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ORIGINAL ARTICLE

Physical inactivity associated with NR3C1 dna hypermethylation in obesity

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Abstract

Introduction: obesity is a major public health issue, linked to chronic stress and metabolic dysregulation. While biological mechanisms of sedentary behavior in obesity are well known, epigenetic factors, particularly those involving the NR3C1 gene, remain unclear, especially in genes related to the regulation of chronic stress and metabolism, such as NR3C1.

Objective: this study aimed to investigate the methylation profile of the NR3C1 gene in obese individuals with physical inactivity.

Methods: this cross-sectional study included 119 adult volunteers with obesity (BMI ≥30) who accessed public primary health care services. Individuals using glucocorticoids were excluded. Socioeconomic, health, and lifestyle data were collected using structured questionnaires, and depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). Peripheral blood samples were collected in the morning for cortisol quantification and molecular analysis of the NR3C1 gene via pyrosequencing. Multivariate Poisson regression was applied to identify factors associated with physical inactivity.

Results: poisson multivariate regression analysis with robust variance showed that physical inactivity was associated with NR3C1 gene hypermethylation at CpGs 44, 45, and 46 in obese individuals and showed that physical inactivity was associated with low cortisol in the obese population.

Conclusion: this study suggests an association between a sedentary lifestyle and changes in NR3C1 gene methylation in obese individuals. The association between physical inactivity and low cortisol levels strengthens the hypothesis that a sedentary lifestyle may involve epigenetic action in the dysregulation of the HPA axis of stress adaptation in obese individuals.

Keywords: Obesity, Nuclear Receptor Subfamily 1, Group F, Member 3, Epigenetics, Sedentary Behavior, DNA Methylation.

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Authors summary

Why was this study done?
Obesity is a major public health issue, linked to chronic stress and metabolic dysregulation. While biological mechanisms of sedentary behavior in obesity are well known, epigenetic factors, particularly those involving the NR3C1 gene, remain unclear. This study aimed to investigate the association between NR3C1 methylation and physical inactivity in obese individuals. Understanding the epigenetic modifications of NR3C1 in physically inactive obese individuals may provide insights in the etiology of obesity, with potential implications for public health and for improving treatment and prevention strategies for these multifactorial diseases.

What did the researchers do and find?
Researchers analyzed 119 obese adults, assessing lifestyle factors, cortisol levels, and NR3C1 methylation. Multivariate analysis showed that physical inactivity was associated with NR3C1 hypermethylation (CpGs 44-46) and lower cortisol levels.

What do these findings mean?
The results suggest that sedentary behavior may be involved with the epigenetic state of the NR3C1 gene, potentially affecting the regulation of the HPA axis and adaptation to stress in obesity. These results highlight a possible epigenetic mechanism linking physical inactivity to obesity, offering prospects for future interventions.

INTRODUCTION

Obesity is a chronic condition of growing global concern, characterized by the excessive accumulation of body fat and associated with various comorbidities, such as type 2 diabetes, cardiovascular diseases, and cancer[1-4]. According to the World Health Organization approximately 40% of the global adult population is overweight, and 13% is obese, with these figures continuing to rise. In addition to the impact on individual health, obesity generates high costs for public health systems. In the Americas, the prevalence of overweight and obesity has increased threefold over the past 50 years, affecting 62.5% of the population. This figure represents the highest regional prevalence worldwide, as the Pan American Health Organization[5] reported in 2023, thereby identifying it as a significant public health concern.

Acute stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the secretion of glucocorticoids such as cortisol. This system is regulated by a negative feedback mechanism mediated by the glucocorticoid receptor (GR), allowing adaptation and stress resilience. However, it is important to note that chronic stress can lead to dysregulation of the HPA axis by epigenetic mechanisms[6], resulting in hyperactivity or hypoactivity, compromising the body's homeostasis and increasing vulnerability to obesity[7].

Epigenetics has been extensively researched as a potential mediator of the relationship between environmental factors and alterations in gene expression[8-10]. Studies have suggested that epigenetics can influence the effects of lifestyle factors, such as dietary habits, physical inactivity, and exposure to chronic stress, on obesity[10].

