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EFFECTS OF HIGH INTENSITY-INTERVAL TRAINING ON CARDIOVASCULAR RISK, BODY MASS INDEX AND METABOLIC MARKERS IN HEALTHCARE WORKERS

EFECTO DE ENTRENAMIENTO POR INTERVALOS DE ALTA INTENSIDAD SOBRE RIESGO CARDIOVASCULAR, ÍNDICE DE MASA CORPORAL Y MARCADORES METABÓLICOS EN PERSONAL DE SALUD

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ABSTRACT

Objectives: The obesity epidemic in Mexico has caused a health crisis. This places great importance in the identification of useful methods to manage it across all populations. In this present study we evaluate the effect of high intensity interval training in healthcare workers. Methods: An intervention was carried out that consisted in 60 sessions of high intensity interval training during a 12 week period aimed at health care workers working at the General Hospital in Montemorelos, Mexico. Variables regarding body composition, cholesterol and arterial blood pressure were evaluated for each individual both before and after the intervention. Pearson coefficients were estimated between the initial and final values. Results: 8 participants were included, 55.6% men aged 32.8 ± 10.9 years with a BMI of 31.69 ± 2.9 . A statistically significant difference was found between the initial and final values of weight, BMI, total cholesterol, mean arterial blood pressure, and cardiovascular risk at 10 years. Conclusions: These results reveal a significant decrease in our variables related to obesity in healthcare workers after a HIIT intervention in an uncontrolled setting. We recommend the further implementation of similar studies with greater sample size, intensity and duration to target obesity which is the root cause of chronic noncommunicable diseases. Further studies are required to confirm the effect of this intervention in the prevention, treatment of obesity in health care workers and to describe its long term effects.

Keywords: Physical Exercise; Overweight; Obesity. (Source: MESH-NLM)

RESUMEN

Introducción: La obesidad juega un papel importante en las enfermedades crónicas no transmisibles que ha provocado una crisis de salud en México. Es de gran importancia encontrar métodos útiles para enfrentarla en todas las poblaciones. OBJETIVOS En el presente estudio evaluamos el efecto del entrenamiento por intervalos de alta intensidad en trabajadores de la salud. Métodos: Se realizó una intervención que consistió en 60 sesiones de entrenamiento con intervalos de alta intensidad durante un período de 12 semanas dirigido a trabajadores de la salud que laboran en el Hospital General de Montemorelos, México. Se evaluaron las variables de composición corporal, colesterol y presión arterial de cada individuo antes y después de la intervención. Se estimaron coeficientes de Pearson entre los valores inicial y final. Resultados: Se incluyeron 8 participantes de 32,8 \pm 10,9 años con un IMC de 31,69 \pm 2,9. Se encontró diferencia estadísticamente significativa entre los valores inicial y final de peso, IMC, colesterol total, presión arterial media y riesgo cardiovascular a los 10 años. Conclusiones: Estos resultados revelan una disminución significativa de nuestras variables relacionadas con la obesidad en el personal de la salud tras una intervención HIIT en un entorno no controlado. Recomendamos la implementación adicional de estudios similares con mayor tamaño de muestra, intensidad y duración para abordar la obesidad.

Palabras claves: Ejercicio físico; Sobrepeso; Obesidad. (Fuente: DeCS-BIREME)

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INTRODUCTION

The World Health Organization (WHO) defines obesity as an excessive accumulation of fat that is detrimental to health. In addition, it recognizes this as a health problem that constitutes a global epidemic (1). Worldwide, the prevalence of obesity has tripled between 1975 and 2016, reaching figures of more than 1.9 billion adults⁽²⁾. Mexico is one of the two countries with the highest prevalence of obesity in the world. In 2016, the combined prevalence of overweight and obesity was an alarming 72.5% (3). Obesity is responsible for more than 200,000 deaths annually in this country, of which more than 80,000 are due to diabetes, and more than 100,000 to cardiovascular diseases (4,5). These figures represent a constant and significant burden for the health sector and Mexicans since their effects negatively impact morbidity, mortality, and the economy.

Health workers, in particular, are exposed to a high risk of being overweight and obese due to their demanding job responsibilities, and therefore, in general, they practice an unhealthy lifestyle ⁽⁶⁾. For this reason, the prevalence of obesity in this particular population is higher than in the general population in Mexico ⁽⁷⁾. The World Obesity Federation has rightly identified and emphasized the need for immediate action for the prevention and control of obesity ⁽⁸⁾. For this reason, the identification of useful tools in the fight against obesity becomes critically important.

