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Relationship Between Aerobic Capacity With Oxidative Stress and Inflammation Biomarkers in the Blood of Older Mexican Urban-Dwelling Population

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Abstract

The maximal oxygen uptake (VO2max) constitutes an indicator of an organism's capacity to integrate oxygen into the metabolism to obtaining energy. The aim of this study was to determine the relationship between VO2max and oxidative stress (OxS) and chronic inflammation in the elderly individuals. A cross-sectional and exploratory study was conducted in a sample of 52 older persons. We measured plasma lipid peroxides (LPO), red blood cell glutathione peroxidase, red blood cell superoxide dismutase, and total antioxidant status. The interleukin 10 and tumor necrosis factor-α (TNF-α) were measured in serum by ELISA. The VO2max was determined by the Rockport aerobic test, and the energy expenditure (caloric expenditure and metabolic equivalence unit (MET) per day) was measured by a 3-day activity record. We observed a positive correlation between VO2 max with IL-10, MET/day•day-1 and kcal•day-1 ($r = 0.31$, $P < .05$, $r = 0.44$, $P < .01$, and $r = 0.29$, $P < .05$, respectively), and a negative correlation with the body mass index, TNF-α, and LPO ($r = -0.27$, $P < .05$, $r = -0.29$, $P < .05$, and $r = -0.40$, $P < .01$ respectively). Our findings suggest that there is an inverse relationship between the aerobic capacity and the OxS and chronic inflammation biomarkers in the blood in older Mexican adults.

Keywords

aerobic capacity, oxidative stress, inflammation, older-Mexican adults

Introduction

Aerobic capacity is a parameter that reflects the potential of the function of the cardiovascular and respiratory systems regarding muscular work without fatigue. This is conducted by means of a harmonic process that coordinates oxygen uptake, transport, and utilization at the cellular level for energy production through aerobic metabolism.[1,2]

It has been considered a measurement and consequence of fitness to physical activity. In this sense, the health benefits of regular exercise are well-documented, it has been demonstrated that exercise significantly reduce the risk of chronic diseases, breast cancer, colon cancer, diabetes, ischemic heart disease, ischemic stroke events, hip fracture, osteoporosis and falls.[3-4] Nevertheless, it has been shown that, during the performance of physical activity in parallel with oxygen consumption, reactive species are generated, which on not being counteracted by antioxidative systems can generate oxidative stress (OxS) and chronic inflammation, processes capable of changing the redox equilibrium of the cell and exerting an impact on cellular physiology and signaling.[5-7]

The chronic inflammatory process has been linked to the aerobic metabolism, given that the excess of reactive oxygen species (ROS) as well as the tissue damage generated stimulate the immune-response effector cells, with the consequent liberation of free radicals, whose signaling activates the transcription factors responsible for the liberation of the proinflammatory cytokines and adhesion molecules implicated in inflammatory-process chronification and acute response to stress.[8-10]

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Notwithstanding this, it has been proposed that when physical exercise is carried out in periodic and moderate fashion, the exposure of the body to thermal, hypoxic, metabolic, mechanic, and oxidative stress activates biochemical messengers and signaling pathways responsible for an adaptive response that can be explained by the hormesis concept which encompasses the notion that low levels of stress stimulate or upregulate existing cellular and molecular pathways that improve the capacity of cells and organisms to withstand greater stress.[11-14]

However, still the relationship between aerobic capacity and OxS and inflammation markers is controversial, particularly in old age, because it has been demonstrated that aging per se increases OxS and generates an inherent inflammatory process termed "inflammaging," in addition to experiencing a progressive diminution in aerobic capacity.[10,13,15-17]

Our objective was to determine the relationship of aerobic capacity with oxidative stress and chronic inflammation biological markers in older Mexicans adults which has been scarcely studied.

Material and Methods

Design and Participants

With previous informed consent, we conducted a cross-sectional and exploratory study. Of the 52 persons $\geq$60 years who participated in the study, 30 (58%) were women and 22 (42%) were men; the mean age of participants was 66 $\pm$ 4 years, without chronic degenerative diseases or controlled diseases (with fasting glucose $\leq$160 mg/dL, blood pressure $\leq$ 160/100), without consumption of antioxidant supplements and/or anti-inflammatory in the last 6 months. The research protocol for this study was approved by the Ethics Committee of the Universidad Nacional Autónoma de México (UNAM) Zaragoza Campus.

