Proinflammatory and Anti-inflammatory Cytokine Response to Isometric Handgrip Exercise and the Effects of Duration and Intensity of the Isometric Efforts in Prehypertensive Participants

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Abstract

Objective: The purpose of this study was to investigate the responses of selected inflammatory cytokines to isometric handgrip exercise and identify possible effects of intensity and duration of the isometric effort on these variables.
Methods: A total of 192 sedentary prehypertensive Nigerian participants aged between 30 and 50 years were recruited into the study and randomly distributed into 3 groups of 64 participants each. The participants performed 24 consecutive days of isometric handgrip exercise at 30% maximum voluntary contraction. At the end of the 24 days, group 1 discontinued the exercise protocol, while group 2 continued the exercise protocol for another 24 consecutive days, and group 3 continued with the exercise protocol for another 24 consecutive days but at 50% maximum voluntary contraction. The parameters used to assess the inflammatory cytokine variables included interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α).
Results: There was an increase in the resting values of IL-10 across the 3 groups, while the resting values of IL-6 and TNF-α were reduced significantly across groups. Generally, the exercise-induced changes in the levels of these cytokines (TNF-α, IL-6, and IL-10) should improve inflammatory and metabolic abnormalities.
Conclusion: The isometric handgrip exercise protocols in this study resulted in elevation of anti-inflammatory cytokine (IL-10) and reductions in the values of proinflammatory cytokines TNF- α and IL-6. (J Chiropr Med 2022;21;177-186)
Key Indexing Terms: *Chronic Disease; Cytokines; Exercise*

Introduction

Chronic low-grade systemic inflammation is a prominent risk factor for several chronic diseases.[1-4] Empirical evidence, as indicated by higher levels of circulating proinflammatory mediators, links low-grade inflammation with diseases and disorders of several body systems, affecting the cardiovascular (atherosclerosis, heart failure), endocrine (insulin resistance, metabolic syndrome), musculoskeletal (sarcopenia, arthritis, osteoporosis), respiratory (chronic obstructive pulmonary disease), and neurological (dementia, depression) systems, including many other adverse health conditions, and the inflammatory pathway is a potential therapeutic target.[4] The prevalence of chronic disease has increased steadily in recent years—nearly half of the population of the world has at least 1 chronic condition, and the number is growing.[5]

According to the Centers for Disease Control and Prevention, more than two-thirds of deaths are the result of chronic diseases.[6] By 2030, the scientific community project that chronic diseases will account for more than three-fourths of deaths worldwide.[7] The advent of the 21st century witnessed an upsurge of chronic diseases, while infectious diseases became relatively less of a burden. While pharmacotherapy may manage some acute diseases, the biomedical model is complicated when dealing with health crises resulting from chronic diseases. Chronic diseases, such as cancer, diabetes, inflammatory bowel disease,

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central nervous system degenerative diseases, hypertension, stroke, heart disease, respiratory diseases, arthritis, obesity, and oral diseases, are largely associated with lifestyle factors and can be minimized or prevented, for the most part, by lifestyle changes.[7]

Due to the increasing longevity and growing aging population and a global scale increase in risk factors for chronic diseases, alternative interventions are required to minimize physician supervision and associated diagnostic and hospitalization costs. Given the scope and prevalence of chronic diseases, a population health approach using preventive measures would be the most appropriate model to adopt to deal with this ubiquitous problem. Such preventative measures would help in reducing the global burden of chronic diseases plaguing the health care systems of the world.[2] Regular physical exercise has been reported to create an anti-inflammatory milieu, leading to reduced resting levels of proinflammatory cytokines and increased levels of anti-inflammatory cytokine concentrations in both younger and older adults.[8,9]

Physical exercise is recognized as an important strategy for reducing the risk of chronic disease, and recent research has focused on its role in the improvement of the inflammatory profile. Physical exercise has equally been shown to represent a quantifiable model of stress, and many physical stressors have been found to induce a pattern of hormonal and immunological responses that have similarities to that of exercise.[10]

