas Moniz (CiiEM), Monte da Caparinca, Caparica, 2829-511, Portugal
3. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, OX3 7LE, UK

ARTICLE INFO

Article history
Received: 31 January 2022
Accepted: 3 March 2022
Published Online: 4 March 2022

Keywords:
Folliculo-stellate cells (FSC)
S-100 protein
Basal metabolism
Pituitary

ABSTRACT

The anterior pituitary gland regulates growth, metabolism, and reproduction by secreting hormones. Folliculo-stellate cells (FSC) are non-endocrine cells located among hormone-producing cells in the anterior pituitary glands, but little is known about the exact roles of those cells. Although, with their net organization, they seem to have an important role in the hormonal cells regulation and maintenance.

In this work, the first ever made in this area, 33 pituitaries of three groups of mice (18 wild type [WT], 11 genetically obese [OB] and 4 under a high-fat diet [HFD]) were studied in order to determine if there was any relation between the number of FSC and alterations of the basal metabolism in each group of mice. For that, immunohistochemical staining using the S-100 protein was used and also the Image-J software, to calculate the percentage of FSC present in each sample.

The authors found that, although there wasn't any significant difference between WT and OB mice, the group of HFD mice tend to have substantially higher percentage of FSC than the mice from other groups. This might suggest some yet unknown link between diet, precisely with a high-fat diet, and the presentation of FSC in the anterior pituitary.

1. Introduction

The pituitary gland (pituitary) is a highly complex endocrine structure that has the ability to respond to multiple signals from both central and peripheral locations [1]. It regulates and acts on different systems of the body, being in close relationship with the hypothalamus [2].

Anatomically there are two lobes, an anterior or adenohypophysis and a posterior or neurohypophysis, of whose physiology and histology there are long and consensual descriptions [3]. Regarding the roles of the anterior pituitary, its action on growth through GH, on lactation with

*Corresponding Author:
Francisco Tortosa,
Instituto de Anatomia Patológica, Faculdade de Medicina, Universidade de Lisboa, Lisbon, 1649-028, Portugal; Center for Interdisciplinary Research Egas Moniz (CiiEM), Monte da Caparinca, Caparica, 2829-511, Portugal;
Email: franciscotortosa.pathology@gmail.com

DOI: https://doi.org/10.30564/jer.v4i2.4426

prolactin, on gonadal activity through FSH and LH, as well as on adrenal and thyroid activity with ACTH and to TSH, respectively, are well known [4]. As for the neurohypophysis, the effects of vasopressin, involved in water balance, and oxytocin, responsible for uterine contractions and lactation, stand out [5]. Although much is still unknown [6]. In the anterior pituitary there are also described cells traditionally reported as support, the folliculo-stellate cells (FSC) [7]. These cells, characterized by their star-like appearance and ability to form follicles, do not appear to have the ability to produce hormones [8,9]. However, due to their network organization, they seem to play an important role in the regulation and maintenance of the population of hormonal cells, as they conduct stimulatory or inhibitory factors from the hypothalamus and transport the secretory products of the gland [10,11].

Even so, the pathophysiological role of the FSC network is still poorly understood. After a long period of research on the pituitary, several hypotheses have been raised about the role of FSC in the adenohypophyseal machine, functions as varied as paracrine regulation, cell turnover and neuroimmune crosstalk, but many problems still remain without solution [12-14].

Other studies also suggest that these cells, which are positive for the S-100 protein, due to their heterogeneous and plural behavior, may have an extrapituitary origin [15,16]. Its proliferation may result from the invasion of the anterior pituitary lobe by other structures during organogenesis [17,18].

While some new studies tried to approach these cells from some different perspectives, none of the ones published focused on the relationship between FSC and alterations of the basal metabolism, although the known relationship between pituitary hormones and metabolism. With this work, the first of its kind, we seek to understand whether there is a relationship between FSC and changes in basal metabolism associated with obesity, using the study of wild type (WT), obese (OB) and induced high-fat diet (HFD) mice.

2. Materials and Methods

B6 (C57BL/B6J, own production of the *Gulbenkian Institute of Science*) and ob/ob (Jackson Laboratory [JAX], stock no. 000632) mice were used in this study. All mice used for the study were male and were kept at controlled temperature and humidity under a 12 hour light/dark cycle. The use of only male mice it was done to limit the hormonal variation that occurs in females and that could affect this study's results. Food and water were provided *without restrictions*. The diet-induced obesity (DIO) model was generated by placing the animals on an HFD at the eighth week and lasting 12 weeks. All animal procedures were approved by the ethics committee of the *Gulbenkian Institute of Science* and by the *National Network of Entities Responsible for Animal Welfare*.

2.1 Histology and Immunohistochemistry

For the preparation of this work, 37 pituitary glands were obtained: 19 from WT mice (of which, due to lack of quality of the remaining samples, we were able to evaluate 18), 14 OB mice (of which, due to lack of quality of the remaining samples, we were able to evaluate 11) and 4 HFD (all evaluated). Sacrifice and sample collection were performed between 01/11/2017 e 01/12/2017.

The mice's pituitary glands were dissected and fixed with 4% buffered formaldehyde immediately after extraction. Subsequently, after performing the macroscopic examination of the glands, they were processed according to the usual technical procedures for obtaining paraffin blocks for complete histological evaluation.

The presence and distribution of FSC was studied by immunohistochemistry in deparaffinized 3-micron histological sections, subjected to antigen recovery and incubated with an individual antibody directed against the specific cellular protein S-100β (polyclonal; provenance: Leica; dilution : 1/400) [19-22].

All samples were evaluated by an experienced pathologist. The staining index for S-100 was calculated as the percentage of positive cells in at least 500 cells in the areas of highest immunostaining, analyzed under an optical microscope with 400x magnification. In all cases, the percentage of FSC was also calculated with the help of an immunohistochemical analysis image processing software (Image J 1.49. National Institutes of Health, United States).

2.2 Statistical Framework

A basic statistical and comparative analysis appropriate to the data distribution was performed. For this, parametric and non-parametric (Kruskal-Wallis) one-way ANOVA statistical tests were used. A value of $p<0.05$ was considered statistically significant, also resorting to non-parametric multiple comparisons (Tukey-Kramer-Nemenyi, Conover's and Dunn's) between the different groups.

3. Results

After analyzing the pituitary glands, the data presented in Tables 1, 2 and 3 were obtained, which represent the percentage of FSC in each pituitary gland evaluated.

In WT mice, Table 1, there was a relative prevalence of FSC ranging from 3% to 60%. Percentage distributions are presented in Figures 1 and 2.

Table 1. Percentage of FSC in WT mice - Percentage of FSC in relation to the total tissue observed in the pituitary sample of each WT mouse.

WT 1	WT 2	WT 3	WT 4	WT 5	WT 6	WT 7	WT 8	WT 9	WT 10	WT 11	WT 12	WT 13	WT 14	WT 15	WT 16	WT 17	WT 18
17%	15%	35%	11%	25%	20%	3%	18%	20%	12%	17%	9%	60%	24%	46%	13%	16%	26%

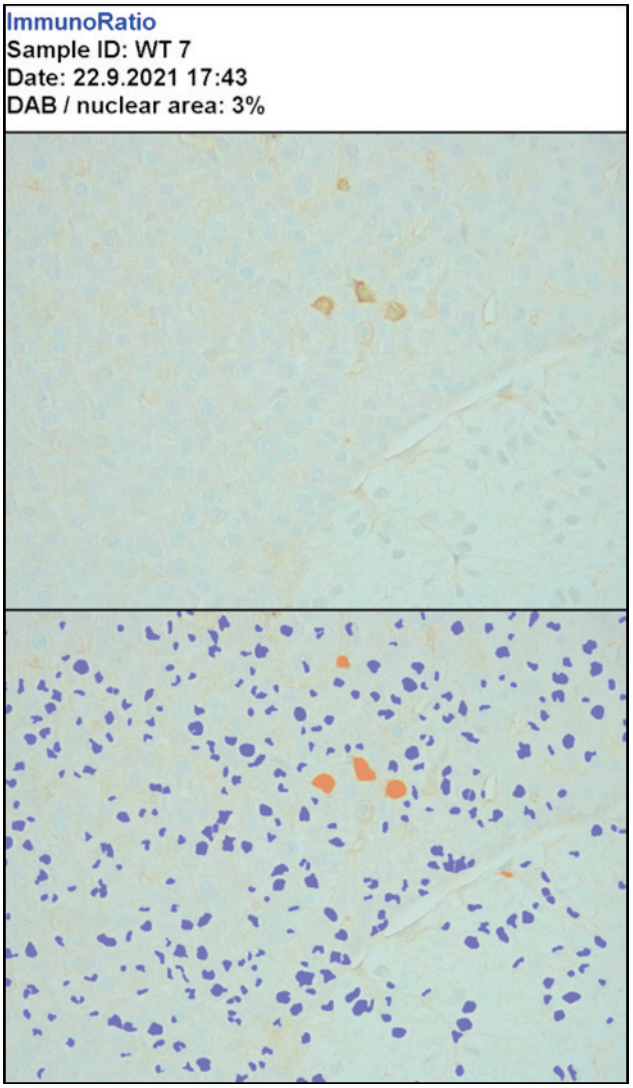


Figure 1. Immunohistochemical staining of S-100 positive cells in the WT7 mouse - Microscopic images of the pituitary gland of a mouse revealing a 3% prevalence of FSC: Above, the immunohistochemical technique (using an antibody against the S-100 protein); below, with an image processor program, the proportionality of these cells (in brown) in relation to the remaining cells (nuclei in blue) is shown (Image J, ImmunoRatio plugin).

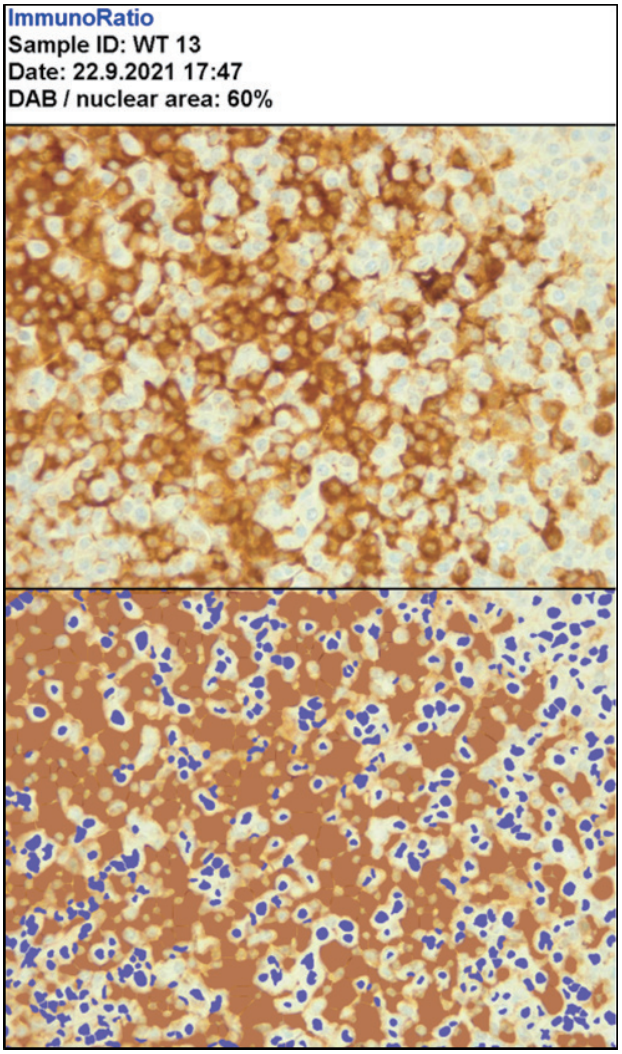


Figure 2. Immunohistochemical staining of S-100 positive cells in the WT13 mouse revealing a 60% prevalence of FSC.

The OB mice, in Table 2, have a similar distribution of FSC, ranging from 10% to 54%. Percentage distributions are presented in Figures 3 and 4.

The group of HFD mice, in Table 3, only varied between 85% and 93% (Figure 5).

Table 2. Percentage of FSC in OB mice - Percentage of FSC in relation to the total tissue observed in the pituitary sample of each OB mouse.

OB1	OB2	OB3	OB4	OB5	OB6	OB7	OB8	OB9	OB10	OB11
22%	25%	54%	10%	17%	16%	12%	26%	25%	19%	29%

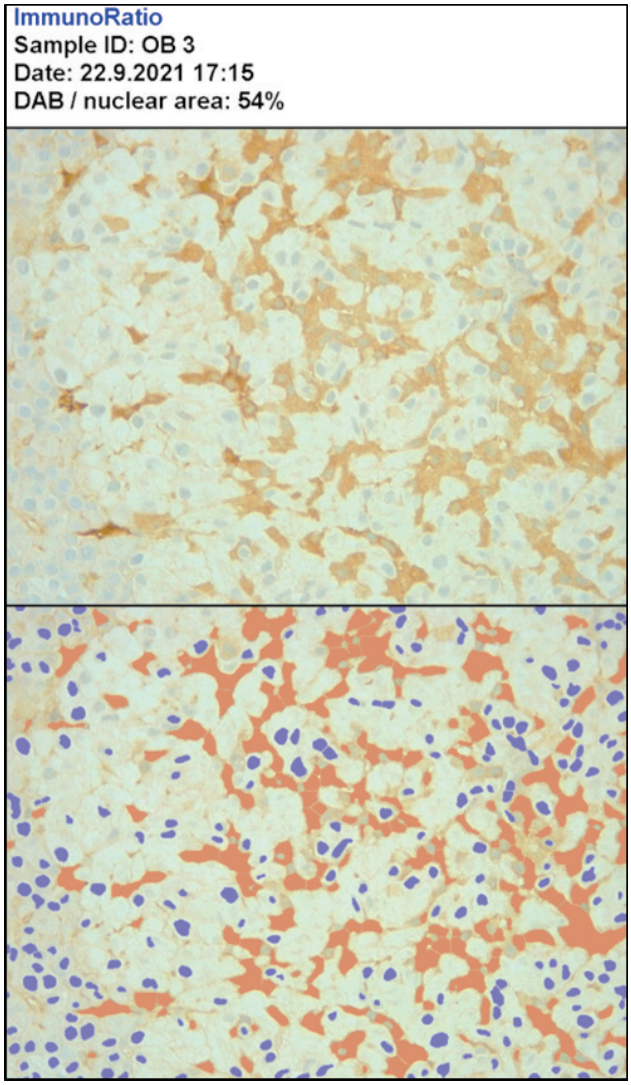


Figure 3. Immunohistochemical staining of S-100 positive cells in the OB3 revealing a 54% prevalence of FSC.