Dietary Intake

All the subjects had a caloric intake between 3000 and 3500 kcal per day measured by 24-hour dietary total recall; nutrient intake (macronutrient and micronutrient) was analyzed using Food Processor® Nutrition Analysis Software. No subject took antioxidant supplements (vitamins or minerals) for at least 6 months prior to initiation of or during the study.

Blood Sampling and Biochemical Analysis

Blood samples were collected after an 8-hour fasting period by venopucture and placed in vacutainer/siliconized test tubes containing a separating gel and no additives. Heparin was used as anticoagulant agent. The following serum quantifications were performed: glucose, urea, creatinine, uric acid, albumin, cholesterol, triglycerides, and high-density lipoprotein cholesterol.

Plasma Lipoperoxides (LPO)

It was used as a thiobarbituric acid reacting substances (TBARS) assay. It was performed as described by Jentzsch et al.[18] In the TBARS assay, one molecule of malondialdehyde (MDA) reacts with 2 molecules of thiobarbituric acid (TBA) to produce a pink pigment with absorption at 535 nm. Amplification of peroxidation during the assay is prevented by the addition of the chain-breaking antioxidant Butylated hydoxytoluene (BHT). Plasma (400 μL) or MDA standard (0.2-4 μmol/L) was prepared by hydrolysis of 1,1,3,3 tetramethoxypropane (Sigma Chemical Co, St Louis, Missouri) and was mixed with 400 μL orthophosphoric acid (0.2 mol/L) (Sigma Chemical Co) and 50 μL BHT (2 mmol/L) (Sigma Chemical Co) in 12 $\times$ 75 mm tubes. We added 50 μL TBA reagent (0.11 mol/L in 0.1 mol/L NaOH) (Fluka Chem., Buchs, Switzerland) and mixed the contents; the contents were then incubated in a water bath at 90°C for 45 min. The tubes were put on ice to stop the reaction. Thiobarbituric acid reacting substances were extracted once with 1000 mL n-butanol (Sigma Chemical Co, St. Louis, MO, USA). The upper butanol phase was read at 535 nm and 572 nm to correct for baseline absorption using an ultra violet spectrophotometer (Shimadzu Corporation, Japan). MDA equivalents (TBARS) were calculated using the difference in absorption at the 2 wavelengths, and quantification was done using the calibration curve.[11]

Total Antioxidant Status (TAS)

Antioxidant quantification was done using 2,2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid, ABTS+ (2,2′-azino-bis-(3-ethylbenzothiazoline-6 sulfonic acid) radical formation kinetics (Randox Laboratories Ltd., United Kingdom). The antioxidants present in the plasma suppress the formation of a bluish green coloration of the ABTS+ cation, which is proportional to the antioxidant concentration level. The kinetics was measured at 600 nm.[19]

Red Blood Cell Superoxide Dismutase (SOD)

The method employs xanthine and xanthine oxidase to generate superoxide radicals, which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride to form a red formazan dye. Superoxide dismutase activity was measured by inhibition of the reaction degree (Randox Laboratories, Ltd). Kinetics was measured at 505 nm.[20]

Red Blood Cell Glutathione Peroxidase (GPx)

In the presence of glutathione reductase and (NADPH), the oxidation of glutathione by cumene hydroperoxide is catalyzed by glutathione peroxidase. Oxidized glutathione is immediately converted into the reduced form with subsequent oxidation of NADPH to NADP+. The decrease in absorbance is measured at 340 nm (Randox Laboratories Ltd.).[21]

SOD/GPx Ratio and Antioxidant Gap

We calculated SOD/GPx ratio[22] and antioxidant gap (AOGAP) with the following equation: AOGAP = (TAS − [(albumin (mmol) × 0.69) + uric acid (mmol)][23]

Oxidative Stress Score (OxS-score)

OxS was evaluated in relation to LPO, SOD, and GPx activities; TAS; SOD/GPx ratio; and AOGAP. On the basis of the 90th percentile of young healthy subjects, alternative cutoff values for each parameter were defined as follows: LPO $\geq$ 0.340 mmol/L; SOD $\leq$ 170 IU/mL; GPx $\leq$ 5500 IU/L; TAS $\leq$ 0.9 mmol/L; SOD/GPx $\geq$ 0.023, and AOGAP $\leq$ 190 mmol/L. An OxS-score was established ranging from 1 to 6, representing the severity of biomarker modification; a score of 1 was given to each value beyond the cutoff. We categorized the subjects according to their OxS-score as follows: without OxS if OxS-score was 0 to 2 and with OxS if OxS-score was 3 to 6.[24]