This pattern of hormonal and immunological responses is characterized as a body's defense response, whose goal is to promote healing and repair. The magnitude of this process, however, is the determinant of the health benefit and is regulated by proinflammatory and anti-inflammatory cytokines. Localized inflammation is thought to be highly beneficial and physiologically protective to initial tissue injury, but an elevated response can result in cytokine release into the circulation known as systemic inflammatory response syndrome or hypercytokinemia, which becomes pathogenic and self-destructive and sometimes fatal to the host.[11] The overproduction of proinflammatory cytokines leads to this syndrome and could result in multiple organ damage associated with thermal and ischemia-reperfusion injury, severe trauma, septic shock, and systemic infections.[12,13]

Over the last century, a sedentary lifestyle increasingly became the norm, with more people becoming less active; thus, this has been promoted either by the alteration in the kind of work or by the adoption of new habits attributable in part to changes in the demands of work. This scenario has resulted in an unexpected increase in the prevalence of chronic diseases.[14] Physical exercise is considered an effective and preventive countermeasure to chronic diseases, and findings from previous studies indicated that physical exercise improves many components of cardiovascular risk factors as well as insulin sensitivity.[15] Unfortunately, physical activity is becoming increasingly difficult to sustain. This may be because society is advancing rapidly in technology that most people today are spared the burden of physical labor, coupled with the fact that most occupations do not require substantial physical activity. Nowadays, leisure time is filled with sedentary behaviors.[16]

Physical exercise recommendations have centered on dynamic exercise, and there have been restrictions and caution regarding the recommendations of isometric exercise. There is a paucity of data regarding recommendations for isometric or resistance exercises.[17] Despite much evidence indicating that increased physical activity is associated with reduced systemic inflammation, the results of intervention studies are still controversial. One promising regimen currently being explored is isometric hand grip exercise training.[17] Preliminary studies have shown that this type of exercise may have a positive impact on the inflammatory profile.

Therefore, the purpose of this study was to investigate the responses of selected inflammatory cytokines to isometric handgrip exercise and identify possible effects of intensity and duration of the isometric effort on these variables. The hypothesis of the study was to see if there was a change in inflammatory cytokine properties following the interventions.

Materials and Method

General Study Design

The procedure of this study consisted of an isometric handgrip exercise trial. One hundred and ninety-two Nigerian people who were prehypertensive (n = 192, 105 men and 87 women, aged 39.04 ± 6.4 years; body mass index, 25.45 ± 2.72 kg/m^2) were recruited for this study. All the participants had been diagnosed and referred by the physician with a blood pressure level classified as prehypertension based on the classification of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This represents a systolic blood pressure range of 120 to 139 mmHg and a diastolic blood pressure range of 80 to 89 mmHg. The participants had an age ranging from 30 to 50 years. This is because inflammatory diseases and prehypertension have been found to have an increased risk in individuals 40 years and above.

A screening session was conducted to assess the baseline parameters and blood pressure of the participants, and blood samples were collected. All blood sample collection and blood pressure measurements were done according to international guidelines. The sample population was randomly selected into any of the 3 groups. The participants were asked to pick from a ballot box, concealing papers marked G1, G2, or G3, to determine which group the participants would belong to. A detailed procedure of the

exercise was then given to the participants before commencement of the exercise training.

Sample Size Calculation

For this study, the minimum number of samples required was computed in accordance with the following Charan and Biswas[18] formula for experimental studies: $N = [(Z_{1\text{-}a/2}{}^2SD^2) / d^2]$. Therefore: $(1.96^2[10^2] / 5^2 = 100 * 3.8416 / 25 = 384.16 / 25 = 16$. In the equation, SD is the standard deviation, $Z_{1\text{-}a/2}$ is the standard normal variate, and d is the absolute error or precision.

A total of 16 participants were to be assigned to each group; however, to ensure more generalization of the results, the sample size was increased to a total of 64 participants randomly assigned to each group, giving rise to a total of 192 participants.

Inclusion criteria

Inclusion into the study was subject to a normal medical examination, determined by a consultant physician. Only participants with no clinical evidence of infectious, inflammatory, and/or chronic diseases were recruited. More so, participants were not on medication, and all recruited participants were sedentary, which was defined by a score of 3 or less using the Rapid Assessment of Physical Activity survey.

Ethics

The participants were properly briefed, and written informed consent was obtained. This study conformed to the Declaration of Helsinki and jointly received institutional ethical approval from the Federal Medical Centre Asaba, Delta State (FMC/ASB/A81.VOLXII/101), and the Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State (REC/FBMS/DELSU/18/16/103) in Nigeria.