In 2013 Donnelly demonstrated through his midwestern exercise test that integrating aerobic exercise exclusively into his participants' habits resulted in a significant decrease in body mass index (BMI) ⁽⁹⁾. Later, in 2017, Weiss and his collaborators found that the benefits of aerobic physical activity, in addition to lowering BMI, included the preservation of fat-free mass and a significant improvement in the efficiency of maximum oxygen consumption⁽¹⁰⁾.

Although recent studies have shown that high-intensity interval training (HIIT) offers a beneficial effect superior to that of aerobic exercise to be effective in losing body fat (11,12), this phenomenon has not been studied in health workers. For this reason, the objective of this work is to identify the effect of a HIIT regimen on health workers.

METHODS

Design and study area

A quasi-experimental study was carried out before and after the intervention.

Population and sample

Using a non-probabilistic convenience sampling, all health workers between 20 and 50 years of age with morning, evening, or night work shifts were invited to participate. Health workers with a history of high-risk cardiovascular disease, symptoms of infection at the time of the study, pregnancy or lactation, and those using lipid-lowering or antihypertensive drugs were excluded.

Variables, procedures, and instruments

The intervention consisted of 60 sessions of 30 minutes of HIIT for 12 weeks aimed at health workers of the General Hospital of Montemorelos, with the aim of promoting increased physical activity. Each session was presented by a certified trainer and consisted of a warm-up and circuits of 5 muscular strengthening and HIIT-type cardiovascular resistance exercises repeated for 5 cycles. Each participant sent audiovisual evidence of each training to the research team as a requirement for the final evaluation. The content and methodology of this intervention are described in Annex A.

Data collection, laboratory taking, and processing of each participant were carried out on 2 occasions, before starting the intervention and after it. An initial clinical interview was obtained to capture data including medication use, history of cardiovascular disease, and measurement of vital signs.

The anthropometric data of each participant was measured using a calibrated OMRON HBF-214 scale and height with a stadiometer. The Body Mass Index⁽¹³⁾ was calculated using formula 1:

BMI = Weight in (Kg)/Height in (cm²) (1)

Blood samples was obtained from each participant after 8-12 hours of fasting and processed in the certified laboratory of the Hospital General de Montemorelos. Total and HDL cholesterol concentrations were





colorimetric assays. The Cholesterol/HDL ratio was calculated using formula 2⁽¹⁴⁾:

HDL Cholesterol Ratio=Total Cholesterol (mg/dl)/HDL Cholesterol (mg/dl) (2)

Blood pressure was measured with a calibrated Welch Allyn DS4411 aneroid sphygmomanometer. Systolic blood pressure was identified by the first phase of the Korotkoff sounds, while diastolic pressure was identified by its 5th phase. The mean arterial pressure was calculated using formula 3⁽¹⁵⁾:

Donde:

MAP = Mean arterial pressure in mmHg SBP = Systolic Blood Pressure in mmHg DPB = Diastolic Blood Pressure in mmHg The cardiovascular risk - cholesterol based on the framingham heart study(16) was obtained using the calculator of the Instituto Mexicano de Seguro Social⁽¹⁷⁾.

Statistic analysis

The data was collected and organized in a database using the Microsoft Office Excel® 2019 program to later process them with the SPSS® Statistics 25 statistical package for descriptive and analytical statistical analysis. The distribution of the variables was determined using the Shapiro-Wilk test (Table 2). Subsequently, correlations were made between the pre and post results of each variable using the Student's t statistical tests for paired samples and the Wilcoxon test to estimate Pearson's correlation coefficients.

Table 2. Results of the Shapiro-Wilk normality test in the pre and post values of each variable.

Variable	P-value
Weight1	0.403
Weight2	0.325
BMI 1	0.647
BMI2	0.744
SBP 1	0.555
SBP 2	0.037
DBP 1	0.357
DBP 2	0.142
MAP 1	0.420
MAP 2	0.150
Col 1	0.334
Col 2	0.690
HDL 1	0.994
HDL 2	0.552
C/HDL 1	0.240
C/HDL 2	0.473
R10 1	0.001
R10 2	0.003

1; Initial value, 2; Final Value, Weight; Body weight in Kg, BMI; Body mass index, CoI; mg/dl of blood cholesterol, HDL; High-density lipoprotein, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, MAP; Mean arterial pressure, C/HDL; HDL Cholesterol Ratio, R10; Cardiovascular risk at 10 years.