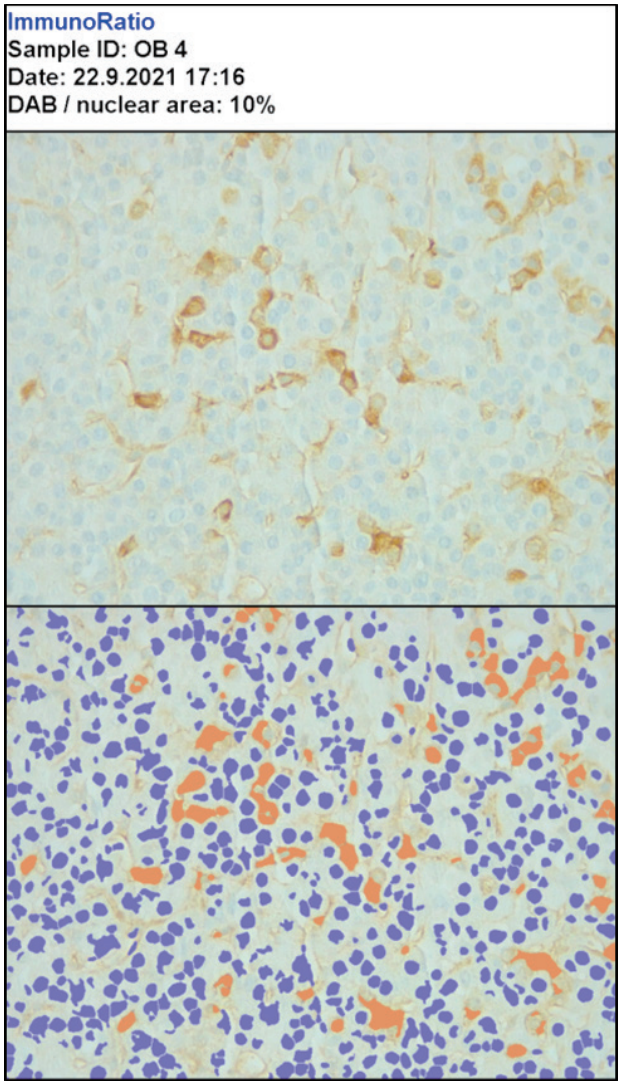


Figure 4. Immunohistochemical staining of S-100 positive cells in the OB4 mouse revealing a 10% prevalence of FSC.

Table 3. Percentage of FSC in HFD mice - Percentage of FSC in relation to the total tissue observed in the pituitary sample of each HFD mouse.

HFD1	HFD2	HFD3	HFD4
89%	93%	85%	93%

As seen in Table 4, an average of 22% FSC in WT mice, 23% FSC in OB mice and 90% FSC in HFD mice could be obtained. None of the data obtained was considered statistically as an outlier, having obtained a dispersion of data that could mean a tendency for the percentage of FSC to be higher when eating a diet rich in fatty acids.

In addition to what has already been described, visualizing the data in the scatter plot (Figure 6), it can be seen that the data referring to the HFD group are always higher than the data from the other two groups, which in turn are distributed very similar.

This difference is better visualized when the boxplots are analyzed in Figure 7. In these, there is a total overlap of the boxplots referring to the WT and OB groups, with no overlap of these to the boxplot of the HFD group.

Based on these descriptive data, as well as the values of the respective averages (22% [WT], 23% [OB] and 90% [HFD]) and standard deviations (0.14% [WT], 0.12% [OB] and 0.04% [HFD]), the data seem to point towards the hypothesis that the means of the observations of the groups are significantly different, more particularly between the HFD group and the rest.

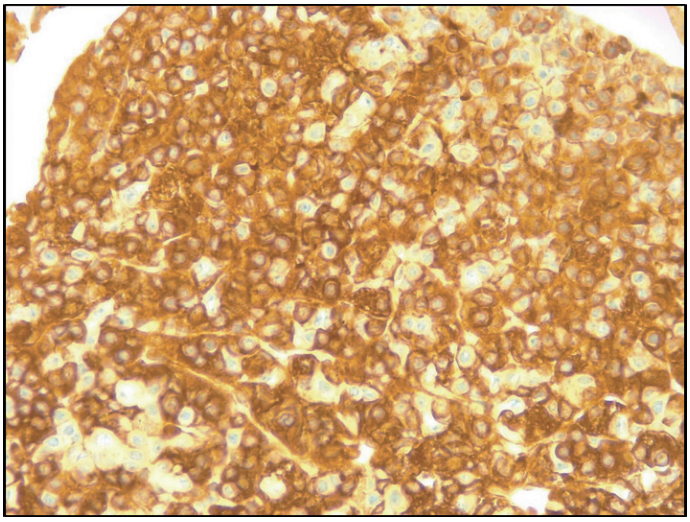


Figure 5. Immunohistochemical staining of S-100 positive cells in the HFD4 mouse - Microscopic images of the pituitary of a mouse revealing a 93% prevalence of CFE (immunohistochemical technique using an antibody against the S-100 protein).

Table 4. Descriptive analysis of the data obtained - Qualitative statistics of each group of mice including Extremes, Quartiles, Interquartile Range, Limit of Upper and Lower Outliers and Mean.

	WT	OB	HFD
Minimum	3%	10%	85%
1ª Quartile	13.50%	16.50%	88%
3º Quartile	24.75%	25.50%	93%
Maximum	60%	54%	93%
IQR	11%	9%	5%
Outliers Lower Limit	-3%	3%	81%
Outliers Upper Limit	77%	68%	101%
Mean	22%	23%	90%

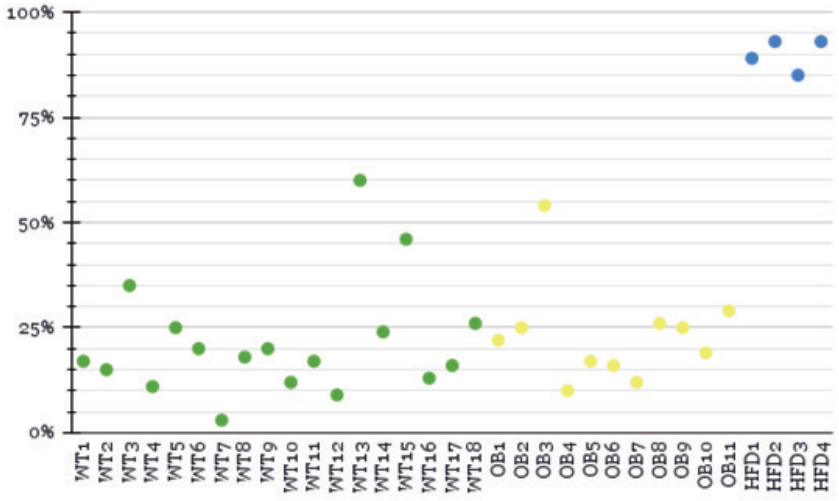


Figure 6. Dispersion of the percentage of FSC in each mouse - Graphic representation of the percentage of FSC in the pituitary of each mouse (WT - green; OB - yellow and HFD - blue).

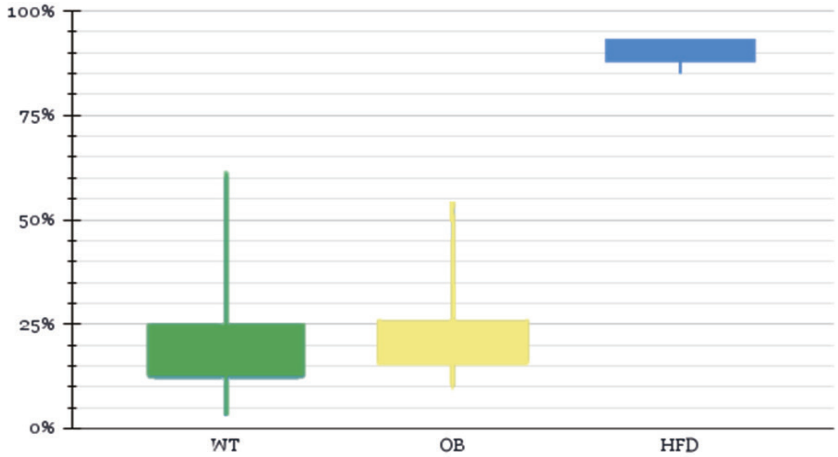


Figure 7. Boxplots distribution of the percentage of FSC in the different groups of mice - Graphic representation of the distribution of the variation of the numerical data obtained through quartiles.

Using the parametric and non-parametric one-way ANOVA (Kruskal-Wallis) statistical tests, we found that the hypothesis of equality of means/medians is rejected by both when they present p-value <0.05 (<<0.001 and 0.005, respectively), with significant differences between the observation groups.

As the assumptions of homogeneity of variances and normality were not verified and in order to better assess the differences between groups, non-parametric multiple comparisons were used (Tukey-Kramer-Nemenyi, Conover's and Dunn's - Tables 5, 6 and 7, respectively) having always verified the existence from two homogeneous groups: one formed by the WT and OB observation groups and the other formed by the HFD observations (p <0.05).

Table 5. Tukey-Kramer-Nemenyi.

	HFD	OB
OB	0,0215	-
WT	0,0032	0,7906

Table 6. Conover's.

	HFD	OB
OB	0,0099	-
WT	0,0015	0,7206

Table 7. Dunn's.

	HFD	OB
OB	0,0156	-
WT	0,0033	0,5133

4. Discussion

As mentioned above, there is a tendency for the percentage of FSC in HFD mice to be higher than in WT and OB mice. This could mean two different things, as we are looking at percentages: an increase in the number of FSC in HFD mice; or that is a decrease in other cell populations in these mice, consequently increasing the relative prevalence of FSC in the pituitary glands of these mice.

As for WT and OB mice, there does not seem to be a significant difference between the two groups of samples, so it can be inferred that FSC are not affected by genetically induced obesity.

In the light of current knowledge, we can try to explain the results obtained through a range of aspects.

It is now known that *in vitro* the Hedgehog signaling pathway leads FSC to stimulate the production and release of GH by the anterior pituitary, but the production of CXCL12 by FSC can have the same effect [23,24]. By establishing a communication network between the FSC and with the hormone-producing cells, this may correspond *in vivo* to a physiological reaction mechanism to the increased intake of fatty acids, evident in HFD mice, influencing the expression of FSC [25,26].

However, recent studies show that S-100 positive cells in the anterior pituitary may not be just FSC, but may even mark pituitary stem/progenitor cells [27,28]. Previously, it was hypothesized that the FSC themselves could be a type of pluripotent adult stem cell [29-31]. This question is still open [32].

It is also suggested by Higuchi, M., *et al.* (2014) [33], that these S-100 positive cells will have the ability, albeit infrequently, to become hormone-producing cells, or the fact of recognizing in folliculo-stellate-like cells an intermediate stage in the differentiation to hormone-producing

cells [34,35]. Through the expression of SOX2 in progenitor cells, the variation in the prevalence of FSC can be influenced [36]. Hence, the increase in FSC in HFD mice may be due to this physiological response of cell differentiation in the attempt to adapt to a diet rich in fatty acids.

On the other hand, the plurality of cells that showed positive S-100 staining may influence the results in the sense that the differences observed may be due not to changes in FSC, but in other populations of S-100 positive cells.

For this exclusion, in future studies, perhaps another specific marker for FSC should be used, or a panel of markers that would make the marking more specific. These could include, among others, Claudin-9, a marker of tight junctions of FSC [37], Aldolase C [38] or IL-6 itself, which is stimulated by Adenosine, produced by FSC [39,40].

FSC are also defined as the major intrapituitary source of cytokines and growth factors [41]. Therefore, there is a need, given the existence of several subtypes of FSC, to characterize them individually and arrange specific markers that allow their study [42,43]. As well as their characterization depending on the age of the individual [44,45].

5. Conclusions

In the vast world that can be a small organ like the pituitary, there are still many questions to be clarified regarding FSC. With this work, we intend to pave the way for what can be followed in further investigations.

Despite the discrepancy between the number of samples within each group, which will need confirmation in studies with a more significant sample, we can intuit that a diet rich in fatty acids will lead to an increase in the relative prevalence of FSC in mice, or at least, to an increase in S-100 positive cell populations, whose physiological mechanisms, both the origin of the alterations and the consequences thereof, should be studied later.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Perez-Castro, C., Renner, U., Haedo, M.R., et al., 2012 Jan. Cellular and molecular specificity of pituitary gland physiology. Physiological Reviews. 92(1), 1-38. DOI: https://doi.org/10.1152/physrev.00003.2011.

[2] Kioussi, C., Carriere, C., Rosenfeld, M.G., 1999 Mar. A model for the development of the hypothalamic–pituitary axis: transcribing the hypophysis. Mechanisms of Development. 81(1-2), 23-35. DOI: https://doi.org/10.1016/s0925-4773(98)00229-9.