Exclusion Criteria

Participants were excluded from the study according to the following exclusion criteria: age below and or above the range of 30 to 50 years; queried health status with clinical evidence of chronic diseases; blood pressure above or below the prehypertension level; participants on medication; and/or participants who declined to participate in the study. Other exclusion criteria for isometric handgrip included individuals experiencing debilitating arthritis, carpal tunnel, peripheral neuropathy, an aneurysm, or mitral valve complications.

Assessment of Participants and Data collection

Following a detailed medical examination, including a 12-lead electrocardiogram by the consultant physician to rule out contraindications to physical exercise, a study of the participant's case notes was done, and important information was noted. The general and more detailed information regarding the participants' health, medication, and lifestyles were personally reported by using both a questionnaire and verbal statement during history taking and medical examination. The succeeding designated health parameters were formerly measured to get hold of further evidence and baseline values of the participants on the relevant parameters to this study.

Initial Resting Parameters

The initial resting parameters are the baseline parameters collected prior to the date of commencement of the intervention. The initial resting parameters were measured between the hours of 7 AM and 9 AM. The measures were repeated twice so that the average of the 2 scores was used for the data. The measurements were carried out after each participant had observed a 15-minute seated rest on arrival.

Final Resting Parameters

The final resting parameters were taken on the 49th day to the commencement of the exercise. These parameters were measured between the hours of 7 AM and 9 AM, following at least a 15-minute seated rest for each patient.

Biodata

Biodata was collected via face-to-face interviews of the participants. As the participants arrived at the clinic, they were made to rest in a chair for at least 10 minutes. The participants were hereafter evaluated via a structured questionnaire.

Height

Height was measured using Stadiometer (Ayrton Corporation, Prior Lake, Minnesota), which is a measuring scale for height calibrated in centimeters. Each participant was instructed to stand barefooted on the platform of the height scale with both feet together. The knees were flexed at 180° while the participants rested against the height scale with the back with the eyes looking forward. The measure of the height was taken as the space from the scale platform to the vertex of the head, which was read and recorded.

Weight

The participants were weighed using a weighing scale. Measurements were taken using the Digital Weighing Scale (BEU-GS27−007, Beurer GmbH, Ulm, Germany). The Digital Weighing Scale has excellent reliability in static limb loading measurement.[19] Each participant was instructed to wear light clothing and stand barefooted, with

1 foot on each side of the scale still standing straightforward on the weighing scale with the arms kept by the side.

Blood Pressure Assessment

The participants were screened to evaluate the blood pressure of prospective candidates. All blood pressure measurements were taken according to the 2019 American College of Cardiology/American Heart Association Guidelines for blood pressure measurement,[20] which require participants to rest in a quiet environment for at least 10 minutes prior to the measurement. Upon coming into the clinic, the participants were made to rest in a sited position for at least 15 minutes, comfortably with the back supported and legs uncrossed. The position adopted by the participants during measurement was an upright position in a chair with the arms supported on a table.

Electronic Sphygmomanometer

Resting blood pressure and pulse rate measurements were made using an automated monitor (Dinamap Pro 300; GE Medical Systems, Berks, United Kingdom). The Dinamap Pro 300 device was evaluated for accurateness and dependability of measurement by means of the mercury sphygmomanometer. The cuff was placed around the participant's left arm over the left brachial artery, about 1.5 cm directly above the antecubital fossa and leveled with the heart. Measuring instructions required that the participants remained silent throughout the procedure. The position adopted by the participants during measurement was an upright position in a chair while the upper limbs were supported on the table, lower limbs uncrossed, and feet positioned flat on the floor. The lowest of 3 measures was used for analysis, as reported by Wiles et al,[21] since it has been previously stated that initial measurements are often higher than subsequent measures and so are not reflective of true resting arterial pressures.[19] Each of the 3 measures was separated by an interval of 60 seconds, which is in agreement by way of earlier recommendations and studies.[21]

Experimental Procedure

On arrival at the clinic on the first day, participants were made to observe a 15-minute seated rest period, after which their blood samples were collected for baseline levels of inflammatory cytokines (interleukin-6 [IL-6], interleukin-10 [IL-10], and tumor necrosis factor-alpha [TNF-α]). A detailed explanation and a demonstration of the exercise protocol were given to the participants, and they were asked to report to the physiotherapy clinic at 4 PM for the exercise daily. The training session for each day took place between the hours of 4 PM and 8 PM daily.

