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Sixteen weeks of aerobic training influence spirometry, s-klotho, and hemodynamic responses to sub-maximal exercise testing in obese men with severe obstructive sleep apnea

Abstract

Purpose: The purpose of the study was to examine the influences of sixteen weeks of aerobic training on s-klotho levels, hemodynamic responses, and spirometry variables in obese men with severe obstructive sleep apnea before, during, and after the Six Minute Walk Test.

Methods: fifty men, age 57.6±6.82years, volunteered to participate in this study. Twenty-five obese subjects and diagnosed with severe OSA underwent sixteen weeks of aerobic exercise. Twenty-five healthy, untrained, age and sex-matching subjects were assigned to the control group. S-klotho levels, hemodynamic responses, and spirometry related values were obtained at various timings before, during, and after the Six Minute Walk Test (6MWT). Repeated measures were obtained upon enrollment, after eight weeks of exercise, and after sixteen weeks of exercise.

Results: Significant effects of time, exercise, and the interaction of time×exercise were noted for s-klotho concentrations and the vast majority of other variables.

Conclusions: sixteen weeks of aerobic training have a positive effect on s-klotho levels, hemodynamic responses at rest, during, and after the Six Minute Walk Test, as well as on spirometry in men with severe OSA.

Keywords: severe OSA, FEV1, FVC, FEV1/FVC ratio, S-klotho, 6MWT, hemodynamic responses, spirometry, blood pressure, lactate, heart rate

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Saghiv M,[1] Manisha Sawhney,[2] Lark Welch,[3] Ben-Sira D,[4] Goldhammer E,[5] Sagiv M[4]

[1]Department of Human Performance and Leisure Studies, North Carolina A & T State University, USA
[2]Department of Psychology, University of Mary, USA
[3]Department of Kinesiology, University of Mary, USA
[4]Department of Life Sciences, The Zinman College of Physical Education at the Wingate Collage, Israel
[5]Heart Institute Bnai-Zion Haifa Medical Center, Israel

Correspondence: Moran S Saghiv, Associate Professor of Clinical Exercise Physiology, Department of Exercise Physiology, Casey Center, Room 141B, University of Mary, 7500 University Drive, Bismarck, ND 58504, USA, Tel 7013558103, Fax 7012557687, Email mssaghiv@umary.edu

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Introduction

Klotho is an enzyme that in humans is encoded by the KL gene.[1] S-klotho is a type I membrane protein first documented in 1997.[2] The protein is associated with the degenerative process, acceleration and/or deceleration of aging, bone lose, and alcohol consumption.[3-7] Furthermore, s-klotho has a role in determining the sensitivity to Insulin, and mediation of the binding of FGF19, FGF20, and FGR23 to their receptors as part of the growth process at the cellular level.[6]

In addition, S-klotho is suspected of having cardiovascular protecting properties via means of endothelium-derived NO production.[8,9] S-klotho affects cellular Calcium homeostasis via increased expression of TRPV5, decreased TRPC6, and increases membrane expression of Inward Rectifier ROMK. In mice, under-expression causes Hyper-vitaminosis of Vitamin D, altered mineral-ion homeostasis resulting in accelerated aging, a syndrome of accelerated aging, arteriosclerosis, impaired endothelium-dependent vasodilation, and impaired angiogenesis.[6,10–13]

Over-expression may prolong life span by 19-31% (in mice). In humans, exercise modalities influence klotho gene expression epigenetically and positively leading to increased expression.[14] Prior studies show improvements in work capacity and performance alike.[15,16]

Sleep apnea (SA) is a respiratory disorder that occurs at night with symptoms that may be present during daytime as well.[17] Three forms of sleep apnea exist, including Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA), and Mixed Sleep Apnea (MSA).[17] OSA is the most common form of SA and is due to blockage of airflow within the respiratory system.[17] OSA is twice as much common in men, affecting up to 6% of adults, most commonly aged 55-60years. OSA may occur in children, though its prevalence is most definitely lower in children.[18]

The leading risk factors for SA include being of male sex, obesity, above age forty, neck diameter of 16–17 inches or greater (40.64-43.18cm), enlarged tonsils or tongue, small jaw bone, gastroesophageal reflux, a variety of allergies, Sinusitis, a family history, and a deviated septum.[19,20] OSA is associated with reduced functional capacity.[18–20] On the other hand, aerobic exercise improves cardiorespiratory aspects of function in people with OSA.[21–25]