[3] Mihai, R., 2014 Oct. Physiology of the pituitary, thyroid, parathyroid and adrenal glands. Surgery (Oxford). 32(10), 504-512. DOI: https://doi.org/10.1016/j.mpsur.2014.07.008.

[4] Yeung, C.M., Chan, C.B., Leung, P.S., et al., 2006 Mar. Cells of the anterior pituitary. International Journal of Biochemistry & Cell Biology. 38(9), 1441-1449. DOI: https://doi.org/10.1016/j.biocel.2006.02.012.

[5] Amar, A.P., Weiss, M.H., 2003 Jan. Pituitary anatomy and physiology. Neurosurgery Clinics of North America. 14(1), 11-23. DOI: https://doi.org/10.1016/s1042-3680(02)00017-7.

[6] Inoue, K., Couch, E.F., Takano, K., et al., 1999 Aug. The structure and function of folliculo-stellate cells in the anterior pituitary gland. Archives of Histology and Citology. 62(3), 205-218. DOI: https://doi.org/10.1679/aohc.62.205.

[7] Allaerts, W., Vankelecom, H., 2005 Jul. History and perspectives of pituitary folliculo-stellate cell research. European Journal of Endocrinology. 153(1), 1-12. DOI: https://doi.org/10.1530/eje.1.01949.

[8] Perryman, E.K., 1989 Feb. Folliculo-stellate cells of the pituitary gland. Bioscience. 39(2), 81-88. DOI: https://doi.org/10.2307/1310906.

[9] Le Tissier, P.R., Hodson, D.J., Lafont, C., et al., 2012 Aug. Anterior pituitary cell networks. Frontiers in Neuroendocrinology. 33(3), 252-266. DOI: https://doi.org/10.1016/j.yfrne.2012.08.002.

[10] Le Tissier, P.R., Mollard, P., 2021 Nov. Renewing an old interest: Pituitary folliculostellate cells. Journal of Neuroendocrinology. 33(11), e13053. DOI: https://doi.org/10.1111/jne.13053.

[11] Pires, M., Tortosa, F., 2016 Oct. Update on pituitary folliculo-stellate cells. International Archives of Endocrinology Clinical Research. 2, 006. DOI: https://doi.org/10.23937/2572-407X.1510006.

[12] Baes, M., Allaerts, W., Denef, C., 1987 Feb. Evidence for functional communication between folliculo-stellate cells and hormone-secreting cells in perifused anterior pituitary cell aggregates. Endocrinology. 120(2), 685-691. DOI: https://doi.org/10.1210/endo-120-2-685.

[13] Marin, F., Stefaneanu, L., Kovacs, K., 1991 Dec. Folliculostellate cells of the pituitary. Endocrine Pathology. 2(4), 180-192. DOI: https://doi.org/10.1007/BF02915206.

[14] Allaerts, W., Carmeliet, P., Denef, C., 1990 Jun. New perspectives in the function of pituitary folliculo-stellate cells. Molecular and Cellular Endocrinology.

71(2), 73-81.
DOI: https://doi.org/10.1016/0303-7207(90)90244-3.

[15] Yamashita, M., Qian, Z.R., Sano, T., et al., 2005 May. Immunohistochemical study on so-called follicular cells and folliculostellate cells in the human adenohypophysis. Pathology International. 55(5), 244-247.
DOI: https://doi.org/10.1111/j.1440-1827.2005.01820.x.

[16] Stojilkovic, S.S., 2001 Nov. A novel view of the function of pituitary folliculo-stellate cell network. Trends in Endocrinology and Metabolism. 12(9), 378-380.

[17] Horiguchi, K., Yako, H., Yoshida, S., et al., 2016 Oct. S100β-positive cells of mesenchymal origin reside in the anterior lobe of the embryonic pituitary gland. PLoS One. 11(10), e0163981.
DOI: https://doi.org/10.1371/journal.pone.0163981.

[18] Elena, P., 2020 Jun. Identification and clinical significance of folliculo-stellate cells in normal hypophysis and adenomas. Moldovan Medical Journal. 63(2), 63-65.

[19] Höfler, H., Walter, G.F., Denk, H., 1984 Mar. Immunohistochemistry of folliculo-stellate cells in normal human adenohypophyses and in pituitary adenomas. Acta Neuropathologica. 65(1), 35-40.
DOI: https://doi.org/10.1007/BF00689825.

[20] Girod, C., Trouillas, J., Dubois, M.P., 1985 Sep. Immunocytochemical localization of S-100 protein in stellate cells (folliculo-stellate cells) of the anterior lobe of the normal human pituitary. Cell Tissue Research. 241(3), 505-511.
DOI: https://doi.org/10.1007/BF00215885.

[21] Nakajima, T., Yamaguchi, H., Takahashi, K., 1980 Jun. S100 protein in folliculostellate cells of the rat pituitary anterior lobe. Brain Research. 191(2), 523-531.
DOI: https://doi.org/10.1016/0006-8993(80)91300-1.

[22] Cocchia, D., Miani, N., 1980 Dec. Immunocytochemical localization of the brain-specific S-100 protein in the pituitary gland of adult rat. Journal of Neurocytology. 9(6), 771-782.
DOI: https://doi.org/10.1007/BF01205018.

[23] Botermann, D.S., Brandes, N., Frommhold, A., et al., 2021 Mar. Hedgehog signaling in endocrine and folliculo-stellate cells of the adult pituitary. Journal of Endocrinology. 248(3), 303-316.
DOI: https://doi.org/10.1530/joe-20-0388.

[24] Horiguchi, K., Ilmiawati, C., Fujiwara, K., et al., 2012 Apr. Expression of chemokine CXCL12 and its receptor CXCR4 in folliculostellate (FS) cells of the rat anterior pituitary gland: the CXCL12/CXCR4 axis induces interconnection of FS cells. Endocrinology. 153(4), 1717-1724.
DOI: https://doi.org/10.1210/en.2011-1937.

[25] Shirasawa, N., Mabuchi, Y., Sakuma, E., et al., 2004 May. Intercellular communication within the rat anterior pituitary gland: X. Immunohistocytochemistry of S-100 and connexin 43 of folliculo-stellate cells in the rat anterior pituitary gland. The anatomical record. Part A, Discoveries in molecular, cellular, and evolutionary biology. 278(1), 462-473.

[26] Fauquier, T., Guérineau, N.C., McKinney, R.A., et al., 2001 Jul. Folliculostellate cell network: a route for long-distance communication in the anterior pituitary. Proceedings of the National academy of Sciences of the United States of America. 98(15), 8891-8896.
DOI: https://doi.org/10.1073/pnas.151339598.

[27] Kato, Y., Yoshida, S., Kato, T., 2021 Nov. New insights into the role and origin of pituitary S100β-positive cells. Cell Tissue Research. 386(2), 227-237.
DOI: https://doi.org/10.1007/s00441-021-03523-7.

[28] Lloyd, R.V., Mailloux, J., 1988 Nov. Analysis of S-100 protein positive folliculo-stellate cells in rat pituitary tissues. American Journal of Pathology. 133(2), 338.

[29] Horvath, E., Kovacs, K., 2002 Jul. Folliculo-stellate cells of the human pituitary: a type of adult stem cell?. Ultrastructural Pathology. 26(4), 219-228.
DOI: https://doi.org/10.1080/01913120290104476.

[30] Inoue, K., Mogi, C., Ogawa, S., et al., 2002 Apr. Are folliculo-stellate cells in the anterior pituitary gland supportive cells or organ-specific stem cells?. Archives of Physiology and Biochemistry. 110(1-2), 50-53.
DOI: https://doi.org/10.1076/apab.110.1.50.911.

[31] Denef, C., 2008 Jan. Paracrinicity: the story of 30 years of cellular pituitary crosstalk. Journal of Neuroendocrinology. 20(1), 1-70.
DOI: https://doi.org/10.1111/j.1365-2826.2007.01616.x.

[32] Devnath, S., Inoue, K., 2008 Jun. An insight to pituitary folliculo-stellate cells. Journal of Neuroendocrinology. 20(6), 687-691.
DOI: https://doi.org/10.1111/j.1365-2826.2008.01716.x.

[33] Higuchi, M., Kanno, N., Yoshida, S., et al., 2014 Sep. GFP-expressing S100β-positive cells of the rat anterior pituitary differentiate into hormone-producing cells. Cell Tissue Research. 357(3), 767-779.
DOI: https://doi.org/10.1007/s00441-014-1890-0.

[34] Vankelecom, H., Chen, J., 2014 Mar. Pituitary stem cells: where do we stand? Molecular and Cellular Endocrinology. 385(1-2), 2-17.
DOI: https://doi.org/10.1016/j.mce.2013.08.018.

[35] Osuna, M., Sonobe, Y., Itakura, E., et al., 2012 Jun. Differentiation capacity of native pituitary folliculo-stellate cells and brain astrocytes. Journal of Endocrinology. 213(3), 231.
DOI: https://doi.org/10.1530/JOE-12-0043.

[36] Fauquier, T., Rizzoti, K., Dattani, M., et al., 2008 Feb. SOX2-expressing progenitor cells generate all of the major cell types in the adult mouse pituitary gland. Proceedings of the National academy of Sciences of the United States of America. 105(8), 2907-2912.
DOI: https://doi.org/10.1073/pnas.0707886105.

[37] Higashi, A.Y., Higashi, T., Furuse, K., et al., 2021 Nov. Claudin-9 constitutes tight junctions of folliculo-stellate cells in the anterior pituitary gland. Scientific Reports. 11(1), 1-14.
DOI: https://doi.org/10.1038/s41598-021-01004-z.

[38] Fujiwara, K., Tsukada, T., Horiguchi, K., et al., 2020 Aug. Aldolase C is a novel molecular marker for folliculo-stellate cells in rodent pituitary. Cell Tissue Research. 381(2), 273-284.
DOI: https://doi.org/10.1007/s00441-020-03200-1.

[39] Rees, D.A., Lewis, B.M., Lewis, M.D., et al., 2003 Oct. Adenosine-induced IL-6 expression in pituitary folliculostellate cells is mediated via A2b adenosine receptors coupled to PKC and p38 MAPK. British Journal of Pharmacology. 140(4), 764.
DOI: https://doi.org/10.1038/sj.bjp.0705488.

[40] Vennekens, A., Laporte, E., Hermans, F., et al., 2021 Jun. Interleukin-6 is an activator of pituitary stem cells upon local damage, a competence quenched in the aging gland. Proceedings of the National academy of Sciences of the United States of America. 118(25), e2100052118.
DOI: https://doi.org/10.1073/pnas.2100052118.

[41] Vlotides, G., Chen, Y.H., Eigler, T., et al., 2009 Jul. Fibroblast growth factor-2 autofeedback regulation in pituitary folliculostellate TtT/GF cells. Endocrinology. 150(7), 3252-3258.
DOI: https://doi.org/10.1210/en.2008-1625.

[42] Morris, J., Christian, H., 2011 May. Folliculo-stellate cells: paracrine communicators in the anterior pituitary. The Open Neuroendocrinology Journal. 4(1), 77-89.
DOI: https://doi.org/10.2174/1876528901104010077.

[43] Allaerts, W., Jeucken, P.H., Debets, R., et al., 1997 Jan. Heterogeneity of pituitary folliculo-stellate cells: implications for interleukin-6 production and accessory function in vitro. Journal of Neuroendocrinology. 9(1), 43-53.
DOI: https://doi.org/10.1046/j.1365-2826.1997.00555.x.

[44] Laporte, E., Vennekens, A., Vankelecom, H., 2021 Jan. Pituitary remodeling throughout life: Are resident stem cells involved? Frontiers in Endocrinology (Lausanne). 11, 604519.
DOI: https://doi.org/10.3389/fendo.2020.604519.

[45] Soji, T., Mabuchi, Y., Kurono, C., et al., 1997 Oct. Folliculo-stellate cells and intercellular communication within the rat anterior pituitary gland. Microscopy Research and Technique. 39(2), 138-149.
DOI: https://doi.org/10.1002/ar.a.20040.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Do Endocrinopathies Differ in Most Prevalent Hemoglobinopathy of Middle East: Beta-thalassemia?

Salma Ahi[1*] Mohsen Adelpour[1] Bahareh Haghdoost[2] Ali Jaberi[3]

1. Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran
2. Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran
3. Student Research Committee, Bushehr University of Medical Science, Bushehr, Iran

ARTICLE INFO

Article history
Received: 13 July 2022
Revised: 1 August 2022
Accepted: 4 August 2022
Published Online: 8 August 2022

Keywords:
Thalassemia
Osteoporosis
Bone mineral densitometry
Endocrinopathies

ABSTRACT

Repeated blood transfusions in thalassemia patients is followed by endocrinopathies as diabetes, hypothyroidism, hypogonadism, hypoparathyroidism, and disorders in calcium and vitamin D homeostasis. The aim of this study was to evaluate the association of beta-thalassemia patients endocrinopathies and osteoporosis. Serum level of some factors related to the function of gonads, thyroid, adrenal, and pancreas along with serum levels of calcium, phosphate, albumin, vitamin D, and iron were measured. Bone marrow density was tested via dual-energy x-ray absorptiometry (DXA densitometry). In this study, 56 patients with major thalassemia were investigated. Paraclinical analysis indicated osteopenia in 17 (30.4%) and osteoporosis in 39 patients (69.6%) in addition to other types of endocrine disorders, such as hypogonadism in 29 (51.8%), hypothyroidism in 13 (23.2%), hypoparathyroidism in 1 (1.8%), hypocortisolism in 2 (3.6%), and diabetes in 9 (16.1%) patients. Endocrinopathies had no significant relationship with osteoporosis and osteopenia in men. However, hypogonadism had a significant relationship with osteoporosis and osteopenia in women with thalassemia. Estradiol level was lower in women with osteoporosis in comparison with women with osteopenia. Ferritin levels had neither association with osteoporosis nor with LH levels (P>0.05). Secondary hypogonadism disorders are the main causes of osteoporosis and osteopenia in female beta-thalassemia patients.