Inflammatory Cytokines

Samples were centrifuged at 2000 rpm for 2 min, and the supernatant was removed and stored at −80°C for further cytokine analysis. Supernatant concentrations of tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) were measured using ELISA. The concentrations of cytokines in the plasma from the patients were measured in duplicate by specific sandwich ELISA as described by the manufacturers (R&D Systems, Inc, Minneapolis).

Maximal Oxygen Uptake (VO2max)

The VO2max was determined by the Rockport 1 mile walking test, and the energy expenditure (metabolic equivalence units [METs] per day and the caloric expenditure by day) was measured by a 3-day activity record.[25,26]

Anthropometric and Blood Pressure Measurements

Weight was measured while the subject was wearing underwear and a clinical smock and in a fasted state (after evacuation). A Torino scale (Tecno Lógica, Mexicana, México, TLM) was used, calibrated before each weight measurement. Height was obtained with an aluminum cursor stadiometer graduated in millimeters. The subject was barefoot, back, and head in contact with the stadiometer in Frankfurt horizontal plane. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in squared meters). Blood pressure was measured in both arms 3 times in the morning, in a fasting condition or 2 hours after breakfast, in sitting and standing positions. A mercurial manometer was used to measure the blood pressure. Participants with pseudohypertension were identified by applying the Osler technique, which is, feeling the radial pulse when the manometer registered values above the true systolic pressure. Blood pressure was taken by medical technicians who had attended training sessions to standardize the procedures. The technicians were supervised to avoid possible biases in measurement.[27]

Table 1. BMI, Blood Pressure, Biochemical Characteristics, and VO2max.

Parameter	N = 52
Age	66.3 ± 2
BMI	27 ± 2
SBP (mm Hg)	119 ± 3.7
DBP (mm Hg)	76 ± 2.6
Glucose (mg/dL)	100 ± 4.3
Urea (mg/dL)	31 ± 2.6
Creatinine (mg/dL)	0.95 ± 0.3
Uric acid (mg/dL)	4.5 ± 1.2
Total cholesterol (mg/dL)	211 ± 7
Triglycerides (mg/dL)	163 ± 9.5
HDL-cholesterol (mg/dL)	54 ± 3.7
Albumin (mg/dL)	4.4 ± 0.5
VO2max (mL/kg/min)	28 ± 3.4

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoproteins; SBP, systolic blood pressure; VO2max, maximal oxygen uptake. The values represent mean ± standard error.

Statistical Analysis

Data were processed with (SPSS) 16.0 standard software (SPSS, Inc, Chicago, Illinois). Descriptive statistics were analyzed by means ± standard error. Likewise, a correlation analysis between VO2 and oxidative stress and inflammation markers, BMI, MET/day and Kcal/day was carried out.

Results

Anthropometric measurements, blood pressure, and blood chemistry parameters were within normal limits (Table 1). Also, the concentrations of OxS and inflammation markers were within the cutoff points for our population (Table 2). The mean of METs shows that all the participants had moderate physical activity.

We observed a statistically significant positive correlation between VO_2 max with IL-10, METs•day-1 and kcal•day-1 ($r = 0.31$, $P < .05$, $r = 0.44$, $P < .01$, and $r = 0.29$, $P < .05$, respectively) and a statistically significant negative correlation with the BMI, TNF-α, OxS-score, LPO, and SOD/GPx ($r = -0.27$, $P < .05$, $r = -0.29$, $P < .05$, $r = -0.26$, $P < 0.05$, $r = -0.40$, $P < .01$, and $r = -0.26$, $P < .05$ respectively) (Table 3).

Discussion

Maximal oxygen consumption is an indicator of aerobic capacity, which reflects the potential to develop a physical activity, given that it represents the aptitude of oxygen uptake at the cellular level and the integration of this into the metabolism. As a measurement of conditioning, higher VO2 has been associated with decreased risk in the incidence of lifestyle-related diseases and has pointed out the existence of a direct

Table 2. Oxidative Stress, Inflammation Markers, and METs/h.