The six Minute Walk Test (6MWT) is an exercise test that may be sub-maximal and/or maximal according to extent of effort on the participant's behalf. As part of the 6MWT the participant is instructed to achieve the greatest distance possible within 6minutes of walking.[26] During the test, it is important to abstain from influencing the performance of the participant in order for the results and process to be genuine and free of external affecters.[27]

The overall distance achieved and the comparison to prior results influence future prognosis.[28] While correlations to positive vs negative prognosis exist regarding the results of the 6MWT, interpretation within the actual distances is complex and perhaps ill-advised.[29]

Spirometry related variables such as FEV1 predicted (%), FVC predicted (%), and FEV1/FVC ratio (also known as the Tiffeneau-Pinelli index) indicate the existence, or lack of, conductance and/or obstructive abnormalities in the respiratory system.[30] People with diagnosed OSA commonly manifest spirometry values of negative implications to function and health.[31] Such values are associated with poor exercise tolerance, decreased aerobic power (maximal oxygen uptake; VO_2max), and a shorter lifespan (years).[32]

To the best of the authors' knowledge, no prior published data exists pertaining the influences of aerobic exercise on s-klotho in men with OSA. Thus, the aim of this study was to investigate the influences of sixteen weeks of aerobic training on s-klotho (pg·mL^{-1}), heart rate (bpm), blood pressure (mmHg), Lactate (mmol·L^{-1}), Oxygen saturation (O_2sat, %), rate of perceived exertion (RPE, Scale), FEV1 predicted (%), FVC predicted (%),FEV1/FVC ratio, and the occurrence of angina and/or dyspnea event before and after a 6MWT in men with severe OSA.

Methods

After achieving IRB approval to conduct this study, twenty-five obese men clinically diagnosed by their physician with severe OSA (BMI>30; AHI>30/h) volunteered to participate in this study and have complied with all the demands of it. Subjects enrolled within 4weeks of their initial diagnosis and were untrained at the beginning of the study.

Twenty-five healthy, untrained, age and sex matching subjects volunteered and were assigned to the control group. Candidates were excluded from participating as control subjects if they presented with any clinical symptoms (physical and mental), were trained, and/or were medicated for more than hypertension. Control group subjects visited with the researchers only once. Subjects diagnosed with OSA visited with the researchers three times in total (enrollment; after eight weeks of exercise; after sixteen weeks of exercise weeks). Subjects were instructed to completely avoid alcohol consumption of any sort, exercise of any sort within twenty-four hours of data collection, caffeine, use of any medications other than subscribe by their physician (OSA diagnosed only), and/or stressful situations at least eight hours prior to their data collection sessions. All subjects self-reported their compliance with these instructions prior to each session.

The first visit was dedicated to signing the informed consent form (if not achieved before), risk stratification according to health history questionnaire (HHQ), inclusion or exclusion from the study, and obtaining baseline measures. Severe OSA diagnosed prospective subjects were excluded if they had diagnosed CAD, PAD, CVD, Diabetes, COPD, overlap syndrome, were post-surgery of any kind, had Cancer, were treated for Cancer, had a mental health condition, were medicated for other health conditions other than hypertension and/or OSA, and/or were not cleared for exercise by their physician. All included subjects were authorized by their physician to abstain from oxygen supplementation of any kind for the duration of the study.

All subjects reported to the lab between 6-8am. Upon arrival, subjects fulfilled a short questionnaire pertaining to their compliance with the pre-data collection instructions and changes to physical and/or mental health. Subjects compliant and asymptomatic were then weighed and seated for five minutes. Following the collection of baseline values (Table 1), the subjects underwent the 6MWT. Researcher have prepared in advance a 30-meter stretch of unimpeded walkway and have positioned three chairs along the way (at every end, and in the middle).

Subjects were instructed to achieve the greatest distance possible within six minutes and were instructed to inform the researchers immediately if they could not continue, had to sit down, or felt bad. Subjects were informed that they are allowed to terminate the test at any time.