1. Introduction

Thalassemia is a genetic disorder resulting in disorders of hemoglobin synthesis which is diagnosed by a lack or shortage of human hemoglobin globin chains [1]. Patients with major beta thalassemia are in need of frequent blood transfusion. Frequent blood transfusion increases iron level of the body [2]. The human body has a limited capacity for controlling such kind of iron overload [3]. Liver, heart, and

*Corresponding Author:
Salma Ahi,
Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran;
Email: salmaahi.61@gmail.com

DOI: https://doi.org/10.30564/jer.v4i2.4888

endocrine glands have the highest sensitivity toward iron overload. However, iron deposits in most of the organs, such as the pancreas, pituitary gland, and parathyroid [4]. The most common disorder of endocrine glands in patients with major thalassemia is hypogonadism which is more commonly caused by iron deposit in pituitary gland [5]. Chelator agents as Deferoxamine (DFO) are used for the prevention of iron overload in major thalassemia patients [6]. However, inappropriate application of chelator agents reduces bone density and causes growth retardation in patients with major thalassemia [7]. Bielinsk et al. reported that all the patients with major thalassemia are exposed to reduced bone density [8]. Reduced bone density emerges as osteoporosis and osteopenia disorders which are the main underlies of disabilities in patients with major thalassemia and increase the risk of bone fracture [9]. Iron overload may cause calcium and vitamin D homeostasis disorders [10]. Vitamin D deficiency in patients with major thalassemia along with iron overload will intensify their bone disorders [11]. Due to the high prevalence of thalassemia in our country, we have decided to investigate the reasons causing osteoporosis in these patients.

2. Materials and Methods

This is an analytic-cross sectional study which investigates patients with major thalassemia who have referred to Motahari Hospital in Jahrom. This study was approved by Research Ethical Committee of Jahrom University of medical sciences (with registration code of IR.JUMS.REC.1395.108). Major thalassemia was diagnosed in the patients based on their number of blood transfusions (more than 8 blood transfusions) in the year before participating in the study and Hb electrophoresis. Excluding criteria is age below 10 or more than 50 years old, celiac and malabsorption and patients who were receiving treatments with growth hormone and glucocorticoids were excluded. Participants' at least have had ten to fifty years of disease duration based on their age and all of them were on chelation/blood transfusions more than 8 times in a year.

3. Evaluation

T-score based densitometry determines the osteoporosis (T-score lower than –2.5 indicates standard deviation in DXA densitometry) and osteopenia (T-score ranging from –1 to –2.5 indicates standard deviation in densitometry) in participants more than 45 years old and z score were used to determine secendary osteoprosis in younger participants, Z Score –2.5 or less is compatible with criteria for definition of secondary osteoporosis [12]. Densitometry in this study was carried out using Hollogic discovery WI DXA device, made in Germany. Cortisol and adrenocorticotropic hormone (ACTH) were investigated via Electrochemiluminescence (ECL) method (ACTH was only estimated in patients with hypocortisolism). T4 level was estimated via ECL method. TSH levels were estimated via ECL method. Thyroid peroxidase autoantibody (TPOAb) was only analyzed in patients with hypothyroidism.

Fasting blood sugar was analyzed by SELECTRA E. Hemoglobin A1c (HbA1C) was only analyzed in patients with diabetes via chemical machine.

Calcium and Phosphate were analyzed by the photometric method. Albumin, which is used for determining hypocalcemia, was analyzed via bromocresol green method. Vitamin D deficiency is lower than 15 ng/mL levels, vitamin D insufficiency is between 15 ng/dL ~ 20 ng/dL levels, and normal vitamin D is higher than 20 ng/mL levels [13].

4. Statistical Analysis

Data analysis was done via SPSS software version 21. The relationships between endocrine disorders were compared based on the Chi-square test. Nonparametric Mann–Whitney test was used to compare the levels of variables in patients with the osteoporosis. Moreover, the correlation between data was analyzed by Pearson test. Normal data were reported as mean ± standard deviation, and nonparametric data were reported as median (first and fourth quartiles). $P < 0.05$ was considered as the significance level.

5. Results

In this study, 56 patients with major thalassemia and the average age of 27.37 ± 7.93 were investigated. Demographic data of the participants are presented in Table 1. Paraclinical analysis indicated osteopenia in 17 (30.4%) and osteoporosis in 39 patients (69.6%) in addition to other types of endocrine disorders, such as hypogonadism in 29 (51.8%), hypothyroidism in 13 (23.2%), hypoparathyroidism in 1 (1.8%), hypocortisolism in 2 (3.6%), and diabetes in 9 (16.1%) patients.

The relationship between Hypogonadism and Osteoprosis has been described in Table 2. According to this table, although there was no significant relationship between hypothyroidism, hypocortisolism, type 1 diabetes, hypoparathyroidism, and hemochromatosis with osteoporosis or osteopenia disaggregated by gender, there was a significant relationship between osteoporosis and hypogonadism in women under investigation ($P < 0.05$). This kind of relationship was not observed in male patients. Hypogonadal women with major thalassemia were 7.55 times more exposed to the risks of osteoporosis in comparison with non-hypogonadal women (CI%95:1.49-

Table 1. Basal characteristics of study subjects.

Characteristic	Men	Women	P Value
Number, n (%)	22	34	-
Age, y	27.63±8.66	27.20±8.07	>0.05
Weight, cm	56.86±8.9	48.35±8.96	0.002
height, kg	163±8.22	153.70±6.85	<0.01
Education *	2(9.09)	8(23.52)	>0.05
Diabetes mellitus History, n (%)	3(13.63)	5(14.70)	>0.05
Fracture History, n (%)	0(0)	7(20.58)	0.023
Heart disease History†, n (%)	0(0)	2(5.88)	>0.05
Thyroid disease History, n (%)	1(4.54)	2(5.88)	>0.05
Dairy consumption**, n (%)	18(81.81)	32(94.11)	>0.05
Sunlight exposure***, n (%)	1(4.54)	14(14.17)	<0.01
Vitamin D****, n (%)	2(9.09)	10(29.41)	0.006

cm: centimeters. y: years of old. kg: kilograms. †: history of being admitted in hospital for cardiac disease**.** *: university educated patients. **: number of patients with lower than 5 unit dairy consumption per day. ***: number of patients with lower than 30 minutes sunlight exposure per day. ****: number of Vitamin D deficient patients.

Table 2. The relationship between Hypogonadism and Osteoporosis

No.		Osteoporosis		Osteopenia		Chi square test
		%	No.	%		
Women	Hypogonadal	17	50	17	50	OR=7.55(CI%95:1.49-38.20) p-value=0.010 chi-square value=6.68
	Non-Hypogonadal	6	17.64	6	17.64	

38.20). The results of paraclinical tests are presented in Table 3.

The results of the Mann-Whitney test in comparison of estradiol level in women with osteoporosis and women with osteopenia, indicated that women with osteoporosis had lower estradiol median (Mann-Whitney U = 37.00, p-value = 0.001). The results of paraclinical tests are presented in Table 3. These results indicate that patients with osteopenia had significantly higher Luteinizing hormone (LH) levels in comparison with patients with osteoporosis ($P < 0.01$). No significant difference was observed between vitamin D levels of patients with osteopenia and osteoporosis.

Correlation of different variables indicated that with an increase in age of osteoporosis patients, parathyroid hormone (PTH) level increases ($r = 0.324$, $p = 0.032$), however, albumin level decreases ($r = –0.384$, $p = 0.035$). With an increase in the weights of patients with osteoporosis, Bone Mineral Density (BMD) increases ($r = 0.322$, $p = 0.045$). Increased levels of follicle stimulating hormone (FSH) and LH in patients with osteoporosis are correlated with decreased levels of BMD ($r = 0.362$, $p = 0.024$ and $r = 0.392$, $p = 0.012$ respectively). Thyroid function tests indicated that T4 increases along with BMD and vitamin D in patients with osteopenia ($r = 0.528$ $p = 0.029$ and $r = 0.553$ $p = 0.021$ respectively).

Table 3. Para clinical Results

	BMD		
	Osteoporosis	Osteopenia	p-value
n	17	39	-
Age	29(21-33)	26(22-27)	0.090
LH	4.2(1.1-7.6)	7.2(4.95-13.25)	0.010
FSH	2.4(0.6-5.5)	2.5(1.84-4.25)	0.817
Testosterone	2.13(0.777-5.61)	4.965(1.92-7.22)	0.269
Estradiol	8.37(5-59)	103.3(33.9-21)	0.001
Cortisol	19(11.9-23)	18.7(14.4-28)	0.340
T4	7.7(6.6-8.9)	8.7(7.3-10)	0.064
TSH	2.8(1.8-4)	3.4(1.715-4.235)	0.568
FBS	95(87-109)	90(81-120.5)	0.318
HBA1c	7.1(4.875-7.8)	8.1(6-8.5)	0.432
Ca	9.7(9.4-10)	9.5(9.35-10)	0.754
p	4.8(4.2-5.4)	4.6(4-5.15)	0.492
Alb	4.5(4.3-4.7)	4.5(4.15-4.8)	0.893
PTH	21.4(9.1-30.5)	13.9(7.05-23.15)	0.222
Vitamin D	18.7(10.5-26)	22.1(10.65-25.85)	0.957
Ferritin	895(677-1004)	951(711.5-1439)	0.206
TPOAb	3.75(1.725-7)	1.8(0.95-3.05)	0.142

TSH: thyroid-stimulating hormone, FBS: Fasting blood sugar, LH: Luteinizing Hormone, FSH: follicle stimulating hormone, HbA1C: Hemoglobin A1C, PTH: parathyroid Hormone, TPOAb: thyroid peroxidase antibody, Alb: Albumin, Ca: Calcium, P: phosphorus

6. Discussion

Bone changes in patients with major thalassemia, and their expansive effects on physiology of endocrine system, have transformed thalassemia into a great dilemma [14]. Osteopenia was observed in 17 (30.4%) and osteoporosis in 39 patients (69.6%) and no healthy person underwent BMD analysis. These results were consistent with the reported results of Bielinski et al. on patients with thalassemia who were exposed to osteopenia and osteoporosis [8]. Anapliotou et al. claimed that all the patients with thalassemia experience decreased the level of BMD [15]. The most common disorders in patients with thalassemia are bone disorders which emerge as rickets, scoliosis, severe bone pains, deformation of spinal cord, severe osteopenia and osteoporosis, and multiple fractures. Pathogens of bone disorders are caused by the endocrine disorders, nutrition disorders, iron overload, reduced trabecular bone, thinning of cortex, and inefficient hematopoiesis [16]. Patients with major thalassemia have low levels of BMD. Most of them suffer from severe bone fractures and pains [17]. The results of this study indicated that, unlike men, there was a significant relationship between osteoporosis and hypogonadism in women. Moreover, there was no significant relationship between other types of endocrine disorders, such as diabetes, hemochromatosis, hypoparathyroidism, hypocortisolism, hypothyroidism, and osteoporosis in both men and women. Hypogonadism in women refers to weak or abnormal axis of hypothalamus- pituitary gland-ovary which may be observed as estradiol deficiency and increased levels of LH and FSH [18]. Primary hypogonadism or hypergonadotropic hypogonadism due to iron overload and iron deposits in gonads, is a possible mechanism of secondary osteoporosis in thalassemia also other mechanism is, hypogonadotropic hypogonadism or secondary hypogonadism due to iron deposits in pituitary and its dysfunction [19]. Estradiol protects the bones and prevents osteoporosis by decreasing apoptosis of osteoblasts and increasing apoptosis of osteoclasts [20]. Our study revealed that lower levels of estradiol are connected to osteoporosis, and patients with hypogonadism have lower levels of estradiol. These findings are consistent with the reposted findings of Anapllotou et al. who indicated that an increase in the level of estrogen of female major thalassemia patients will improve the BMD status [15]. Therefore, Hypogonadal women with major thalassemia were 7.55 times more exposed to the risks of osteoporosis in comparison with non-hypogonadal women (CI%95:1.49-38.20). These findings are consistent with the results of previous researches. Iron overload causes hypogonadism in gonadotropic cells of the pituitary gland of patients with

major thalassemia [21]. In the present study higher levels of ferritin was correlated with reduced serum level of calcium in men ($p = 0.06$, $r = 508$). These results are consistent with the reported results of Li Wang et al. They claimed that extracellular iron overload reduces absorption of calcium [22]. The role of calcium deficiency in development of osteoporosis is well documented [23,24]. Furthermore, our study indicated that high levels of FSH and LH in patients with osteoporosis will reduce BMD. However, women with osteopenia had significantly higher levels of LH than patients with osteoporosis. The exact role of LH in skeletal hemostasis is an area of uncertainty [25]. Bone protection is caused by strong effect of FSH hormone on bones and gender differences. Jie Wang also has referred to destructive role of FSH on bones [26]. But our subjects were patients with thalassemia which may reduce the value of this comparison. Berge et al. stated that ferritin has not a direct relationship with the level of female sex hormones [27], however, it has a direct relationship with male sex hormones [28]. Xu ZR et al.'s study, which was carried out on the society of Chinese women, indicated that increased LH decreases BMD [29]. These results are consistent with our findings. It seems that the relationship between LH level and osteoporosis or osteopenia is not dependent on the number of blood transfusions in patients with thalassemia. In fact, iron overload and its deposit in gonads may be followed by a simultaneous increase of LH and FSH levels, while this was not the case with our subjects. Therefore, primary ovarian failure was not observed in our subjects and we should look after other factors for hypo-gonadotropic hypogonadism. Thyrotoxicosis or excessive increase in thyroid hormones is associated with osteoporosis. Hypothyroidism can also reduce BMD [30]. But our study showed that T4 increase is positively correlated with an increase in BMD scores. However, the increase in T4 of our patients occurred in the normal range. So the appropriate increase in T4 levels can reduce the risk of osteoporosis in thalassemia patients. T4 accelerates bone remodeling. High levels of thyroid hormones in hyperthyroidism, due to excessive increase in the velocity of the bone remodeling cycle, can lead to incomplete cycles and osteoporosis [31]. In a cohort study in patients undergoing thyroidectomy, it was shown that thyroidectomy increases the chance of osteoporosis [32]. While several researches revealed that in the absence of endogenous thyroid hormone production after total thyroidectomy, replacement therapy with exogenous T4 does not affect BMD [33], it seems that thyroid hormones at normal concentrations tend to regulate bone metabolism and reduce the risk of BMD. Increased T4 was also correlated with increased vitamin D in osteoporosis patients. According to studies, thyroid hormones in hyperthyroid patients reduce the level of vitamin D by suppressing the transcription of the 25-Hydroxyvitamin D3 1α-Hydroxylase gene that is responsible for the production of vitamin D in the kidney [34]. It seems that these results are not consistent with our study, but changes in the T4 concentration of our subjects are occurring in normal range and vary with changes due to abnormal levels. However, there was no relationship between vitamin D levels of our participants and osteoporosis.