The participants, upon arrival at the clinic, were made to observe a 15-minute seated rest period, after which they were asked to squeeze the dynamometer with their dominant hand twice for a maximum of 2 seconds with a 5-minute rest in between so as to determine their respective maximum voluntary contraction (MVC) for each session. The mean of the 2 readings was taken as the MVC for each participant for that session. Participants were thereafter instructed to squeeze and sustain the dynamometer for 2 minutes at 30% MVC. The dynamometer pointer, which read the scale, gave visual feedback to the participants for the maintenance of the 30% MVC.

This procedure was repeated twice for each training session with a 5-minute rest in between. The position adopted by the participants throughout the exercise training was sitting with upper limbs supported on a table. The exercise protocol was performed for 24 consecutive days. Group 1 (G1) discontinued, with the exercise protocol after 24 days, while group 2 (G2) continued for another 24 consecutive days at 30% MVC. On the other hand, group 3 (G3) continued with the exercise protocol for another 24 consecutive days but at 50% MVC. At the end of the 48 days, blood samples were collected on the 49th day for assessment of the resting data of the inflammatory cytokines (TNF-α, IL-6, and IL-10) parameters.

Blood Sample Collection and Analysis of Cytokines

Five mL of overnight fasting (10-12 hours) blood samples were intravenously collected before and after exercise. The pre-exercise blood sample collection was done on the first day of the screening prior to the commencement of the exercise between the hours of 7 AM and 9 AM, and the post-exercise blood sample was collected on the 49th day to the commencement of the exercise at the same time. After 10 minutes of resting in a chair, venous blood from the antecubital vein was collected into a serum tube. Immediately following collection, blood samples were allowed to settle at room temperature for 20 minutes to 1 hour in the vacutainer tubes using standard aseptic techniques to be clotted and then were centrifuged (1000 g) at 4°C for 20 minutes to separate serum from plasma.

Serum samples were then allocated into 1.5 mL tubes and immediately frozen for further analyses. Commercially available ELISA kits were then used to measure IL-6, IL-10, and TNF-α concentrations. Samples were analyzed in duplicate, and all techniques and materials were used according to the manufacturer's instructions by qualified and licensed medical laboratory scientists. All samples for any one participant were analyzed using the same assay to eliminate inter-assay variance.

Data Collection and Analysis

Three major inflammatory cytokines were selected based on their peculiar role and/or characteristics and ease of laboratory assay with regard to available resources and facilities.

Table 1. *Descriptive Demographic Data of the Participants*

Variable	N	Mean	Standard Deviation
Age (y)	192	39.04	6.441
Height (m)	192	1.7000	.11299
Weight (kg)	192	73.3750	9.00975
Body mass index (kg/m^2)	192	25.4487	2.72359

These were IL-6, IL-10, and TNF-α, which are major proinflammatory cytokines and have been shown to modulate multiple signaling pathways with wide-ranging downstream effects.[19,22] TNF-α plays a vital role in the typical immune response through modulation of pathways that involves an immediate inflammatory response with subsequent proliferation and programmed cell death. It has been shown in a number of inflammatory diseases, particularly in rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease,[22] while IL-6 exerts a proinflammatory effect when the signaling receptor protein, which activates the membrane-bound signaling receptor protein, thus, higher levels of cardiopulmonary fitness have been associated with lower circulating concentrations of both IL-6 and c-reactive protein at rest.[1,2,9]

The collected data were statistically analyzed using descriptive and inferential statistics. The descriptive statistics employed in this study were the mean and standard deviation. The inferential statistics used in the analysis of the data included a 1-tailed Student's *t* test to determine the intragroup differences in the initial and final values of the parameters of the 3 groups. One-way analysis of variance (ANOVA) was thereafter used to compare the means of the 3 groups to determine their level of relationship. Furthermore, a 2-tailed Student *t* test was used to determine the intragroup differences in the initial and final resting values of the parameters of G1 and G2 and with G2 and G3 to determine the effect of continuation (duration) and increase in dosage (intensity) of the isometric effort, respectively.