Ethical aspects:

The study was approved by the Montemorelos University research and ethics committee, and written informed consent was obtained from all participants.

RESULTS

A participation of 8 participants with an average age of 32.8 years was obtained. The general characteristics of the study population are shown in Table 1.

Table 1. General Description of the Population.

Characteristic	Result
Age(in years)	32,8 ± 10,9
Smoking	Negativo 100%(8)
Diabetes Mellitus	Negativo 100%(8)
Workshift	Matutino 100%(8)
Size(Centimeters)	163 ± 10,2
Weight(Kilograms)	84,1 ± 9,9
Body Mass Index	31,69 ± 2,9

The cardiovascular risk results were 2.3 ± 2 . The initial and final values with standard deviation and the Pearson correlation coefficients between the initial values and the values are presented. results of each variable in Table 3. A statistically significant

difference was found between the initial and final values of weight, BMI, systolic blood pressure, diastolic blood pressure, mean blood pressure, total cholesterol and cardiovascular risk at 10 years.

Table 3. Results of Statistical Analysis of the participants.

Variable	Mean and Standard Deviation	P-value
Weight 1	84,14 ± 9.9	0.027
Weight 2	82,45 ± 9.8	
BMI 1	31,69 ± 2.92	0.033
BMI 2	31,07 ± 3	
SBP 1	121,2 ± 12,5	0,006
SBP 2	111,3 ± 6,4	
DBP 1	81,750 ± 6,7	0,033
DBP 2	75.8 ± 8.3	
MAP 1	94,9 ± 8,5	0,008
MAP 2	87,6 ± 6,9	
Col1	163,4 ± 33,2	0,010
Col2	148.8 ± 30.6	
HDL1	42,5 ± 9,4	0,740
HDL2	43,1 ± 12,3	
C/HDL1	3,99 ± 1,12	0,017
C/HDL2	$3,62 \pm 1,03$	
R101	2,3 ± 2	0,059
R102	1,7 ± 2,4	

1; Initial value, 2; Final Value, Weight; Body weight in Kg, BMI; Body mass index, CoI; mg/dl of blood cholesterol, HDL; High-density lipoprotein, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, MAP; Mean arterial pressure, C/HDL; HDL Cholesterol Ratio, R10; Cardiovascular risk at 10 years.





DISCUSSION

To our knowledge, this study is among the first to assess the effect of an exclusive HIIT intervention in healthcare workers. Our results show a significant improvement in anthropometric values, metabolic indicators and blood pressure figures. HIIT interventions with a duration of more than 10 weeks have been shown to be effective for weight loss and improvement of body composition data (18), for this reason multiple studies (19-21) have postulated it as a useful tool to decrease body fat percentage and BMI in overweight and obese populations. Our results are in line with this position given that after a 12-week HIIT intervention, our participants reported a statistically significant decrease in obesity measurements, with BMI -0.62 (P Value 0.033) and total body weight -1.69kg. (P-value 0.027). Causal mechanisms of HIIT-induced fat loss include the generation of catecholamines that increase the rate of fat oxidation and fat release from visceral fat stores, decrease post-exercise appetite, and increase body oxygen consumption. excess after exercise resulting in increased fat loss (20-22).

Added to these results, a significant decrease in MAP(-7.3mmHg) SBP(-9.9mmHg) and DBP(-5.95mmHg) was found. These results are very similar to the metaanalysis carried out by Cornelissen⁽²³⁾ where an average decrease in SBP(-10.9mm Hg) and DBP(-6.4mm Hg) was recorded. The improvement in blood pressure induced by exercise is explained by a decrease in total resistance to both peripheral and central blood flow (24). Physiological mechanisms implicated in this improvement include improved endothelial and homeostatic function in resistance vessels, decreased oxidative stress, and adequate autonomic regulation (25). It is feasible to attribute these positive endothelial adaptations to the higher vascular shear stress on endothelial cells induced by HIIT intensity. This improvement is clinically relevant given that arterial hypertension is one of the modifiable risk factors for cardiovascular diseases (26).

In this context, another important result to highlight was a significant improvement in blood lipids. Total cholesterol had an average decrease of-14.6 mg/dl

(P value 0.010) while an average increase of +0.6 mg/dl of HDL-cholesterol was recorded, accompanied by a consequent decrease in the cholesterol/HDL ratio of -0.37 (P-value 0.017). These results agree with the meta-analysis carried out by Kelley⁽²⁷⁾ demonstrating the lipid-lowering efficacy of HIIT in the obese population. The decrease in total cholesterol and increase in HDL levels after HIIT sessions has been related to its modulating effect on the activity of cholesterol ester transfer protein and lecithin cholesterol acyl transferase^(28,29).