7. Conclusions

Hypogonadotropic hypogonadism is the most common endocrine disorder which was observed in our subjects (51.8%). Moreover, there was a significant relationship between osteoporosis and hypogonadism in our female subjects. It can be deducted that secondary hypogonadism disorders in women may lead in osteoporosis and osteopenia. However, there was no significant relationship between hypogonadism, hypothyroidism, hypocortisolism, type-1 diabetes, and hypoparathyroidism with osteoporosis or osteopenia in men.

Acknowledgment

We have to appreciate department of Internal Medicine and Endocrinology of Jahrom University of medical sciences.

Statement of Ethics

This manuscript was approved by Ethics committee of Jahrom University of medical sciences.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Dr. Salma Ahi has designed the whole study. Bahareh Haghdoost, has collected the samples of thalassemia patients and followed the preclinical tests. Study has been analyzed and written by Ali Jaberi and Mohsen Adelpour.

References

[1] Galanello, R., Origa, R., 2010. Beta-thalassemia. Orphanet Journal of Rare Diseases. 5(1), 11.

[2] Mishra, A.K., Tiwari, A., 2013. Iron overload in beta thalassaemia major and intermedia patients. Maedica. 8(4), 328.

[3] Porter, J.B., 2005. Monitoring and treatment of iron overload: state of the art and new approaches. Semi-

nars in Hematology. 42(2 Suppl 1), S14-18.

[4] Andrews, N.C., 1999. Disorders of iron metabolism. New England Journal of Medicine. 341(26), 1986-1995.

[5] Chern, J.P., Lin, K.H., Tsai, W.Y., et al., 2003. Hypogonadotropic hypogonadism and hematologic phenotype in patients with transfusion-dependent beta-thalassemia. Journal of Pediatric Hematology /Oncology. 25(11), 880-884.

[6] Giardina, P.J., Grady, R.W., 1995. Chelation therapy in beta-thalassemia: the benefits and limitations of desferrioxamine. Seminars in hematology. 32(4), 304-312.

[7] De Virgillis, S., Congia, M., Frau, F., et al., 1988. Deferoxamine-induced growth retardation in patients with thalassemia major. The Journal of Pediatrics. 113(4), 661-669.

[8] Bielinski, B.K., Darbyshire, P., Mathers, L., et al., 2001. Bone density in the Asian thalassaemic population: a cross-sectional review. Acta Paediatrica. 90(11), 1262-1266.

[9] Haidar, R., Musallam, K.M., Taher, A.T., 2011. Bone disease and skeletal complications in patients with β thalassemia major. Bone. 48(3), 425-432.

[10] Root, A.W., Diamond, F.B., 2002. Calcium metabolism, normal homeostasis and disorders of calcium metabolism in the child and adolescent. Sperling MA, editor. Pediatric endocrinology. 2nd ed. Philadelphia: Saunders. pp. 65-110.

[11] Soliman, A., De Sanctis, V., Yassin, M., 2013. Vitamin D status in thalassemia major: an update. Mediterranean Journal of Hematology and Infectious Diseases. 5(1).

[12] Blake, G.M., Fogelman, I., 2007. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgraduate Medical Journal. 83(982), 509-517.

[13] Altrichter, S., Boodstein, N., Maurer, M., 2009. Matrix metalloproteinase-9: a novel biomarker for monitoring disease activity in patients with chronic urticaria patients? Allergy. 64(4), 652-656.

[14] Vogiatzi, M.G., Macklin, E.A., Fung, E.B., et al., 2009. Bone disease in thalassemia: a frequent and still unresolved problem. Journal of Bone and Mineral Research. 24(3), 543-557.

[15] Anapliotou, M.L., Kastanias, I.T., Psara, P., et al., 1995. The contribution of hypogonadism to the development of osteoporosis in thalassaemia major: new therapeutic approaches. Clinical Endocrinology. 42(3), 279-287.

[16] Benigno, V., Bertelloni, S., Baroncelli, G.I., et al., 2003. Effects of thalassemia major on bone mineral density in late adolescence. Journal of Pediatric Endocrinology & Metabolism. 16(Suppl 2), 337-342.

[17] Voskaridou, E., Terpos, E., 2008. Pathogenesis and management of osteoporosis in thalassemia. Pediatric Endocrinology Reviews: PER. 6, 86-93.

[18] Rothman, M.S., Wierman, M.E., 2008. Female hypogonadism: evaluation of the hypothalamic–pituitary–ovarian axis. Pituitary. 11(2), 163.

[19] Emerit, J., Beaumont, C., Trivin, F., 2001. Iron metabolism, free radicals, and oxidative injury. Biomedicine & Pharmacotherapy. 55(6), 333-339.

[20] Okman-Kilic, T., 2015. Conference proceedings. Estrogen Deficiency and Osteoporosis.

[21] Srisukh, S., Ongphiphadhanakul, B., Bunnag, P., 2016. Hypogonadism in thalassemia major patients. Journal of Clinical & Translational Endocrinology. 5, 42-45.

[22] Wang, L., Li, Q., Duan, X.L., et al., 2005. Effects of extracellular iron concentration on calcium absorption and relationship between Ca^{2+} and cell apoptosis in Caco-2 cells. World Journal of Gastroenterology: WJG. 11(19), 2916.

[23] Sahota, O., 2000. Osteoporosis and the role of vitamin D and calcium-vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency. Age and Ageing. 29(4), 301-304.

[24] Rodrıguez-Martınez, M.A., Garcıa-Cohen, E.C., 2002. Role of Ca^{2+} and vitamin D in the prevention and treatment of osteoporosis. Pharmacology & therapeutics. 93(1), 37-49.

[25] Mills, E.G., Yang, L., Nielsen, M.F., et al., 2021. The Relationship between Bone and Reproductive Hormones beyond Estrogens and Androgens. Endocrine Review. 42(6), 691-719.

[26] Wang, J., Zhang, W., Yu, C., et al., 2015. Follicle-stimulating hormone increases the risk of postmenopausal osteoporosis by stimulating osteoclast differentiation. PLoS One. 10(8), e0134986.

[27] Liu, Z., Ye, F., Zhang, H., et al., 2013. The association between the levels of serum ferritin and sex hormones in a large scale of Chinese male population. PloS one. 8(10), e75908.

[28] Berge, L.N., Bønaa, K.H., Nordøy, A., 1994. Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. Arteriosclerosis and Thrombosis: A Journal of Vascular Biology. 14(6), 857-861.

[29] Xu, Z.R., Wang, A.H., Wu, X.P., et al., 2009. Relationship of age-related concentrations of serum FSH and LH with bone mineral density, prevalence of osteoporosis in native Chinese women. Clinica Chimi-

ca Acta. 400(1-2).

[30] Dhanwal, D.K., 2011. Thyroid disorders and bone mineral metabolism. Indian Journal of Endocrinology and Metabolism. 15(Suppl2), S107.

[31] Ahn, H.Y., 2018. Effects of Abnormal Thyroid Function Status to Bone Metabolism. International Journal of Thyroidology. 11(1), 21-25.

[32] Hung, C.L., Yeh, C.C., Sung, P.S., et al., 2018. Is Partial or Total Thyroidectomy Associated with Risk of Long-Term Osteoporosis: A Nationwide Population-Based Study. World Journal of Surgery. 14, 1-8.

[33] Kim, C.W., Hong, S., Oh, S.H., et al., 2015. Change of bone mineral density and biochemical markers of bone turnover in patients on suppressive levothyroxine therapy for differentiated thyroid carcinoma. Journal of Bone Metabolism. 22, 135–141.

[34] Kozai, M., Yamamoto, H., Ishiguro, M., et al., 2013. Thyroid hormones decrease plasma 1α, 25-dihydroxyvitamin D levels through transcriptional repression of the renal 25-hydroxyvitamin D3 1α-hydroxylase gene (CYP27B1). Endocrinology. 154(2), 609-622.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

MINI REVIEW

Evaluating the Effect of Irisin on Obesity-Concerning Physical Activity

Onur Oral[1*] Pınar Tatlibal[2] Evangelia Stavropoulou[3]

1. Faculty of Sports Sciences, Ege University, Izmir, Turkey
2. Necat Hepkon Faculty of Sports Sciences, Dokuz Eylül University, Izmir, Turkey
3. Research in Information and Communication, University of Lorraine, France

ARTICLE INFO

Article history
Received: 11 August 2022
Revised: 29 August 2022
Accepted: 30 August 2022
Published Online: 31 August 2022

Keywords:
Physical activity
Irisin
Obesity

ABSTRACT

Background: The study aims to investigate and evaluate the impact of irisin on physical activity and obesity. **Materials and Methods:** In the search for scientific literature related to this review the US National Library of Medicine (PubMed) used MEDLINE and SportDiscus data and the terms "irisin", "physical activity", and "obesity", were used. The relevant literature has also taken its source from the research of relevant articles from reference lists derived from data studies. **Results:** Irisin, an emerging myokine in the scientific community, has received high attention as a potential contributor to obesity. This hormone is also associated with physical activity. **Conclusions:** Irisin was recently identified as a myokine known to respond to physical activity. Adequate recognition of this hormone may play an active role in the prevention and treatment of obesity.

1. Introduction

Obesity is a global public health problem in several countries. Mexico and the U.S are the countries with the highest rates of obesity [1]. Due to the positive effects of physical exercise and activities on the prevention of obesity, it is important that exercise is an indispensable part of a healthy life. The sedentary lifestyle, which occurs when children and adolescents who were born and grew up in the digital age, that is, intensively use modern age technologies such as the internet and smart phones, tablets, computers, spend excessive time on computers and information technologies, can increase the risk of obesity in children and dolescents [2-4].

Irisin was recently identified as a myokine that is known to be responsive to physical activity. In their study, Boström et al. [5] introduced irisin to the world of science as a PGC-1α-dependent myokine. Irisin affects white adipose tissue to stimulate UCP1 expression in mitochondria and enhances thermogenesis [5]. Data state that irisin causes white fat to become brown, thus provoking mitochondria to burn more of the stored fat [6,7].

*Corresponding Author:
Onur Oral,
Faculty of Sports Sciences, Ege University, Izmir, Turkey;
Email: onur.oral@ege.edu.tr

DOI: https://doi.org/10.30564/jer.v4i2.4955

Irisin is a myokine that was newly revealed in the world of science. According to the latest studies, cytokines and other peptides play important roles in multifactorial pathogenic mechanisms concerning obesity [8].

Irisin has received high interest as a potential contributing factor to obesity. Irisin, a hormone, is secreted from fibronectin type III domain-containing protein 5 (FNDC5), which is found in skeletal muscle [5,9,10].

Irisin is viewed as an attractive potential curative element for obesity and metabolic disorders. Nonetheless, the physiological determinants of irisin and its secretion form are not yet known exactly [11-14].

2. Discussion

In a research study of Boström et al. add further information about irisin and in particular that irisin promotes mitochondrial biogenesis which improves fat metabolism. In addition, according to the mice study, when irisin level increases, more calories are spent regardless of the physical activity level. Another result of the study is that regular physical activity increases irisin levels, suggesting an exercise period of 3 weeks for mice and 10 weeks for humans. Boström and colleagues conducted a study on mice. The research resulted in increased irisin levels measured up to 65% after 3 weeks of swimming exercise [5]. A similar human study by these investigators indicated consistent results as irisin levels increased after endurance exercise of 2.5 months [15].

The amount of irisin release from adipose tissue was determined to be lower in lean rats than in obese rats [16].

Short-term endurance exercise triggered the release of irisin by sc and visceral adipose tissue in rat studies. Similarly in a study that was conducted on human subjects, acute aerobic training increased circulating irisin but only transiently [6,17,18].

In one study targeting pigs, however, no effect of exercise on FNDC5 gene expression was found [19]. But however, another study found that exercise increased irisin release in mice and humans [5].

A study by Stengel et al. determined lower plasma irisin levels in people with anorexia and a linear association between irisin and BMI [20].