Parameter	N = 52
Lipid peroxides (μmol/L)	0.237 ± 0.2
SOD (U/ml)	171 ± 4
GPx (U/L)	8118 ± 84
TAS (mmol/L)	0.885 ± 0.4
AOGap (μmol/L)	158 ± 9.2
SOD/GPX	0.030 ± 0.018
OxS-score	2.4 ± 1.2
TNF-α (pg/ml)	1.5 ± 1.3
IL-10 (pg/ml)	4.5 ± 2.6
MET/h	4.5 ± 1.1

Abbreviations: AOGAP,antioxidant Gap; GPx, glutathione peroxidase; IL-10, interleukin-10; MET/h, metabolic equivalents per hour; OxS-score, oxidative stress score; SOD, superoxide dismutase; TAS, total antioxidant status; TNF-α, tumor necrosis factor-α. The values represent mean ± standard error.

relationship between oxidative stress and inflammation markers and the consumption of oxygen; in that on increasing the oxidative metabolism, ROS are generated, which strengthens the theoretical focus with the development of OxS associated with physical exercise.[7,8]

However, across the time, a great of deal of research has been undertaken to try to understand the sources and identity of the species generated, the factors influencing their generation, and their biological effects. In this sense, it has been pointed out that exercise and regular physical activity counteract the deleterious effects of aging, by combating the major triggers of oxidative stress and inflammation in aging (sarcopenia, obesity, and mitochondrial dysfunction) but also by exerting additional antioxidant and anti-inflammatory actions.[28-31]

It has been demonstrated that the acute exercise increases resistance to oxidative stress in young but not older adults,[32,33] likewise that regular exercise with improved fitness leads to increased resistance to oxidative stress in older middle-aged adults.[34] However, it has also been found that chronic exercise from middle age to old age increases oxidative damage.[35]

In this respect, our results show that in the study population whose activity level is moderate (4-6 METs, aerobic capacity entertains a direct relationship with energy-expenditure markers, which confirms that individuals who perform greater physical activity also have a higher energy expenditure, and consequently, their capacity for utilizing oxygen is greater, as has been noted in some other studies.[34,36]

Regarding the determined oxidative stress markers, we observed an inverse relationship between VO2 and LPO, the SOD/GPx ratio and the oxidative stress index, all indicators of oxidative damage. These results differ from studies in which a direct relationship between oxidation markers and aerobic capacity has been pointed out, given that a greater oxygen capture allows a greater generation of reactive species to be assumed; however, it is important to note that in this population the intensity of the activity performed is moderate, hence we can suggest that in this case, we observe the result of a beneficial effect that has allowed the development of an adaptive response that manifests as an inverse relationship between

Table 3. Correlation Between VO2 and Oxidative Stress and Inflammation Markers, BMI, MET/day, and Kcal/day.

	VO2	TNF-α	BMI	IL-10	MET/day	Kcal/day	OxS-score	LPO	SOD	GPx	SOD/GPx
r											
VO2	1	−0.291	−0.272	0.314	0.441	0.295	−0.261	−0.408	0.192	0.205	−0.264
TNF-α		1.000	0.061	0.069	−0.181	−0.182	−0.055	−0.048	−0.134	−0.067	−0.088
BMI			1.000	−0.068	−0260	0.330	−0.014	0.239	0.002	0.143	−0.012
IL-10				1.000	0.155	0.024	0.073	−0.342	0.047	0.630	−0.288
MET/day					1.000	0.574	0.066	−0.306	0.149	0.090	−0.056
Kcal/day						1.000	−0.078	−0.026	0.129	0.122	0.159
OxS-score							1.000	0.155	−0.189	−0.312	0.523
LPO								1.000	−0.238	−0.258	0.306
SOD									1.000	0.056	−0.111
GPx										1.000	−0.563
SOD/GPx											1.000
P											
VO_2		0.032	0.043	0.023	0.002	0.031	0.049	0.004	0.115	0.100	0.048
TNF-α			0.352	0.333	0.129	0.128	0.366	0.382	0.201	0.339	0.291
BMI				0.336	0.050	0.017	0.466	0.066	0.446	0.187	0.469
IL-10					0.167	0.440	0.324	0.014	0.386	0.000	0.034
MET/day						0.000	0.340	0.026	0.176	0.288	0.365
Kcal/day							0.314	0.436	0.211	0.224	0.160
OxS-score								0.166	0.118	0.023	0.000
LPO									0.067	0.052	0.026
SOD										0.365	0.245
GPx											0.000
SOD/GPx											