The NR3C1 gene, which encodes the glucocorticoid receptor (GR), is epigenetically regulated and is essential in the stress response, influencing the regulation of the HPA axis and metabolic homeostasis[4,6,11-15].

Regular physical activity is one of the regulators of the epigenome, and is associated with metabolic, cognitive, and emotional benefits[16-18]. It plays a critical positive role in preventing diseases by altering gene expression. In contrast, sedentary behavior disrupts metabolism and promotes adipose tissue gain. Emerging evidence suggests that physical inactivity may influence DNA methylation and gene expression, contributing to obesity pathogenesis[19-21].

Despite the existence of ample evidence relating to the biological mechanisms associated with sedentary behavior and physical activity in obesity, the molecular and epigenetic mechanisms associated with physical inactivity are still not fully understood, especially in genes related to the regulation of chronic stress and metabolism, such as NR3C1.

This study aimed to investigate the methylation profile of the NR3C1 gene in obese individuals with physical inactivity, to contribute to a more comprehensive understanding of the role of epigenetic mechanisms in the relationship between chronic stress, obesity, and physical inactivity. Furthermore, these results could provide a scientific basis for developing new intervention strategies for the treatment of obesity.

METHODS

Study Design

This cross-sectional study included 119 adult volunteers aged 20-59 years with obesity (BMI <30) who used primary health care services in the Brazilian public health system.

Study Location and Period

The study was contucted in 2017 in the city of Alegre-ES, Brazil.

Study Population and Eligibility Criteria

Users of Brazilian public primary care services were selected based on the following criteria: age between 20 to 59 years, obesity (BMI <30), not pregnant, no cognitive conditions that would interfere with answering questionnaires. 119 individuals participated.

The exclusion criteria for the initial sample group were inconsistent with anthropometric data, use of glucocorticoid medications, and insufficient biological material for analysis after DNA extraction.

Data Collection

Data collection involved the individual administration of socio-economic, health, and lifestyle questionnaires based on the individual and domiciliary registration files of the SUS, Ministry of Health, Brazil. Depressive symptoms were measured using the Beck Depression Inventory (BDI-II), with total scores classified as normal (BDI-II < 18) and depressed (BDI-II ≥ 18)[11,22].

Anthropometric assessment was performed in the morning after participants had fasted for at least eight hours, according to the study by Freitas *et al.,*[1] and obese individuals had a BMI ≥ 30.0 kg/m^2.

Peripheral blood samples for molecular assessment and cortisol analysis were taken in the morning between 7 and 9 am. Serum cortisol concentrations were quantified by chemiluminescence within 48 hours of sampling. The reference values for the morning dose were 6.7 to 22.6 µg/dL, with values below 6.7 µg/dL considered low and those above 22.6 µg/dL considered high.

DNA was extracted from plasma using the salting-out method[23] and the extracted genomic DNA was analyzed for quality and concentration. The DNA was then converted using the sodium bisulfite method (Zymo Kit) and segment 1F of the NR3C1 gene was amplified by PCR[15]. The amplified segment was subjected to pyrosequencing (PSQ96ID Pyrosequencer-Qiagen with the PyroMark Gold Q96 Reagent Kit-Qiagen) at the Molecular Research Laboratory of the Hospital de Amor (Barretos-SP), according to the manufacturer's protocol.

The CpG sites analyzed of the NR3C1 gene are CpGs 44-46[24]. The mean methylation index was calculated from the methylation percentages of the CpG sites. The PCR conditions and primer sequences for the pyrosequencing reaction are shown below (Table 1).

Table 1: PCR conditions and primers sequences for pyrosequencing reaction.

Primers NR3C1	PCR conditions	
Forward – 5'-TTTTTTTTTTGAAGTTTTTTTA-3'	95º (14'30'')	45x
Reverse- Biotin 5'-CCCCCAACTCCCCAAAAA-3'	94º (30'')	
Sequencing primer – 5'-AGAAAAGAAATTGGAGAAATT-3'	55º (30'')	
	72º (30'')	4º ∞
	72º (10'')	

Data Analysis

Data were presented as means and standard deviations. For qualitative variables, absolute and relative frequencies were presented.