Pardo et al. claimed that for every 1kg increase in fat mass, there is a twofold increase in irisin [21]. And research on adults demonstrated that FNDC5/irisin secretion increases after short periods of endurance training [16]. And in another research in obese subjects determined an increase of irisin levels by 12% after 12 months of lifestyle change. However, they weren't found associated with BMI alterations [22].

Irisin is a recently discovered hormone. It is reported to have an important role in energy homeostasis and obesity [23-25].

Results of a study demonstrated a positive relationship between irisin and BMI, fasting blood glucose, TG, and diastolic BP. In addition, the study indicated a negative relationship between irisin and circulating HDL cholesterol [20,26].

3. Conclusions

It is possible to come across many scientific publications that physical activity is a very effective method among many methods for the healthy regulation of energy balance in the treatment process of the obesity problem, which is increasing its impact all over the world due to a sedentary life and unhealthy eating habits. With a more comprehensive examination of this positive effect in terms of the irisin hormone, the importance of this hormone for a healthy life will be understood more clearly.

It is known that a physically active life is very important for a healthy life. The habit of regular exercise, which increases the secretion of irisin and some other hormones, especially increases muscle endurance, muscle strength, muscle flexibility, as well as prevents obesity (excessive weight), helps maintain weight, reduces the risk of cardiovascular disease, regulates sleep quality, increases bone mineral density, increases blood flow. It has been shown that it contributes to the reduction of fat and glucose levels, thus reducing the incidence of certain types of cancer and chronic health complaints that may occur with aging.

Acknowledgement

We would like to express our special thanks of gratitude to George N. NOMIKOS for his very successful contribution to the literature research process and unique academic support in the publication during the process of this review article.

Conflict of Interest

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

The author certifies that there is no funding from any financial organization regarding the material discussed in the manuscript.

Author's Contributions

All authors read and approved the final version of the manuscript.

References

[1] Elder, J.P., 2013. Mexico and the USA: the world's leaders in the obesity epidemic. Salud Pública México. 55, 355.

[2] González-Gross, M., Gómez-Lorente, J.J., Valtueña, J., et al., 2008. The "healthy lifestyle guide pyramid" for children and adolescents. Nutrición hospitalaria. 23(2), 159-168.

[3] Oral, U., 2020. Political Perception Of Generation Z In Turkey. International Journal of Advanced Science and Technology. 29(11s), 493-500.

[4] Martinez-Gomez, D., Moreno, L.A., Romeo, J., et al., 2011. Combined influence of lifestyle risk factors on body fat in Spanish adolescents-the Avena study. Obesity Facts. 4(2), 105-111.

[5] Boström, P., Wu, J., Jedrychowski, M.P., et al., 2012. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 481, 463-468.

[6] Kraemer, R.R., Shockett, P., Webb, N.D., et al., 2014. A transiently elevated irisin blood concentration in response to prolonged, moderate aerobic exercise in young men and women. Hormone and Metabolic Research. 46(2), 150-154.

[7] Wu, J., Boström, P., Sparks, L.M., et al., 2012. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 150, 366-376.

[8] Pedersen, B.K., Febbraio, M.A., 2012. Muscles, exercise, and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology. 8(8), 457-465.

[9] Elizondo-Montemayor, L., Silva-Platas, C., Torres-Quintanilla, A., et al., 2017. Association of Irisin Plasma Levels with Anthropometric Parameters in Children with Underweight, Normal Weight, Overweight, and Obesity. BioMed Research International. 2628968.
DOI: https://doi.org/10.1155/2017/2628968

[10] Jedrychowski, M.P., Wrann, C.D., Paulo, J.A., et al., 2015. Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metabolism. 22(4), 734-740.

[11] Anastasilakis, A.D., Polyzos, S.A., Saridakis, Z.G., et al., 2014. Circulating Irisin in Healthy, Young Individuals: Day-Night Rhythm, Effects of Food Intake and Exercise, and Associations With Gender, Physical Activity, Diet, and Body Composition. The Journal of Clinical Endocrinology & Metabolism. 99(9), 3247-3255.
DOI: https://doi.org/10.1210/JC.2014-1367

[12] Moreno-Navarrete, J., Ortega, F., Serrano, M., et al., 2013. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. The Journal of Clinical Endocrinology and Metabolism. 98, E769-E778.

[13] Polyzos, S.A., Kountouras, J., Shields, K., et al., 2013. Irisin: a renaissance in metabolism? Metabolism. 62, 1037-1044.

[14] Boström, P.A., Fernández-Real, J.M., Mantzoros, C., 2014. Irisin in humans: recent advances and questions for future research. Metabolism. 63, 178-180.

[15] Saraslanidis, P., Petridou, A., Bogdanis, G.C., et al., 2011. Muscle metabolism and performance improvement after two training programmes of sprint running differing in rest interval duration. Journal of Sports Sciences. 29, 1167-1174.

[16] Roca-Rivada, A., Castelao, C., Senin, L.L., et al., 2013. FNDC5/irisin is not only a myokine but also an adipokine. PLoS ONE. 8(4), e60563.

[17] Huh, J.Y., Panagiotou, G., Mougios, V., et al., 2012. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism: Clinical and Experimental. 61(12), 1725-1738.
DOI: https://doi.org/10.1016/j.metabol.2012.09.002

[18] Norheim, F., Langleite, T.M., Hjorth, M., et al., 2014. The effects of acute and chronic exercise on PGC-1α, irisin, and browning of subcutaneous adipose tissue in humans. Federation of European Biochemical Societies Journal. 281, 739-749.

[19] Fain, J.N., Company, J.M., Booth, F.W., et al., 2013. Exercise training does not increase muscle FNDC5 protein or mRNA expression in pigs. Metabolism. 62, 1503-1511.

[20] Stengel, A., Hofmann, T., Goebel-Stengel, M., et al., 2013. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity—correlation with body mass index. Peptides. 39(1), 125-130.

[21] Pardo, M., Crujeiras, A.B., Amil, M., et al., 2014. Association of Irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. International Journal of Endocri-

nology. Article ID 857270, 9 pages.

[22] Blüher, S., Panagiotou, G., Petroff, D., et al., 2014. Effects of a 1-Year Exercise and Lifestyle Intervention on Irisin, Adipokines, and Inflammatory Markers in Obese Children. Obesity.
DOI: https://doi.org/10.1002/oby.20739

[23] Park, K.H., Zaichenko, L., Brinkoetter, M., et al., 2013. Circulating irisin in relation to insulin resistance and the metabolic syndrome. The Journal of Clinical Endocrinology and Metabolism. 98(12), 4899-4907.
DOI: https://doi.org/10.1210/jc.2013-2373

[24] Timmons, J., Baar, K., Davidsen, P., et al., 2012. Is irisin a human exercise gene? Nature. 448, E9-E10.

[25] Villarroya, F., 2012. Irisin, turning up the heat. Cell Metab. 15, 277-278.

[26] Liu, J.J., Wong, M.D., Toy, W.C., et al., 2013. Lower circulating irisin is associated with type 2 diabetes mellitus. Journal of Diabetes and Its Complications. 27, 365-369.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

REVIEW

Cortisol Response in Breast Cancer: The Role of Physical Activity and Exercise

Margarida Marinho[1] **Sílvia Rocha-Rodrigues**[1,2*]

1. Escola Superior de Desporto e Lazer, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun'Alvares, 4900-347 Viana do Castelo, Portugal
2. Tumour & Microenvironment Interactions Group, INEB- Institute of Biomedical Engineering, i3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen, 208, 4200-153 Porto, Portugal

ARTICLE INFO

Article history
Received: 1 August 2022
Revised: 31 August 2022
Accepted: 1 September 2022
Published Online: 13 September 2022

Keywords:
Physically active
Chronic stress
Depression
Cancer
Women

ABSTRACT

Chronic stress is a consistent sense of feeling pressured and overwhelmed for a long period of time and it has been defined as a maladaptive state that is associated with altered hypothalamic pituitary adrenal (HPA) axis. The hyperactivity of the HPA axis is commonly assessed by cortisol levels. Physical activity (PA) and exercise have been demonstrated to regulate cortisol patterns in different healthy study populations, but also in BC patients and survivors. The PA and exercise are related but have distinct concepts that are commonly misused. Nowadays, the regular practice of PA and exercise has been widely recognized as one main strategy to manage chronic stress and its related markers, like cortisol, remains elusive. In the present review, the authors focused on the evidence of the PA and exercise on cortisol patterns of BC patients and survivors.

1. Introduction

Breast cancer (BC) is the leading cause of death in women, with diagnosis numbers growing each year [1]. Almost two million cases of BC were diagnosed in last years, according to the World Health Organization (WHO) [2]. Both non-pharmacological and pharmacological treatments of BC can result in adverse side-effects at distinct levels, such as physical function, metabolic, cardiorespiratory and psychological [3,4]. These consequences may be associated with an interaction between pharmacological therapies and physiopathological and psychological conditions of each woman at the moment of diagnosis. After a diagnosis of BC, women experience emotional distress,

*Corresponding Author:
Sílvia Rocha-Rodrigues,
Escola Superior de Desporto e Lazer, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun'Alvares, 4900-347 Viana do Castelo, Portugal; Tumour & Microenvironment Interactions Group, INEB- Institute of Biomedical Engineering, i3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen, 208, 4200-153 Porto, Portugal;
Email: silviadarocharodrigues@gmail.com

DOI: https://doi.org/10.30564/jer.v4i2.4943

depression and anxiety, which can persist for prolonged periods, irrespective of the clinical treatment outcome [5].

Chronic stress is a consistent sense of feeling pressured and overwhelmed for a long period of time and it has been defined as a maladaptive state that is associated with altered immunity, hypothalamic pituitary adrenal (HPA) axis, and sympathetic nervous system (SNS) functioning [3]. Although research is still limited, the dysregulation of HPA axis and SNS, depression and anxiety have been reported in BC patients and survivors [5]. Studies show that almost 50% of BC patients experienced depression and/or anxiety during cancer treatments [4,6] and approximately 25% of women have clinically important levels of emotional distress up to 12 months after treatment [5].

The hyperactivity of the HPA axis in response to a chronic stress is commonly assessed by cortisol awakening responses (CAR), i.e., the rapid increase in cortisol secretion roughly within the first 30 min of wakening that of wakening that occurs daily, signifying the physiological stress response to waking [7]. Cortisol levels are usually highest before awakening and decrease during the day [7]; however, the majority (>60%) of patients with BC show flattened circadian profiles, high levels, or unpredictable fluctuations [8,9].

Physical activity (PA) and exercise have been recognized as a part of a healthy lifestyle, being associated with reduced risk of BC through several mechanisms, including by regulating sex-steroids hormones [10], maintaining a healthy weight [11], reducing inflammation [12], and improving the immune response [13]. Some studies reported that PA and exercise were able to decrease levels of cortisol across different healthy study populations [14-16]. In the systematic review and meta-analysis conducted by De Nys et al. [17], ten original studies were comprised including randomized controlled trial (RCTs) and non-RCTs with relevant control group. Here, they found moderate-certainty evidence for PA as an effective strategy in lowering cortisol levels in women with different clinical conditions. Although the PA and exercise are related they are distinct concepts that in this study were misused. In addition, the role of PA and exercise as beneficial strategy to manage chronic stress and its related markers, such as cortisol, remains elusive. In the present review, we focused on the evidence of the PA and exercise on cortisol fluctuations of BC patients and survivors.

2. Hypothalamic-pituitary-adrenal Axis in Response to Chronic Stress

In response to chronic stress, the physiologic mechanisms involve the neuroendocrine pathways constituting the SNS and HPA axis [3,4]. Both mechanisms are initiated by releasing several neurotransmitters and hormones that affluence behavioural and biochemical changes [18]. Under chronic stress, the brain's nerve impulses can continuously activate the hypothalamus to produce the corticotropin-releasing factor, which is targets the pituitary gland. In its turn, pituitary gland releases the adrenocorticotropic hormone (ACTH) [19] that reaches the adrenal cortex by blood stream and promotes the synthesis of corticosteroids, including cortisol. In addition, SNS was triggered by chronic stress and, thus, stimulating the production and secretion of as norepinephrine and epinephrine, both known as catecholamines [18,19]. Both, corticosteroids and catecholamines, may contribute to a decline in the functions of the prefrontal cortex and the hippocampus, and may enhance the activation of the SNS and the HPA by regulating the expression of glucocorticoid receptors [18,20].

A hyperactivation of the SNS and HPA axis in response to a chronic stress has been demonstrated to contribute, at least in part, for several cancer-promoting processes, such as tumorigenesis, progression, metastasis, and multi-drug resistance, by altering the tumour microenvironment (TME) [21]. A stressed TME is characterized by the increased proportion of cancer-promoting cells and cytokines, reduced and dysfunction of immune-supportive cells and cytokines, increased angiogenesis and epithelial-mesenchymal transition, as well as damaged extracellular matrix [19,21]. Of note that the enhanced β-adrenergic signalling and glucocorticoid signalling in TME can be induced by not only chronic, but also TME hypoxia [22].

Several studies have been attributed associations between stress and cancers, such as prostate [23,24], breast [25,26], gastric [27] and lung [28], suggesting that chronic stress can induce tumorigenesis and promote cancer development.

3. Cortisol

Cortisol is an adrenal hormone with many functions in the human body, such as mediating the stress response, regulating metabolism, inflammatory and immune functions [29]. Considering that cortisol is a glucocorticoid and the glucocorticoid receptors are present in almost tissue in the body, it affects nearly every organ system, including nervous, immune, cardiovascular, respiratory, reproductive, musculoskeletal muscle, and integumentary [29].

Cortisol displays strong circadian rhythmicity, with high levels in the morning in the first 30-45 min after awakening, known as CAR and a gradual decline follows this peak during the waking day to reach the lowest levels at midnight [29]. This diurnal fluctuation is indicative of HPA axis reactivity [30]. Additionally, evidence has been demonstrated that salivary cortisol levels highly correlate with plasma and serum cortisol levels [31].