Results

Table 1 presents descriptive demographic data of all the participants. There were 192 participants total, with a mean age of 39.04 ± 6.4 years, height 1.7 ± 0.11 m, weight 73.4 ± 9.0 kg, and body mass index of 25.4 ± 2.7 kg/m^2.

The body mass index distribution of the participants showed that 3.1%, 15.6%, 34.4%, and 46.9% of the participants were morbidly obese, obese, overweight, and normal with their weight, respectively (Table 1). There were 6 people who were morbidly obese, 30 participants were obese, 66 participants were overweight, and 90 participants had normal weight. From this data, weight may be related to prehypertension since the participants were randomly selected, though this was not the focus of the study.

The distribution of the participants was based on their sex—a total of 54.7 % (105) were men while the rest 45.3% (87) were women. It could be deduced from this data that prehypertension is more associated with men.

Table 2 shows the pre- and post-exercise mean values of the inflammatory cytokines of the exercise for G1. Results obtained revealed a mean reduction of 0.05 ± 0.036 pg/mL and 0.036 ± 0.017 pg/mL in TNF-α and IL-6, respectively, and a mean increase of 0.53 ± 0.14 pg/mL in IL-10. These values were statistically significant. This means that the exercise protocol of G1 produced a significant mean reduction in the values of TNF-α and IL-6 and a significant mean increase in IL-10. It appears then that isometric handgrip exercise at 30% MVC has an anti-inflammatory effect in humans.

Table 3 shows the pre- and post-exercise mean values of the inflammatory cytokines of the exercise for G2. The participants showed a mean reduction of 0.065 ± 0.026 pg/mL and 0.057 ± 0.014 pg/mL in TNF-α and IL-6, respectively, and an increase of 0.493 ± 0.24 pg/mL in IL-10. The values were statistically significant. This means that isometric handgrip exercise at 30% MVC over a longer duration also promotes an anti-inflammatory effect in humans.

Table 4 shows the pre- and post-exercise mean values of the inflammatory cytokines of exercise G3. The participants also had a mean reduction of 0.10 ± 0.11pg/mL and 0.07 ± 0.28 pg/mL in TNF-α and IL-6, respectively, and an increase of 0.77 ± 0.32 pg/mL in IL-10. The values were statistically significant. This means that isometric handgrip exercise at 30% MVC over a longer duration and at increased intensity also promotes an anti-inflammatory effect in humans.

Table 2. *Pre- and Post-Exercise Mean Values of the Inflammatory Cytokines of Exercise Group 1*

Parameter	Pre-Exercise	Post-Exercise	Diff.	Df	Sig. (2-tailed)	Remark
TNF-α (pg/mL)	1.63 ± 0.26	1.58 ± 0.26	−0.05 ± 0.04	63	<.001[a]	Significant
IL-6 (pg/mL)	0.45 ± 0.08	0.42 ± 0.08	−0.04 ± 0.01	63	<.001[a]	Significant
IL-10 (pg/mL)	6.5 ± 1.58	7.03 ± 1.59	0.53 ± 0.14	63	<.001[a]	Significant

Data are expressed as the mean ± standard deviation (n = 64) unless otherwise indicated.
Diff, difference in exercise protocol; *Df,* degree of freedom; *IL-6*, interleukin-6; *IL-10*, interleukin-10; *Sig*, significance;*TNF-α*, tumor necrosis factor-alpha.
[a] $P < .05$.

Table 3. *Pre- and Post-Exercise Mean Values of the Inflammatory Cytokines of Exercise Group 2*

Parameter	Pre-Exercise	Post-Exercise	Diff.	Df	Sig. (2-tailed)	Remark
TNF-α (pg/mL)	1.47 ± 0.27	1.41 ± 0.26	−0.07 ± 0.03	63	<.001[a]	Significant
IL-6 (pg/mL)	0.47 ± 0.10	0.41 ± 0.09	−0.06 ± 0.01	63	<.001[a]	Significant
IL-10 (pg/mL)	6.2 ± 1.3	6.69 ± 1.44	0.49 ± 0.24	63	<.001[a]	Significant

Data are expressed as the mean ± standard deviation (n = 64) unless otherwise indicated.
IL-6, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-alpha.
[a] $P < .05$.