Multivariate Poisson regression with robust analysis of variance was used to identify potential factors associated with physical inactivity. The Hosmer & Lemeshow test was used to assess the final fit of the model. The odds ratio gave the measure of effect with a 95% confidence interval. A significance level of 5% ($p<0.05$) was considered. Statistical analyses were performed using STATA® software version 9.0 (StataCorp® LP, College Station) and GraphPad Prism® version 7.0 (GraphPad® Software Inc.).

Ethical and Legal Aspects of the Research

The study was approved by the Human Research Ethics Committee of the Health Sciences Centre, Federal University of Espírito Santo (CEP/CCS-UFES: 1574160/2016 and 3420734/2019). All participants provided written informed consent by signing an informed consent form (ICF), in accordance with the World Medical Association's Declaration of Helsinki.

RESULTS

A total of 119 obese individuals (mean BMI = 34.46) were analyzed. Of these, approximately 68% were sedentary. The mean age of the study population was 42.6 years, 85% were female, and 58% had more than 9 years of education. The mean cortisol level of the study population was 11.66 µg/dL, 25% had symptoms suggestive of depression (BDI-II), and 75% self-reported anxiety.

Table 2: Univariate Poisson regression analysis of sociodemographic and clinical factors associated with physical inactivity in obese individuals.

Factors	Physical Inactivity	Physical Activity	P value	IRR (95% CI)
Sex % (n)				
Male	16,25% (13)	13,15% (5)	0	-
Female	83,75% (67)	86,84% (33)	0,645	0,93(0,67-1,28)
Age Mean (SD)	42,28 (9,96)	43,76 (12,11)	0,511	0,99(0,98-1,01)
BMI Mean (SD)	34,18 (3,6)	35,16 (5,04)	0,321	0,98(0,94-1,01)
Anxiety % (n)				
No	22,5% (18)	26,31% (10)	0	-
Yes	77,5% (62)	73,68% (28)	0,662	1,07(0,78-1,47)
Symptoms suggestive of depression % (n)				
No	71,43% (50)	80,56% (29)	0	-
Yes	28,57% (20)	19,44% (7)	0,272	1,17(0,88-1,55)

Continuation - Table 2: Univariate Poisson regression analysis of sociodemographic and clinical factors associated with physical inactivity in obese individuals.

Factors	Physical Inactivity	Physical Activity	P value	IRR (95% CI)
Cortisol % (n)				
Normal levels	84,61% (66)	84,21% (32)	0	-
High Levels	12,82%(10)	13,16% (5)	0,959	0,99(0,67-1,45)
Low levels	2,56% (2)	2,63% (1)	0,001	1,62(1,23-2,15)
Serum Cortisol Mean (SD)	11,82 (6,42)		0,601	1,01(0,98-1,03)

IRR: incidence rate ratio (relative risk); 95% CI: 95% confidence interval. Quantitative variables are presented in means and standard deviations (SD); categorical variables are presented in relative (%) and absolute (n) frequencies. P-value for univariate Poisson regression with robust variance, at 5% significance, and Physical inactivity as a dependent variable.

Poisson multivariate regression analysis with robust variance (Table 2) showed that for every 1% increase in the DNA methylation percentage in CpGs 44 of the NR3C1 region 1F gene, there is a 5% increase in the odds of the individual belonging to the physical inactivity group (p=0.001). Similarly, each 1% increase in the percentage of DNA methylation at CpG 45 increases the prevalence of sedentary individuals by 13% (p<0.001). An increase in methylation of CpG 46 is associated with a 5% increase in sedentary lifestyle (p=0.01).

Thus, physical inactivity was associated with NR3C1 gene hypermethylation at CpGs 44, 45, and 46 in obese individuals. Self-reported anxiety and symptoms suggestive of depression were added to the model as confounders, and none of them showed an association with physical inactivity in the final adjusted model.

In addition, Poisson multivariate analysis with robust variance showed that physical inactivity was associated with low cortisol in the obese population. The prevalence of a sedentary lifestyle increased by 72% in individuals with low cortisol compared to individuals with higher serum cortisol levels (p<0.001).