Table 1 Timing of obtaining measures before, during, and after the six minute walk test

Variable	Rest	+2	+4	IP	+5	+10	+15	+45
Weight (kg)	yes							
Height (m)*	yes							
BMI (Kg·m^{-2})†	yes							
Neckb (cm)	yes							
AHI (E/hr)†	yes							
S-klotho (pg·mL^{-1})	yes			yes			yes	yes
HR (bpm)	yes	yes	yes	yes	yes	yes	yes	yes
BP (mmHg)	yes			yes	yes	yes	yes	yes
FPG (mg·dL^{-1})	yes			yes	yes	yes	yes	yes
LA (mmol·L^{-1})	yes			yes	yes	yes	yes	yes
Angina‡	yes	yes	yes	yes	yes	yes	yes	yes
Dyspnea‡	yes	yes	yes	yes	yes	yes	yes	yes
RPE‡	yes	yes	yes	yes	yes	yes	yes	yes
O2sat (%)	yes	yes	yes	yes	yes	yes	yes	yes
FEV1 (L)	yes			yes				
FVC (L)	yes			yes				
FEV1/FVC†	yes			yes				

m, meter; Kg, kilogram; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; O2sat, oxygen saturation; mmHg, millimeter of Mercury; dL, deciliter; mmol, millimole; mg, milligram; bpm, beats per minute; pg, picogram; mL, milliliter; †, calculated ratio; ‡, scale; FPG, fasting plasma glucose; LA, lactate; b, circumference; AHI, apnea hypopnea index; hr, hour; E, event of hypopnea; RPE, rate of perceived exertion; FEV1, forced expiratory volume; FVC, forced vital capacity; *, measured only once during first visit and assumed as of no change throughout the study

Excluding the need for informed consent and HHQ, the protocol detailed in visit 1, was the same for all visits pertaining to subjects with OSA.

In between visits to the lab, subjects with OSA were instructed to exercise three times per week at a target heart rate of 95-105bpm (≈60% of age-estimated maximal heart rate); according to the formula of 0.6×(220-age). During the first week, the duration of every exercise session was 20minutes; session duration was increased by 30seconds from week to week. Thus, during the second week of the study, every session was 20.5minutes long; 21minutes long during the sessions of the third week, etc. Heart rate range was kept constant throughout the study, causing the subjects to move faster if needed in order to stay within that range.

All blood samples were obtained according to universal precautions for blood borne pathogens from the Median Cubital Vein and stored in BD Vacutainer™ Venous Blood Collection Tubes: SST™ Serum Separation Tubes with Conventional Stopper until analyzed; samples were immediately refrigerated.

Blood samples were analyzed via Soluble Klotho (Human serum) ELISA Kit SK00708-08 (Adipo Bioscience, Inc.), with a Standard range of 313-20,000 pg·mL^{-1}, Sensitivity of 80 pg·mL^{-1}; Intra-CV of 4-6%; and Inter-CV of 8-10%. Blood pressure was obtained utilizing an Omron sphygmomanometer; heart rate via FS2c Polar Heart Rate Monitor and strap, Oxygen saturation was obtained via KNIGHTRO-OXIMETER 5.2 Bluetooth Fingertip Pulse Oximeter; Lactate and fasting plasma glucose (FPG; mg·dL^{-1}) were obtained via Point-of-Care testing using a Lactate "Scout" Analyzer (Basic) B7023-255 and a Roche Diagnostics CoaguChek XS Professional Meter Kit respectively. The treadmill used in this study was a Bowflex Results Series™ BXT216 Treadmill. Spirometry was conducted via a MIR Spirobank II Smart BLE spirometer. A charged AED was present in the lab at all times, as well as a landline phone, and backup cellphone. During all data collection sessions, at least one of the researchers was ACLS certified.

Statistical analysis

A two way ANOVA with repeated measures was utilized to analyze the data obtained. Data is presented as mean and standard deviation when appropriate with significance levels (P value).

Results

Overview, enrollment, and descriptive data

All subjects completed this study without any prolonged adverse reactions. Some subjects had a temporary reaction to their blood being drawn (dizziness, elevated heart rate, hypertension, hypotension, and in two cases subjects reacted with syncope). Nine different subjects had acute adverse reactions to the Six Minute Walk Test including shortness of breath, Angina, and lightheadedness on several occasions. All subjects left the lab without any adverse clinical signs other than pre-existing due to their OSA.