Table 4. *Pre- and Post-Exercise Mean Values of the Inflammatory Cytokines of Exercise Group 3*

Parameter	Pre-Exercise	Post-Exercise	Diff.	Df	Sig. (2-tailed)	Remark
TNF-α (pg/ mL)	1.52 ± 0.16	1.41 ± 0.16	−0.10 ± 0.11	63	.003[a]	Significant
IL-6 (pg/mL)	0.47 ± 0.11	0.40 ± 0.10	−0.07 ± 0.28	63	<.001[a]	Significant
IL-10 (pg/mL)	6.53 ± 1.25	7.31 ± 1.30	0.77 ± 0.32	63	<.001[a]	Significant

Data are expressed as the mean ± standard deviation (n = 64) unless otherwise indicated.
IL-6, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-alpha.
[a] $P < .05$.

Table 5 shows the effects of cessation and continuation of the exercise protocol in the mean values of the inflammatory cytokine parameters for G1 and G2. The table shows an increase with average values of 0.015 ± 0.01 pg/mL and 0.021 ± 1.35 pg/mL in TNF-α and IL-6, respectively, and a mean decrease of 0.042 ± 0.10 pg/mL in IL-10 following a continuation of the exercise protocol as seen in G2. This means that cessation of the exercise protocol after 24 days, as seen in G1, produced a lesser effect compared to continuation of the exercise protocols, as seen in G2. However, the changes were not statistically significant except with IL-6. The results of Table 5 clearly demonstrate that the effects of duration on the observed changes were not statistically significant.

Table 6 shows the effects of continuation and increase in the intensity of the exercise protocol in the mean values of the parameters of the inflammatory cytokines. Results showed an increase with average values of 0.045 ± 0.07 pg/mL and 0.013 ± 0.35 pg/mL in TNF-α and IL-6, respectively, and a mean decrease of 0.2 ± 0.06 pg/mL in IL-10, following an increase in the intensity of the exercise protocol as seen in G3. These values were, however, not significant, except with IL-10. The results of Table 6 clearly demonstrate that the effect of increase in the intensity of the exercise protocols on the observed changes was not statistically significant but significantly boosted the anti-inflammatory effect.

Table 7 shows 1-way ANOVA of the inflammatory cytokine mean difference across the 3 groups. There was no statistical significance following 1-way ANOVA in the 3 exercise procedures on the values of the inflammatory cytokine parameters. The results of Table 7 above clearly demonstrate that isometric handgrip exercise at 30% MVC promotes an anti-inflammatory effect that is not predominantly affected by the duration and or increase in intensity.

Table 5. *The Comparative Effects of Cessation and Continuation of the Exercise Protocol at the End of 48 Days on Inflammatory Cytokines*

Parameter	Exercise Group 1	Exercise Group 2	Diff.	Df	Sig. (2-tailed)	Remark
TNF-α (pg/mL)	0.05 ± 0.036	0.07 ± 0.026	0.015 ± 0.01	127	.553	Insignificant
IL-6 (pg/mL)	0.036 ± 0.017	0.06 ± 0.014	0.021 ± 1.35	127	.001[a]	Significant
IL-10 (pg/mL)	0.53 ± 0.14	0.49 ± 0.24	0.04 ± 0.10	127	.956	Insignificant

Data are expressed as the mean ± standard deviation (n = 128) unless otherwise indicated.
IL-6, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-alpha.
[a] $P < .05$.

Table 6. *The Comparative Effects of Continuation and Increase in Intensity of the Exercise Protocol at the End of 48 Days on Inflammatory Cytokines*

Parameter	Exercise Group 2	Exercise Group 3	Diff.	Df	Sig. (2-tailed)	Remark
TNF-α (pg/mL)	0.065 ± 0.026	0.10 ± 0.11	0.045 ± 0.07	127	.197	Insignificant
IL-6 (pg/mL)	0.057 ± 0.014	0.07 ± 0.28	0.013 ± 0.35	127	.082	Insignificant
IL-10 (pg/mL)	0.493 ± 0.24	0.77 ± 0.3	0.2 ± 0.06	127	.009[a]	Significant

Data are expressed as the mean ± standard deviation (n = 128) unless otherwise indicated.
IL-6, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-alpha.
[a] $P < .05$.