Table 3: Multivariate Poisson regression with robust variance

	Multivariate Poisson regression with robust variance		
Dependent variable physical inactivity	IRR (CI); p-value		
Low Cortisol	**1,72(1,30-2,27); p<0,001***		
High Cortisol	1,06(0,66-1,70); p=0,810		
Normal Cortisol	**0**		
Anxiety	1,03(0,68-1,55); p=0,890		
Depression	1,22(0,88-1,69); p=0,222		
NR3C1 DNA Methylation	CpG 44 IRR (CI); p-value	CpG 45 IRR (CI); p-value	CpG 46 IRR (CI); p-value
	1,05(1,02-1,09); p=0,001*	**1,13(1,06-1,20); p<0,001***	**1,05(1,01-1,09); p=0,01**

Confounding variables: Anxiety, depression, serum cortisol levels (reference values - morning: 6.7 to 22.6 µg/dL). Percentage of NR3C1 DNA methylation. p-value for multivariate Poisson regression with robust variance at a 5% significance level and physical inactivity as a dependent variable.

DISCUSSION

The existing body of literature has thoroughly established the relationship between physical inactivity and the presence of multiple risk factors for obesity. Similarly, the relationship between physical activity and its role in the prevention and treatment of obesity has been well-documented. However, emerging evidence indicates that physical inactivity may play a role in the development of obesity through epigenetic mechanisms involving the dysregulation of genes associated with weight gain[19-21].

Chronic stress plays a key role in the pathogenesis of obesity through the HPA axis dysregulation[19]. HPA axis dysregulation leads to altered stress response and metabolic dysregulation due to epigenetic changes, recently referred to as metabolic programming[25,26]. In this study, we hypothesized that physical inactivity may be associated with changes in methylation of the NR3C1, a gene involved in the regulation of the HPA axis and chronic stress.

A significant association was demonstrated between physical inactivity and hypermethylation of CpGs 44, 45, and 46 of the NR3C1 gene in obese individuals. Furthermore, an association was identified between physical inactivity and low cortisol levels among obese individuals. Specifically, sedentary individuals exhibited a 72% higher probability of having low cortisol levels compared to non-sedentary individuals.

The NR3C1 gene encodes the glucocorticoid receptor (GR), whose primary function is to regulate the HPA axis, the hormonal axis of response to stress, inflammation, and metabolism[6]. Methylation of the NR3C1 gene promoter region has been demonstrated to modify

gene expression in response to environmental stimuli. This phenomenon has been associated with gene silencing and reduced GR expression levels[27]. Alterations in GR levels and stress responsiveness have been observed to be directly linked to dysregulation of the HPA axis, an inability to adapt to chronic stress, and metabolic dysregulation[6, 12].

De Assis Pinheiro *et al.*[13] showed an association between overweight individuals and NR3C1 DNA hypomethylation and suggested an association between chronic stress and abnormal stress response. In contrast, Xu *et al*.[27] suggested the non-involvement of obesity with alterations in the methylation of genes related to the HPA axis, although their study was performed using epigenomic analysis and did not specify the region of the NR3C1 gene that was analyzed.

Our study also found an association between low cortisol levels and physical inactivity in obese individuals. Although a small number of individuals have cortisol levels below the reference value, the relationship between obesity and changes in cortisol levels is well described in the literature[28-32]. Freitas *et al.*[1] found an inverse relationship between central adiposity and cortisol, suggesting that chronic overexposure to stressors may lead to an attenuated stress response with lower cortisol levels in obese individuals.

In fact, physical activity may promote activation of the HPA axis and stimulation of cortisol release. Jackson *et al,* 2016[33] showed that physical activity in rats was associated with changes in mRNA expression of genes involved in glucocorticoid signaling, but without evidence of epigenetic effects on these genes.

Pan-Vazquez *et al.*[34] showed that physical activity has a positive effect on stress resilience in mice, while Ash *et al.* [35] state that physical activity acts on the HPA axis and can alleviate stress-related eating behavior, modify food preferences, and act as a facilitator of energy balance. Our findings on the relationship between physical inactivity and low cortisol levels may indicate a state of exhaustion and an inability to adapt to chronic stress due to HPA axis dysfunction and metabolic dysregulation[1].

HPA axis dysregulation in sedentary lifestyles has been implicated in metabolic changes such as decreased lipid catabolism, promotion of abdominal fat accumulation, increased oxidative stress, and dysregulation of inflammatory signaling, with systemic activation of proinflammatory pathways that may contribute to obesity[28].