Cortisol Behaviour in Breast Cancer

BC patients and survivors likely have a dysregulation of the HPA axis and nonstandard secretion of cortisol, as previously demonstrated by [8,9]. Previous research demonstrated that BC survivors may experience significant alterations in their cortisol secretion patterns, as well as disruptions in the circadian rhythm of the HPA axis [9,32,33]. In the Obradović et al.'s study [33], the increase in glucocorticoids during BC progression was related to a lower survival rate, which is in agreement with a stimulatory effect of cortisol on cell proliferation observed in different cancer cell lines [27,34]. On the other hand, women with advanced BC and tamoxifen as first-line treatment presented significant elevations in basal cortisol levels compared to age-matched healthy women [8]. These findings suggest that BC is associated with a hyperactive adrenal gland, which may be due to the physiological stress associated with the presence of (micro)metastases or tumour cells in the circulation, in combination with administration of tamoxifen.

4. Physical Activity and Exercise

Although PA and exercise have been used confusingly, PA is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure." [35] PA is closely related to, but distinct from exercise concept. Exercise is a subset of PA defined as "planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness." [35].

Therefore, exercise practice has been widely recognized to improve cardiorespiratory fitness that positively affects health and self-efficacy [36], reduces insomnia-related distress [10] by improving nocturnal sleeping [37], and, consequently, body recovery [36,37]. At psychosocial domain, exercise has several benefits, including favours interpersonal relations, which are important to attenuate depression and anxiety-related symptoms [38,39].

4.1 Effects of Physical Activity on Cortisol Levels in Breast Cancer

As shown in Table 1, only two studies studied the hypothetical association between PA and salivary cortisol [40,41]. Lambert et al. [40] found no associations in cortisol of physically activity BC women in post-treatment phase. On the other hand, Castonguay et al. [41] reported a decrease of salivary cortisol in 145 moderate-to-vigorous physically active BC women at least 12 months post-treatment. Both studies used healthy women without BC history as a comparator group. Taken together, these findings revealed that little is known about the role of PA in cortisol levels of BC women.

4.2 Effects of Exercise on Cortisol Levels in Breast Cancer

Regarding the effects of exercise intervention program on cortisol variations, controverse data exists, as seen in Table 2. Some of studies reported no changes after 14 weeks of home-based walking [42], 16 weeks of aerobic combined with strength exercise [43], 6 weeks of qigong [44], 3 weeks of dance movement therapy [45] or 48 weeks of supervised and unsupervised exercise sessions [46] in BC women.

Three studies used an exercise program where yoga classes were included with different period of time, one study lasted for 14 weeks [47] and two studies lasted for 6 weeks [48,49]. Ratcliff et al. [49] hypothesized that 6 weeks of yoga-based exercise intervention during radiotherapy would be beneficial for women with high baseline depressive symptoms compared with their counterparts par-

Table 1. Synthesis of studies evaluating the role of physical activity in BC women

Study Ref.:	Sample	Study Design	Main Finding
Castonguay et al. 2017 [41]	N=145 BC women post-treatment phase (≥12 months) Age: ≥ 18 years Comparator group: healthy women Country: Canada	PA was evaluated by leisure-time exercise questionnaire and then, combined the scores of the moderate and vigorous activities	Cortisol (salivar) ↓
Lambert et al. 2019 [40]	N=25 BC women post treatment phase (at least 6 months) Age: 57.9 years Comparator group: women without BC history Country: Canada	Self-reported PA frequency Participants were dichotomized into groups based on: ≤1x/week, 2-3x/week, 4-5x/week, 6-7x/week and ≥7x/week	Cortisol (salivar) ↔

Table 2. Synthesis of the effects of exercise in BC women

Study Ref.:	**Sample**	**FIIT plan**				**Main Finding**
		Frequency	**I**ntensity	**T**ime	**T**ype	
Payne et al. 2008 [42]	N=10 BC post-menopausal women at post-treatment phase receiving hormonal therapy Age: 64.7±6.3, ranged 56 to78 years Comparator group: usual care (n=10) Country: USA	4 x/week	Moderate, but without monitoring	20 min	Home-based walking exercise	Cortisol (serum) ↔
		During 14 weeks				
Banasik et al. 2010 [47]	N=9 BC women in post-treatment phase (≥2 months) Age: 63.33±6.9 years Comparator group: waitlist Country: USA	2 x/week	Not mentioned	90 min	Yoga classes	Cortisol (salivar) ↓ at morning and 5 p.m.
		During 14 weeks				
Chen et al. 2013 [44]	N=49 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 45.3±6.3, ranged 29 to 58 years Comparator group: waitlist receiving the clinical treatments Country: China	5x/week	Not mentioned	30-40 min	Qigong program	Cortisol (serum) ↔
		During 6 weeks				
Izzicupo P et al. (2013) [54]	N=32 BC in post-treatment phase Age: 56.38±4.33 Comparator group: (no access to full-text)	4x/week	Moderate (no reference what intensity parameter has been used)	40-50 min	Walking	Cortisol (plasma) ↔
		12 weeks				
Saxton et al. 2014 [55]	N= 44 overweight BC women at posttreatment phase (mean of 9.0±5.5) Age: 55.8±10.0 years Comparator group: control group received healthy eating booklet and advice to keeping active Country: UK	3x/week	65-85% age-predicted maximal heart rate	30 min	Aerobic followed by 10-15 min muscle strengthening exercises	Cortisol (salivar) ↑ at 8 a.m.

Table 2 continued

		Lifestyle intervention during 24 weeks: combination of exercise and hypocaloric diet				
Chandwani et al. 2014 [48]	N= 35 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 52.38±1.25, ranged 26 to 77 years Comparator group: stretching and waitlist Country: USA	3x/week	Not mentioned	60 min	Yoga classes	Cortisol (salivar) steeper slope ↓
		During 6 weeks				
Ratcliff et al. 2016 [49]	N=53 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: ≥ 18 years Comparator group: stretching and waitlist Country: USA	3x/week	Not mentioned	60 min	Yoga classes	Cortisol (salivar) steeper slope ↓
		During 6 weeks				
Ho et al. 2016 [45]	N=72 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: ≥ 18 years Comparator group: usual care Country: China	2x/week	Not mentioned	90 min	DMT	Cortisol (salivar) slope ↓
		During 3 weeks				
Evans et al. 2016 [50]	N=9 BC women in post-treatment phase Age: 50±6 VO_2 peak: 18.1±2.7 Comparator group: healthy women (without BC) Country: USA	1 bout of acute exercise	60% VO_2 peak was determined using Astrand cycle ergometer maximal test	30 min (10x3-min of exercise intercalated with 1.5 min of rest, for a total of 30 min of exercise in a 43.5-min period.	Aerobic and intermittent at cycle ergometer	Cortisol (plasma): ↓ post-exercise
Di Blasio et al. 2017	N= 33 BC women in post-treatment phase Age: 51.71±3.17 Comparator groups: i) healthy women and ii) physically active women Country: Italy	3x/week	1st to 4th week: 10 -11 RPE 5th to 8th week: 12 -13 RPE 9th to 12th: 13 -14 RPE	70 min	Nordic walking	Cortisol (salivar) negatively correlated with PA item Cortisol (salivar) ↓

Table 2 continued

		During 12 weeks				
Ho et al. 2018 [56]	N= 69 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 49.1±7.8 Comparator group: usual care receiving radiotherapy Country: China	2x/week	Not mentioned	Not mentioned	DMT	Cortisol (salivar) ↔ At high levels of baseline perceived stress, the DMT group showed a steeper cortisol slope
		During 3 weeks				
Friedenreich C et al. 2019 [46]	N=400 postmenopausal, physically inactive BC women were randomized into 2 groups: i) moderate-volume: 150 min/week or ii) high-volume: 300 min/week Age: 59,6±5.1 years in moderate-volume group 59.4±4.9 years in high-volume group VO_{2max}: 26.8±4.9 mL/kg/min in moderate-volume group and 26.8±5.2 mL/kg/min in high-volume group	5x/week	70–80% heart rate reserve	Not mentioned	Not mentioned 3 supervised sessions and 2 unsupervised sessions	↔ between baseline vs. after 48 weeks and between groups
		During 48 weeks (1 year)				
Toohey K et al. 2020 [57]	N=17 BC and physically inactive women in post-treatment phase Age: 61±7.92 (control group); 65±7.68 (CMIT) and 60±8.12 (HIIT) Comparator group: waitlist Country: Australia	3x/week	50% of maximal power (watts) obtained in cycloergometer	HIIT: completed seven 30 s intervals (as hard as they could) with 2 min of active recovery between each. CMIT: 30 min	Aerobic exercise at cycloergometer	Cortisol (salivar) ↑, expressed as percent change from waking to 30 min post waking in HIIT group

Legend: HIIT: high-intensity interval training, CMIT: continuous and moderate-intensity training; PA: physical activity; DMT: dance movement therapy; RPE: rate of perceived exertion

ticipating in stretching or waitlist control groups. In this study, yoga group was associated with a steeper cortisol slope compared with stretching and waitlist groups. In this line, findings [39,48] support the idea that yoga intervention provided a huge mental health–related benefits for women with elevated sleep disturbance and, to a lesser extent, depressive symptoms prior to the start of radiotherapy. This effect varied in time with differences emerging especially 3 and 6 months after radiotherapy. Of note, some of these findings should be looked with some caution as the reduced reliability of cortisol slopes assessed at later follow-up points (because of a smaller sample size) may have limited the power to detect the effects of cortisol slopes [49]. Moreover, two of these [48,49] studies have assessed salivary cortisol after chemotherapy and during the radiotherapy, excluding other treatments phases. Interestingly, no study has studied the effects of exercise on cortisol variations during diagnosis, chemotherapy or after surgery.

In an exploratory investigation, Evans et al. (2016) [50] aimed to study the effects of one bout of acute exercise on plasma cortisol in BC women in post-treatment phase. Although healthy women without BC history have been used as a comparator group, both groups (intervention and comparator) display identical body index mass, oxygen requirements (18.1±2.7 vs. 18.5±0.83 mL O_2/min/kg, workload (107±19 vs. 106±17 watts), heart rate (68±6 vs. 66±9 bpm) and RPE (12±1 vs. 12±1). This point is very pertinent as the responsiveness of stress hormones is directly proportional to physical and physiological demands of the body [51]. This study brings novel findings demonstrating that cortisol levels changed across time in the BC survivor group with a decrease immediately after exercise session cessation, but without significant changes after 2 h. The intermittent nature of the exercise training protocol may have stimulated the metabolic and hormonal responses differently than continuous exercise, which explain partly the unexpected cortisol variations. Therefore, the implementation of exercise programs with these characteristics (i.e., intercalated with high-intense periods with low-to-moderate periods of exercise) specially in BC patients/survivors are utmost importance to know the potentially of this exercise type.

Exercise-induced fluctuations in plasma cortisol levels typically follow a threshold effect in which exercise at ≥60% of maximal oxygen consumption (VO_2max) of intensity induce increased plasma cortisol concentrations [51]. However, in the Evans's study [50] the intensity prescription was based on VO_2 peak, which is usually slightly lower than VO_2 max. Thus, exercise may not have reached the threshold that was necessary for eliciting an increase in plasma cortisol concentration, and the decreases in plasma cortisol may have occurred because the rate of removal exceeded the rate of secretion [50]. Another important factor that may help to explain the Evan's findings could be the suppressive role of selective estrogens receptor modifiers, such as Tamoxifen, on adrenal corticosteroids release [52]. In fact, Tamoxifen is a selective estrogen receptor modulator widely used in adjuvant therapy for estrogen receptor–positive BC [53]. Considering that BC women generally received chemotherapy and, thereafter, intake hormonal therapy medication, some controverse results may be in part due to the use of current medication.

5. Conclusions

Based on compelling data from studies, the current state of knowledge supports that PA and exercise are interventions that should be included in a BC women's health care program due to their fundamental role in chronic stress management. Although few studies suggest a beneficial effect of exercise in cortisol of BC women during or after radiotherapy, no study has considered other cancer treatments phases. Future studies are warranted to address the effects of PA and also exercise on cortisol patterns of BC women at different cancer treatments phases, along with chronic stress evaluation and other psychological parameters.

Disclosure Statement

The authors do not have any financial interest and did not receive any financial benefit from this research.

Conflict of Interest

The authors state no conflict of interest.

References

[1] Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics. Ca A Cancer Journal for Clinicians. 1(1), 7-34.
DOI: https://doi.org/10.3322/caac.21551

[2] Mattiuzzi, C., Lippi, G., 2020. Cancer statistics: a comparison between World Health Organization (WHO) and Global Burden of Disease (GBD). European Journal of Public Health. 1(5), 1026-1027.
DOI: https://doi.org/10.1093/eurpub/ckz216

[3] Cuevas, B.T., Hughes, D.C., Parma, D.L., et al., 2014. Motivation, exercise, and stress in breast cancer survivors. Support Care Cancer. 4, 911-917.
DOI: https://doi.org/10.1007/s00520-013-2038-6

[4] Botto, R., Leonardis, B.D., Salussolia, A., et al., 2022. Assessment of anxiety, depression, and dis-

tress in breast cancer patients: A comparison among different phases of illness. Health Care for Women International. 1-13.
DOI: https://doi.org/10.1080/07399332.2022.2078325

[5] Sanchez, L., Fernandez, N., Calle, A.P., et al., 2019. Long-term treatment for emotional distress in women with breast cancer. European Journal of Oncology Nursing. 126-133.
DOI: https://doi.org/10.1016/j.ejon.2019.09.002

[6] Phoosuwan, N., Lundberg, P.C., 2022. Psychological distress and health-related quality of life among women with breast cancer: a descriptive cross-sectional study. Supportive Care in Cancer. 4, 3177-3186.
DOI: https://doi.org/10.1007/s00520-021-06763-z

[7] Wüst, S., Wolf, J., Hellhammer, D.H., et al., 2000. The cortisol awakening response - normal values and confounds. Noise Health. 7, 79-88.