Discussion

The widespread deleterious health effect of the augmented inflammatory state critically calls for identification of therapies that could reduce inflammation, and physical exercise is currently becoming a promising panacea to this ubiquitous health burden. The main focus of this study was to assess the responses of selected cytokines to isometric handgrip exercise and identify possible effects of continuation, cessation, and increase in the intensity of the isometric exercise. The effects of physical activity on systemic inflammation have not been extensively studied, and available data have shown controversial reports.[2,3] The outcome of this investigation shows that the isometric handgrip exercise protocols lead to a significant alteration in the resting values of the inflammatory cytokines post-exercise. Conspicuously, the isometric handgrip exercise occasioned a decline in the proinflammatory cytokines and gave way to a rise in anti-inflammatory cytokines. The results further revealed that continuation of the exercise protocol after 24 days enhanced and produced a significant decrease of proinflammatory cytokines and a rise in anti-inflammatory cytokines. The exercise-induced changes in inflammatory cytokine levels have been reported to be related to the type, intensity, and duration of exercise and endurance capacity of the participant.[15] Many studies indicated that acute exercise increased inflammatory cytokines, but opposite effects were observed after chronic exercise.[9] Several studies have reported reductions in proinflammatory cytokines following physical activities, indicating that long-term exercise training may reduce chronic low-grade systemic inflammation.[15,23]

The exercise trials in this study resulted in significant changes in the post-exercise resting values of the inflammatory cytokines. Notably, there was a reduction in the proinflammatory cytokines and an increase in the anti-inflammatory cytokines. The results further revealed that a continuation of the exercise protocol after 24 days, as seen in G2, resulted in a further reduction of the proinflammatory cytokines and an increase in anti-inflammatory cytokines compared to cessation of the exercise protocol after 24 days, as seen in G1, although the changes were not statistically significant except with IL-6. On the other hand, the increase in the intensity of the exercise protocol, as seen in G3, significantly further reduced the resting values of IL-6 and increased IL-10, but the reduction on TNF-α was not significant compared to continuation of the exercise protocol after 24 days.

Table 7. *Analyses of Variance for the 3 Groups on Inflammatory Cytokine Parameters Inflammatory Biomarkers*

Parameter		Sum of Squares	Df	Mean Square	F	Sig.
TNF-α (pg/mL)	Between-groups	.026	2	.013	2.420	.100
	Within-groups	.240	189	.005		
	Total	.266	191			
IL-6 (pg/mL)	Between-groups	.010	2	.005	11.611	.060
	Within-groups	.020	189	.000		
	Total	.030	191			
IL-10 (pg/mL)	Between-groups	.705	2	.353	6.167	.054
	Within-groups	2.574	189	.057		
	Total	3.279	191			

IL-6, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-alpha.

Moreover, increase in exercise intensity, as seen in G3, significantly further reduced the resting values of IL 6 and TNF-α but increased IL-10. In G1, there was a mean reduction of 0.05 $\pm$ 0.036 pg/mL in TNF-α and 0.057 $\pm$ 0.014 pg/mL in IL-6, whereas a mean rise of 0.53 $\pm$ 0.14 pg/mL in IL-10 was observed. Similarly, the G2 participants showed a mean reduction of 0.065 $\pm$ 0.026 pg/mL and 0.057 $\pm$ 0.014 pg/mL in the TNF-α and IL-6, respectively, and an increase of 0.493 $\pm$ 0.24 pg/mL in IL-10. In G3, the participants also had a mean reduction of 0.10 $\pm$ 0.11 pg/mL and 0.07 $\pm$ 0.28 pg/mL in TNF-α and IL-6, respectively, and an increase of 0.77 $\pm$ 0.32 pg/mL in IL-10. These changes were interestingly statistically significant in all 3 exercise groups; thus, it appears that inflammatory cytokines have a high sensitivity to isometric exercise protocols. Despite the seeming controversies surrounding the effect of physical exercises, the potential for regular physical exercise as an anti-inflammatory intervention is increasingly being recognized.[4]