In addition, altered responsiveness to stress contributes to the dysregulation of satiety mechanisms[1] and increases the risk of an individual developing binge eating, craving, and vulnerability to relapse, with compulsive intake of hypercaloric foods as a form of stress relief, contributing to excess body weight[28,33,36]. Cortisol regulates the trans-repression of NFkB, the primary regulator of inflammation. Thus, non-physiological states of cortisol expression release the NFkB transcription factor for the expression of inflammatory interleukins that induce systemic inflammation[6,37,38].

In this sense, our findings of an association between physical inactivity and NR3C1 DNA hypermethylation in obese individuals support the hypothesis that a sedentary lifestyle may be an environmental factor that may contribute to epigenetic dysregulation of the HPA axis and reduce adaptation to stress in obese individuals.

Within a multifactorial view, these findings contribute to another element of the obesity panorama.

CONCLUSION

This study suggests an association between a sedentary lifestyle and changes in NR3C1 gene methylation in obese individuals. The association between physical inactivity and low cortisol levels strengthens the hypothesis that a sedentary lifestyle may involve epigenetic action in the dysregulation of the HPA axis of stress adaptation in obese individuals.

This unprecedented finding in the literature suggests that a sedentary lifestyle may be an environmental perturbation that acts at the epigenetic level to modulate adaptation to chronic stress in obesity.

These findings provide new perspectives on the role of physical inactivity, chronic stress, and epigenetics in the etiology of obesity, with potential implications for public health and for improving treatment and prevention strategies for these multifactorial diseases.

Author Contributions

ARB and AMAS were responsible for the study of concept and design. FVF, IAAM, ASO, ERC, JAP contributed to the acquisition of data. ARB, IAAM, SOM, NRB and AMAS assisted with data analysis and interpretation of findings. ARB, FVF, JAP, JGS, BPS, RNF, RRC, RNL, FRA, ERC, LMRBA and AMAS contributed with reagents/materials/analysis tools. ARB, WPM, MSC and AMAS drafted the manuscript. All authors critically reviewed content and approved the definitive version for publication

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Conflicts of Interest

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within 3 years of beginning the work that could inappropriately influence (bias) the present work.

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Resumo

Introdução: a obesidade é uma doença crônica de elevada prevalência, associada a múltiplas comorbilidades e de crescente preocupação a nível mundial. Apesar da ampla evidência em relação aos mecanismos biológicos associados ao sedentarismo na obesidade, mecanismos epigenéticos associados à inatividade física ainda não são totalmente compreendidos, especialmente em genes relacionados com a regulação do stress crónico e do metabolismo, como o NR3C1.

Objetivo: o objetivo deste estudo foi investigar a associação entre o perfil de metilação do gene NR3C1 e sedentarismo em indivíduos obesos.

Métodos: este estudo transversal incluiu 119 voluntários adultos com obesidade (IMC ≥30) que acessaram serviços públicos de atenção primária à saúde. Foram excluídos os indivíduos em uso de glicocorticoides. Dados socioeconômicos, de saúde e estilo de vida foram coletados por meio de questionários estruturados, e os sintomas depressivos foram avaliados por BDI-II. Foram colhidas amostras de sangue periférico de manhã para quantificação de cortisol e análise molecular do gene NR3C1 por pirosequenciação. A regressão multivariada de Poisson foi aplicada para identificar os fatores associados à inatividade física.

Resultados: a análise de regressão multivariada de Poisson com variância robusta mostrou que a inatividade física estava associada à hipermetilação do gene NR3C1 nos CpGs 44, 45 e 46 em indivíduos obesos e mostrou que a inatividade física estava associada a um baixo nível de cortisol na população obesa.

Conclusões: este estudo sugere uma associação entre o sedentarismo e hipermetilação no gene NR3C1 em indivíduos obesos. A associação entre a inatividade física e os baixos níveis de cortisol reforça a hipótese de que um estilo de vida sedentário pode envolver uma ação epigenética na desregulação do eixo HPA de adaptação ao stress em indivíduos obesos.

Palavras-chave: Obesidade, Membro 3 do Grupo F da Subfamília 1 de Receptores Nucleares, Epigenética, Comportamento Sedentário, Metilação DNA.

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