Abbreviations: BMI, body mass index; GPx, glutathione peroxidase; IL-10, interleukin 10; LPO, lipid peroxides; MET/day, metabolic equivalents per day; OxS-score, oxidative stress score; SOD, superoxide dismutase; TNF-α, tumor necrosis factor; VO2max, maximal oxygen uptake; SOD/GPx, SOD/GPx ratio.

stress markers and VO2, perhaps mediated by an increase in antioxidant response as suggested by direct (though not significant) VO2 relationships with SOD and GPx. This has been noted by several authors, and it has been proposed that regular physical exercise increases the level of antioxidant defense and decreases the rate of production of reactive species.[9,37-39]

Overall, according to the results, we can assume that in this population the oxidative stimulus has allowed an increase in the antioxidant response that coincides with the studies where it has been reported that even in aged people, moderate exercise allows the development of an antioxidant response, a finding that can also be explained under the theoretical approach of hormesis, which describes a biphasic response that allows a stimulus or stressor applied at low level or concentrations to stimulate a response of the body such is inhibited by increased intensity of the stimulus. Regarding the concept of hormesis, although its initial application was in the toxicological area, recent analyses show that it allows explaining a great variety of biological phenomena that fit the model of a biphasic response; the adaptation of the organisms to physical exercise is considered an example of an event where thermal, mechanical, metabolic, and oxidative stress can generate adaptive response at low level and tissue damage when exhaustive.[13,14,39-41]

Regarding the mechanism by which the exercise achieves an adaptive response, it has been widely documented that the practice of exercise generates the controlled liberation of ROS; the latter constituting a mild and constant stimulus that activates a chronic response to stress through signaling cascades that imply transcription factors such as nuclear kappa B factor and mitogen-activated protein kinases, whose signaling results in a persistent increase of antioxidant enzymes and anti-inflammatory cytokines in a stimulus-proportionate manner that translates into a beneficial effect.[14 42,43]

These results are consistent with the observations in relation to the determined cytokines; we suppose that an adaptive response is reflected through the existence of an inverse relationship between VO2 and TNF-α inflammation marker as well as through a direct relationship with IL-10, whose activity is anti-inflammatory. This cytokine is a factor that impedes the synthesis of anti-inflammatory proteins in various cell types; particularly in those of monocytic lineage; it has been shown that this inhibits TNF-α and IL-1 production, as well as that of chemokines, such as interleukin-8 in activated monocytes. These cyto- and chemokines play a critical role in the activation of granulocytes, monocytes/macrophages, natural killer cells, and T and B cells, and their recruitment to inflammation sites; this arouses the supposition that IL-10 plays an important role in the regulation of the anti-inflammatory response, which we can suppose is present in this group of elderly persons, given the direct relationship with IL-10 and an inverse relationship with TNF-α. These results coincide with what has been reported by several authors, and it is also recognized that the health benefits of regular exercise can be additionally ascribed to the anti-inflammatory effects of exercise.[44-46]

Taken together, these results allow us to infer the presence of an adaptive response in the group of elderly people studied, which can be explained under the dose–response nature of the hormetic approach that has been adopted in the exercise field arguing that exposure to homeostatic disturbances that involves programmed physical activity stimulates the release of biochemical messengers that activate signaling pathways that in turn regulate the molecular machinery controlling gene expression that elicits the appropriate adaptive responses; this coincides with our results, given that the activity that they perform is moderate, and the global profile of the markers leads to the supposition of antioxidant and anti-inflammatory activity.[47]

Finally, the limitations of our study are as follows: the design was cross-sectional and exploratory, the sample was taken at convenience, and its size was not representative. Therefore, our findings cannot be generalized. Also several data were obtained through self-report. In addition, the measurement of lipoperoxides is not the best biological marker to assess free radicals. Currently, it is recognized that the measurement of F2-isoprostanes (F2-IsoPs) could be a better biological marker in comparison with lipoperoxides, although the measurement of F2-IsoPs also has limitations.[48] Another limitation of the study was the measurement of VO2max by the Rockport protocol. In this sense, the direct measurement of maximal oxygen is considered the most accurate method of assessing individual aerobic capacity; however, the Rockport protocol is accepted as a reliable approximation for measuring the VO2max.[49]

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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