Futhermore to being an indicator of metabolic health, the cholesterol/HDL ratio is considered an indicator of cardiovascular risk ⁽³⁰⁾. The clear improvement in the initial and final values of this index suggests a trend of improvement and its possible usefulness in the prevention of these cardiovascular diseases.

Finally, although our population was within the range of low cardiovascular risk, a 0.6% decrease in cardiovascular risk was recorded at 10 years in Framingham. This method of estimating cardiovascular risk has proven to be a reliable indicator of mortality in multiple populations (31,32). Since the calculation of this considers non-modifiable variables and only 2 modifiable (blood pressure and smoking) (33), it is likely that the generalized decrease in blood pressure is responsible for these results. Future studies will be necessary to confirm these findings and study the effect of HIIT on cardiovascular health.

A particular strength of this study is the duration of the intervention, which made it possible to record mediumterm changes in the participants. In addition, the evaluation of the lipid profile allowed to describe the changes in cardiovascular and metabolic risk of each participant. We acknowledge that our limitations include a small sample size and the absence of a quantifiable measure of habits related to body weight change. However, our method is helpful in documenting significant effects even in an uncontrolled setting.

CONCLUSIÓN

In this particular manuscript, we aim to describe the effect of HIIT on metabolic and anthropological indicators and blood pressure figures in health workers. Our HIIT intervention significantly improved the lipid





profile anthropometric values, and systolic and diastolic pressure figures. The results of this study could be of important contribution in the formulation of interventions aimed at the prevention and treatment of obesity in health workers and, as a consequence, reduce the diseases related to it. Furthermore, these results lay the groundwork for future research that

should include a large population, controlled intervention and focus on describing the long-term effects of HIIT on healthcare workers.

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REFERENCES

- Noncommunicable diseases country profiles 2018 [Internet]. [cited 2021 Nov 6]. Available from: https://www.who.int/publications-detail-redirect/ncd-country-profiles-2018
- 2. Obesity and overweight [Internet]. [cited 2021 Nov 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
- Shamah-Levy T, Campos-Nonato I, Cuevas-Nasu L, Hernández-Barrera L, Morales-Ruán M del C, Rivera-Dommarco J, et al. Sobrepeso y obesidad en población mexicana en condición de vulnerabilidad. Resultados de la Ensanut 100k. Salud Pública México. 2019 Dec 5;61(6, nov-dic):852.
- Marrón-Ponce JA, Tolentino-Mayo L, Hernández-F M, Batis C. Trends in Ultra-Processed Food Purchases from 1984 to 2016 in Mexican Households. Nutrients. 2018 Dec 26;11(1):45.
- Rivera Dommmarco JA. La obesidad en México estado de la política publica y recomendaciones para su prevención y control. 2018.
- 6. Jahan Y, Rahman A. Lifestyle Associated Health Implications among the Healthcare Professionals in Developing Countries. 2018;1:2.
- Prevalencia de obesidad en trabajadores del Instituto Mexicano del Seguro Social en Tijuana, BC [Internet]. [cited 2021 Nov 3]. Available from: http://www.scielo.org.mx/scielo.php?script=sci arttext&pid=S0036-36342013000400001
- 8. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation Bray 2017 Obesity Reviews Wiley Online Library [Internet]. [c i t e d 2 0 2 1 N o v 6]. A v a i l a b l e f r o m : https://onlinelibrary.wiley.com/doi/10.1111/obr.12551
- Donnelly JE, Honas JJ, Smith BK, Mayo MS, Gibson CA, Sullivan DK, et al. Aerobic exercise alone results in clinically significant weight loss for men and women: Midwest Exercise Trial-2. Obes Silver Spring Md. 2013 Mar;21(3):E219–28.
- Weiss EP, Jordan RC, Frese EM, Albert SG, Villareal DT. Effects of Weight Loss on Lean Mass, Strength, Bone, and Aerobic Capacity. Med Sci Sports Exerc. 2017 Jan;49(1):206–17.
- Türk Y, Theel W, Kasteleyn MJ, Franssen FME, Hiemstra PS, Rudolphus A, et al. High intensity training in obesity: a Meta analysis. Obes Sci Pract. 2017 May 29;3(3):258–71.
- Vázquez-Martínez JL, Gómez-Dantés H, Gómez-García F, Lara-Rodríguez M de los A, Navarrete-Espinosa J, Pérez-Pérez G. Obesity and overweight in IMSS female workers in Mexico City. Salud Pública México. 2005 Jul;47(4):268–75.
- 13. Body mass index BMI [Internet]. [cited 2021 Nov 6]. Available from: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi
- Acevedo M, Krämer V, Tagle R, Corbalán R, Arnaíz P, Berríos X, et al. Relación colesterol total a HDL y colesterol no HDL: los mejores indicadores lipídicos de aumento de grosor de la íntima media carotidea. Rev Médica Chile. 2012 Aug; 140(8):969–76.
- DeMers D, Wachs D. Physiology, Mean Arterial Pressure. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Nov 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538226/
- Framingham Heart Study [Internet]. [cited 2021 Nov 6]. Available from: https://framinghamheartstudy.org/
- Riesgo cardiovascular colesterol [Internet]. [cited 2021 Nov 6]. Available from: http://www.imss.gob.mx/salud-en-linea/apps-sano/riesgo-cardiovascular-colesterol