[8] van der Pompe, G., Antoni, M.H., Heijnen, C.J., 1996. Elevated basal cortisol levels and attenuated ACTH and cortisol responses to a behavioral challenge in women with metastatic breast cancer. Psychoneuroendocrinology. 4, 361-374.
DOI: https://doi.org/10.1016/0306-4530(96)00009-1

[9] Touitou, Y., Bogdan, A., Benavides, M., et al., 1996. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens. British Journal of Cancer. 8, 1248-1252.
DOI: https://doi.org/10.1038/bjc.1996.524

[10] Rocha-Rodrigues, S., 2021. Physical exercise and sex steroid hormones in breast cancer. Human Movement. 2, 1-8.
DOI: https://doi.org/10.5114/hm.2021.100006

[11] Jia, T.T., Liu, Y.F., Fan, Y.Y., et al., 2022. Association of Healthy Diet and Physical Activity With Breast Cancer: Lifestyle Interventions and Oncology Education. Front Public Health. 797794.
DOI: https://doi.org/10.3389/fpubh.2022.797794

[12] Lee, K.J., An, K.O., 2022. Impact of High-Intensity Circuit Resistance Exercise on Physical Fitness, Inflammation, and Immune Cells in Female Breast Cancer Survivors: A Randomized Control Trial. International Journal of Environmental Research and Public Health. 9.
DOI: https://doi.org/10.3390/ijerph19095463

[13] Enayatjazi, M., Esfarjani, F., Reisi, J., et al., 2022. Studying the Effect of Garlic Consumption and Endurance Training on Serum Levels of Some Pro-and Anti-inflammatory Cytokines in Female Mice with Breast Cancer - A Randomized Trial. International Journal of Preventive Medicine. 13(1), 38.
DOI: https://doi.org/10.4103/ijpvm.IJPVM_315_20

[14] Corazza, D.I., Sebastião, É., Pedroso, R.V., et al., 2014. Influence of chronic exercise on serum cortisol levels in older adults. European Review of Aging and Physical Activity. 1, 25-34.
DOI: https://doi.org/10.1007/s11556-013-0126-8

[15] Laugero, K.D., Falcon, L.M., Tucker, K.L., 2011. Relationship between perceived stress and dietary and activity patterns in older adults participating in the Boston Puerto Rican Health Study. Appetite. 1, 194-204.
DOI: https://doi.org/10.1016/j.appet.2010.11.001

[16] Hayes, L.D., Grace, F.M., Baker, J.S., et al., 2015. Exercise-induced responses in salivary testosterone, cortisol, and their ratios in men: a meta-analysis. Sports Medicine. 5, 713-726.
DOI: https://doi.org/10.1007/s40279-015-0306-y

[17] De Nys, L., Anderson, K., Ofosu, E.F., et al., 2022. The effects of physical activity on cortisol and sleep: A systematic review and meta-analysis. Psychoneuroendocrinology. 143, 105843.
DOI: https://doi.org/10.1016/j.psyneuen.2022.105843

[18] Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues in Clinical Neuroscince. 4, 383-395.
DOI: https://doi.org/10.31887/DCNS.2006.8.4/ssmith

[19] Wendel, J., Verma, A., Dhevan, V., et al., 2021. Stress and Molecular Drivers for Cancer Progression: A Longstanding Hypothesis. Biomedical Journal of Scintific and Technical Research. 1, 29134-29138.
DOI: https://doi.org/10.26717/bjstr.2021.37.005953

[20] Arnsten, A.F., 2015. Stress weakens prefrontal networks: molecular insults to higher cognition. Nature Neuroscince. 10, 1376-1385.
DOI: https://doi.org/10.1038/nn.4087

[21] Tian, W.T., Liu, Y., Cao, Ch.H., et al., 2021. Chronic Stress: Impacts on Tumor Microenvironment and Implications for Anti-Cancer Treatments. Frontiers in Cell and Developmental Biology. 777018.
DOI: https://doi.org/10.3389/fcell.2021.777018

[22] Chiarugi, P., Filippi, L., 2015. β3-adrenoreceptor and tumor microenvironment: a new hub. Oncoimmunology. 11, e1026532.
DOI: https://doi.org/10.1080/2162402x.2015.1026532

[23] Fabre, B., Grosman, H., Gonzalez, D., et al., 2016. Prostate Cancer, High Cortisol Levels and Complex Hormonal Interaction. Asian Pacific Journal of Cancer Prevention. 7, 3167-3171.

[24] Flores, I.E., Sierra, F.J.A., Davalos, O., et al., 2017.

Stress alters the expression of cancer-related genes in the prostate. BMC Cancer. 1, 621.
DOI: https://doi.org/10.1186/s12885-017-3635-4

[25] Bowen, D., Poole, S.F., White, M., et al., 2021. The Role of Stress in Breast Cancer Incidence: Risk Factors, Interventions, and Directions for the Future. International Journal of Environmental Research and Public Health. 4.
DOI: https://doi.org/10.3390/ijerph18041871

[26] Sistigu, A., Musella, M., Galassi, C., et al., 2020. Tuning Cancer Fate: Tumor Microenvironment's Role in Cancer Stem Cell Quiescence and Reawakening. Frontiers in Immunology. 2166.
DOI: https://doi.org/10.3389/fimmu.2020.02166

[27] Zhang, X., Zhang, Y., He, Z., et al., 2019. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death and Disease. 11, 788.
DOI: https://doi.org/10.1038/s41419-019-2030-2

[28] Jafri, S.H., Ali, F., Mollaeian, A., et al., 2019. Major Stressful Life Events and Risk of Developing Lung Cancer: A Case-Control Study. Clinical Medicine Insights Oncology. 1179554919835798.
DOI: https://doi.org/10.1177/1179554919835798

[29] Kadmiel, M., Cidlowski, J.A., 2013. Glucocorticoid receptor signaling in health and disease. Trends in Pharmacology Sciences. 9, 518-530.
DOI: https://doi.org/10.1016/j.tips.2013.07.003

[30] Smyth, J.M., Ockenfels, M.C., Gorin, A.A., et al., 1997. Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology. 2, 89-105.
DOI: https://doi.org/10.1016/s0306-4530(96)00039-x

[31] Lee, D.Y., Kim, E., Choi, M.H., 2015. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB Reports. 4, 209-216.
DOI: https://doi.org/10.5483/bmbrep.2015.48.4.275

[32] Spiegel, D., Giese-Davis, J., Taylor, C.B., et al., 2006. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology. 10, 1231-1244.
DOI: https://doi.org/10.1016/j.psyneuen.2006.09.004

[33] Obradović, M.M.S., Hamelin, B., Manevski, N., et al., 2019. Glucocorticoids promote breast cancer metastasis. Nature. 7749, 540-544.
DOI: https://doi.org/10.1038/s41586-019-1019-4

[34] Zhao, X.Y., Malloy, P.J., Krishnan, A.V., et al., 2000. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. Nature Medicine. 6, 703-706.
DOI: https://doi.org/10.1038/76287

[35] Caspersen, C.J., Powell, K.E., Christenson, G.M., 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports. 2, 126-131.

[36] Ficarra, S., Thomas, E., Bianco, A., et al., 2022. Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review. Breast Cancer. 3, 402-418.
DOI: https://doi.org/10.1007/s12282-022-01347-z

[37] Yang, H.Ch., Yang, Zh., Pan, H.Y., et al., 2021. Effects of physical activity on sleep problems in breast cancer survivors: a meta-analysis. Support Care Cancer. 7, 4023-4032.
DOI: https://doi.org/10.1007/s00520-020-05914-y

[38] Marinho, M.S., Rocha-Rodrigues, B.S., 2021. Depression And Quality Of Life In Physically Active Breast Cancer Survivors. Proceedings of XVI International Conference in Physical Education, Leisure and Health. 49.

[39] Di Blasio, A., Morano, T., Cianchetti, E., et al., 2017. Psychophysical health status of breast cancer survivors and effects of 12 weeks of aerobic training. Complementary Therapies in Clinical Practice. 19-26.
DOI: https://doi.org/10.1016/j.ctcp.2017.01.004

[40] Lambert, M., Brunet, J., Couture-Lalande, M.E., et al., 2019. Aerobic physical activity and salivary cortisol levels among women with a history of breast cancer. Complementary Therapies in Medicine. 12-18.
DOI: https://doi.org/10.1016/j.ctim.2018.10.018

[41] Castonguay, A.L., Wrosch, C., Sabiston, C.M., 2017. The roles of negative affect and goal adjustment capacities in breast cancer survivors: Associations with physical activity and diurnal cortisol secretion. Health Psychology. 4, 320-331.
DOI: https://doi.org/10.1037/hea0000477

[42] Payne, J.K., Held, J., Thorpe, J., et al., 2008. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncology Nursing Forum. 4, 635-642.
DOI: https://doi.org/10.1188/08.Onf.635-642

[43] Arikawa, A.Y., Thomas, W., Patel, S.R., et al., 2013. No effect of exercise on urinary 6-sulfatoxymelatonin and catecholamines in young women participating in a 16-week randomized controlled trial. Cancer Epidemiology, Biomarkers and Prevention. 9, 1634-1636.
DOI: https://doi.org/10.1158/1055-9965.Epi-13-0583

[44] Chen, Z., Meng, Z., Milbury, K., et al., 2013. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized

controlled trial. Cancer. 9, 1690-1698.
DOI: https://doi.org/10.1002/cncr.27904

[45] Ho, R.T., Fong, T.C.T., Cheung, I.K.M., et al., 2016. Effects of a Short-Term Dance Movement Therapy Program on Symptoms and Stress in Patients With Breast Cancer Undergoing Radiotherapy: A Randomized, Controlled, Single-Blind Trial. Journal of Pain Symptom Manage. 5, 824-831.
DOI: https://doi.org/10.1016/j.jpainsymman.2015.12.332

[46] Friedenreich, C.M., Wang, Q., Shaw, E., et al., 2019. The effect of prescribed exercise volume on biomarkers of chronic stress in postmenopausal women: Results from the Breast Cancer and Exercise Trial in Alberta (BETA). Preventive Medicine Reports. 100960.
DOI: https://doi.org/10.1016/j.pmedr.2019.100960

[47] Banasik, J., Williams, H., Haberman, M., et al., 2011. Effect of Iyengar yoga practice on fatigue and diurnal salivary cortisol concentration in breast cancer survivors. Journal of the American Academy of Nurse Practice. 3, 135-142.
DOI: https://doi.org/10.1111/j.1745-7599.2010.00573.x

[48] Chandwani, K.D., Perkins, G., Nagendra, H.R., et al., 2014. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. Journal of Clinical Oncology. 10, 1058-1065.
DOI: https://doi.org/10.1200/jco.2012.48.2752

[49] Ratcliff, C.G., Milbury, K., Chandwani, K.D., et al., 2016. Examining Mediators and Moderators of Yoga for Women With Breast Cancer Undergoing Radiotherapy. Integrative Cancer Therapies. 3, 250-262.
DOI: https://doi.org/10.1177/1534735415624141

[50] Oppermann, H., Dulz, A., Helmeke, C., et al., 2016. Adrenal Hormone and Metabolic Biomarker Responses to 30 min of Intermittent Cycling Exercise in Breast Cancer Survivors. International Journal of Sports Medicine. 12, 921-929.
DOI: https://doi.org/10.1055/s-0042-110654

[51] McMurray, R.G., 1993. *E*xercise and Sport Science Reviews, Volume 21 JO Holloszy,(Ed.). LWW.

[52] Genazzani, A.R., Lombardi, I., Borgioli, G., et al., 2003. Adrenal function under long-term raloxifene administration. Gynecological endocrinology. 2, 159-168.

[53] An, K.C., 2016. Selective Estrogen Receptor Modulators. Asian Spine Journal. 4, 787-791.
DOI: https://doi.org/10.4184/asj.2016.10.4.787

[54] Izzicupo, P., D'Amico, M.A., Bascelli, A., et al., 2013. Walking training affects dehydroepiandrosterone sulfate and inflammation independent of changes in spontaneous physical activity. Menopause. 4, 455-463.
DOI: https://doi.org/10.1097/gme.0b013e31827425c9

[55] Saxton, J.M., Scott, E.J., Daley, A.J., et al., 2014. Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomised controlled trial. Breast Cancer Research. 2, R39.
DOI: https://doi.org/10.1186/bcr3643

[56] Ho, R.T.H., Fong, T.C.T., Yip, P.S.F., 2018. Perceived stress moderates the effects of a randomized trial of dance movement therapy on diurnal cortisol slopes in breast cancer patients. Psychoneuroendocrinology. 119-126.
DOI: https://doi.org/10.1016/j.psyneuen.2017.10.012

[57] Toohey, K., Pumpa, K., McKune, A., et al., 2020. The impact of high-intensity interval training exercise on breast cancer survivors: a pilot study to explore fitness, cardiac regulation and biomarkers of the stress systems. BMC Cancer. 1(1), 787.
DOI: https://doi.org/10.1186/s12885-020-07295-1

BILINGUAL
PUBLISHING CO.
Pioneer of Global Academics Since 1984

Tel: +65 65881289
E-mail: contact@bilpublishing.com
Website: ojs.bilpublishing.com

2630-5224
02
9 772630 522221