Exercises have been applied as a means of intervention in inflammatory and immune system disorders, even in conditions where it was previously contraindicated.[24,25] Comparing the effects of cessation and continuation of the exercise protocols showed an increase, with average values of 0.015 $\pm$ 0.01 pg/mL and 0.021 $\pm$ 1.35 pg/mL in TNF-α and IL-6, respectively, and a mean decrease of 0.042 $\pm$ 0.10 pg/mL in IL-10 following a continuation of the exercise protocol as seen in G2, showing that duration of the exercise protocol has a direct proportional effect in the values of these parameters. Nevertheless, these differences did not show any statistical significance except with IL-6. On the other hand, the comparative effects of continuation and increase in intensity of the exercise protocol showed an increase, with average values of 0.045 $\pm$ 0.07 pg/mL and 0.013 $\pm$ 0.35 pg/mL in TNF-α and IL-6, respectively, and a mean decrease of 0.2 $\pm$ 0.06 pg/mL in IL-10, following an increase in the intensity of the exercise protocol as seen in G3. These differences were also not statistically significant except for IL-10. ANOVA showed no significant difference in the 3 exercise groups in all of the variables analyzed.

Observational data from large population cohort studies consistently show an association between physical activity and inflammation. A linear trend for lower IL-6 and TNF-α has been reported with greater amounts of physical activity in the health, aging, and body composition study.[26] In a cross-sectional and prospective study, Taaffe et al[27] reported that IL-6 concentrations were inversely proportional to the number of reported hours of moderate and strenuous exercise spent in a year. Reuben et al[28] also reported low concentrations of IL-6 in elderly persons with the highest levels of recreational activity. Specifically, lower proinflammatory cytokine concentrations were observed in individuals who reported performing more frequent and more intense physical activity.[2]

These reports are consistent with the results of this study. However, this study employed an intervention designed with a quantifiable exercise protocol in contrast to the aforementioned reports. Since elevated levels of TNF-α and IL-6 have been linked to morbidity and mortality of conditions such as obesity, insulin resistance, type 2 diabetes, cardiovascular diseases, and inflammatory diseases like rheumatoid arthritis, Crohn disease, ankylosing spondylitis, and psoriasis,[2,9,22,23,29] the reductions observed in the values of these cytokines in this present study would be of much health benefit. The results of this study showed that 24 to 48 consecutive days of isometric handgrip exercise resulted in reductions in the values of proinflammatory cytokines (decreased serum levels of TNF- α and IL-6) and elevation of anti-inflammatory cytokines (IL-10) in middle-aged prehypertensive individuals.

Limitations and Future Studies

This study had prominent limitations, including a lack of consistency in exercise protocols and quantification of intensity of the exercise utilized. Furthermore, numerous sources of bias, as well as the attitude of participants towards the experimental protocol, were tentative limitations to the scope and content of the present research. This study was limited to people who had been diagnosed with prehypertension who were 30 to 50 years of age and who lived in Nigeria. Therefore, our findings may not necessarily apply to people of different ages or who live in different regions. Future studies using the same exercise protocols should focus on monitoring the chronic effect over a longer duration.

Conclusion

The isometric handgrip exercise protocols in this study resulted in elevation of anti-inflammatory cytokine (IL-10) and reduction in the values of proinflammatory cytokines TNF- α and IL-6.

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No funding sources or conflicts of interest were reported for this study.

Contributorship Information

Concept development (provided idea for the research): O.G.U., N.E.K., I.J.C.
Design (planned the methods to generate the results): O.G.U., N.E.K., N.B.C., U.F.C.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): N.E.K., I.J.C.

Data collection/processing (responsible for experiments, patient management, organization, or reporting data): N.B.C., E.E., C.E.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): O.G.U., N.B.C., C.E.
Literature search (performed the literature search): U.F.C., E.E.
Writing (responsible for writing a substantive part of the manuscript): O.G.U., N.E.K., N.B.C.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): N.B.C.

Practical Applications

- We investigated the responses of selected inflammatory cytokines to isometric handgrip exercise.
- We found an increase in the resting values of interleukin 10 across the 3 groups.
- Isometric handgrip exercise protocols resulted in the elevation of anti-inflammatory cytokines (interleukin 10) and reductions in the values of proinflammatory cytokines tumor necrosis factor-α and interleukin 6.

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