- Abarzúa V. J., Viloff C. W., Bahamondes V. J., Olivera P.Y., Poblete-Aro C., Herrer a-Valenzuela T., et al. Efectividad de ejercicio físico intervalado de alta intensidad en las mejoras del fitness cardiovascular, muscular y composición corporal en adolescentes: una revisión. Rev Médica Chile. 2019 Feb;147 (2):221–30.
- Racil G, Ben Ounis O, Hammouda O, Kallel A, Zouhal H, Chamari K, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. Eur J Appl Physiol. 2013 Oct;113(10):2531–40.
- Boutcher SH. High-Intensity Intermittent Exercise and Fat Loss. J Obes. 2011;2011:868305.
- Paoli A, Moro T, Marcolin G, Neri M, Bianco A, Palma A, et al. High-Intensity Interval Resistance Training (HIRT) influences resting energy expenditure and respiratory ratio in non-dieting individuals. JTransl Med. 2012 Nov 24;10:237.
- LaForgia J, Withers RT, Gore CJ. Effects of exercise intensity and duration on the excess post-exercise oxygen consumption. J Sports Sci. 2006 Dec; 24(12):1247–64.
- 23. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013 Feb 1;2(1):e004473.
- Lopes S, Mesquita-Bastos J, Alves AJ, Ribeiro F. Exercise as a tool for hypertension and resistant hypertension management: current insights. Integr Blood Press Control. 2018 Sep 20:11:65–71.
- Millar PJ, McGowan CL, Cornelissen VA, Araujo CG, Swaine IL. Evidence for the role of isometric exercise training in reducing blood pressure: potential mechanisms and future directions. Sports Med Auckl NZ. 2014 Mar;44(3):345–56.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT. Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. The Lancet. 2006 May 27;367(9524):1747–57.
- Kelley GA, Kelley KS, Tran ZV. Aerobic Exercise and Lipids and Lipoproteins in Women: A Meta-Analysis of Randomized Controlled Trials. J Womens Health. 2004 Dec 1;13(10):1148-64.
- Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipids Health Dis. 2017 Jul 5;16:132.
- Rahmati-Ahmadabad S, Azarbayjani M-A, Farzanegi P, Moradi L. High-intensity interval training has a greater effect on reverse cholesterol transport elements compared with moderate-intensity continuous training in obese male rats. Eur J Prev Cardiol. 2021 Jul 1;28(7):692–701.
- Calling S, Johansson S-E, Wolff M, Sundquist J, Sundquist K. The ratio of total cholesterol to high density lipoprotein cholesterol and myocardial infarction in Women's health in the Lund Area (WHILA): a 17-year follow-up cohort study. BMC Cardiovasc Disord. 2019 Oct 29;19(1):239.
- 31. Damen JA, Pajouheshnia R, Heus P, Moons KGM, Reitsma JB, Scholten RJPM, et al. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. BMC Med. 2019 Jun 13;17(1):109.
- Jahangiry L, Farhangi MA, Rezaei F. Framingham risk score for estimation of 10-years of cardiovascular diseases risk in patients with metabolic syndrome. J Health Popul Nutr. 2017 Nov 13;36(1):32
- Christensen JF, Bandak M, Campbell A, Jones LW, Højman P. Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship. Acta Oncol Stockh Swed. 2015 May;54(5):592–9.