Control group were insignificantly older and shorter (p>0.05). Experimental group's weight and BMI were significantly higher (p≤0.05). Neck circumference and AHI were significantly higher for the experimental group (p≤0.01).

Weight, BMI, and Neck circumference were insignificantly lower for the experimental group at the end of the study (p>0.05). AHI decreased significantly by the end of the study (p≤0.01). Relevant data are presented in Table 2.

Table 2 Resting† descriptive data and changes in obtained measurements, according to visits. (Mean±SD)

Variable	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
No intervention		**Exercise intervention**		
N	**25**	**25**	**25**	**25**
Age (years)	58.51±3.6	56.25±4.8	*	*
Height (m)	1.75±3.6	1.77±2.1	*	*
Height (in)	68.89±1.41	69.68±0.82	*	*
Weight (Kg)	81.73±4.3	116.27±5.1	113.81±4.2	111.56±5.5
Weight (lb)	179.8±9.46	255.2±11.22	250.38±9.24	245.43±12.1
BMI (Kg·m^{-2})	26.71±0.59	37.15±1.98	36.33±1.25	35.61±1.34
Neck[b] (cm)	35.21±2.59	42.15±4.48	40.33±4.18	40.17±4.28
AHI (E/hr)	3.01±0.53	45.45±14.48	41.7±17.48	40.15±15.3

N, number of subjects; m, meter; in, inch; Kg, kilogram; lb, pound; BMI, body mass index; SD, standard deviation; *, variable values assumed the same as in baseline;b, circumference; AHI, apnea hypopnea index; hr, hour; E, event of hypopnea; EXS, exercise; Wk, weeks;

The design of this study includes a vast number of variables, with a very high number of possible comparisons. In order to avoid over burdening the reader as much as possible, the significance of the comparisons are presented in essence only.

S-klotho (pg mL-1)

All possible comparisons within and between groups were significant (p≤0.05). All data regarded s-klotho are presented in Table 3.

Table 3 s-klotho concentrations before and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

S-klotho (pg mL^{-1})	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
No intervention		**Exercise intervention**		
N	**25**	**25**	**25**	**25**
Rest†	475.5±102	262.4±58	323.6±52	371.45±62
Immediate-post	677.3±98	342.64±88	416.18±52	462.05±55
15min post	637.4±88	292.3±81	351.48±62	409.33±75
45min post	554.61±97	272.3±85	336.48±43	402.0±65

N, number of subjects; pg, picogram; mL, milliliter; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Heart rate (HR; bpm)

a. Rest to 45minutes post (control)- Differences between rest, 10minutes post, 15minutes post, 45minutes post, and between immediate-post and 2minutes within were insignificant (p>0.05).
b. Rest to 45minutes post (experimental; Enrollment) - Differences between rest, 15minutes post, and 45minutes post were insignificant (p>0.05).
c. Rest to 45minutes post (experimental; +8weeks) - Differences between rest, 15minutes post, 45minutes post, and between 2 and 4minutes within were insignificant (p>0.05).
d. Rest to 45minutes post (experimental; +16weeks) - Differences between rest, 15minutes post, 45minutes post, and between 2minutes and 4minutes within were insignificant (p>0.05).
e. Rest (between groups)- All comparisons were significantly lower for the control group, excluding after 16weeks of exercise (p≤0.05).
f. Rest (experimental)- HR was significantly higher while untrained compared to while trained (p≤0.05). Differences while trained were insignificant (p>0.05).
g. 2minutes within (between groups) - All comparisons were significant (p≤0.05).
h. 2minutes within (experimental) - HR upon enrollment was significantly higher compared to all other sessions (p≤0.05). All other comparisons were insignificant (p>0.05).
i. 4minutes within (between groups) - All comparisons were significant (p≤0.05).

j. 4minutes within (experimental) - All comparisons were insignificant (p>0.05).

k. Immediate-post (between groups) - The comparison upon enrollment was insignificant (p>0.05). All other comparisons were significant (p≤0.05).

l. Immediate-post (experimental)- Comparison between enrollment and 8weeks was significant (p≤0.05). All other comparisons were insignificant (p>0.05).

m. 5minutes post (between groups) - All comparisons were significant (p≤0.05).

n. 5minutes post (experimental)- Comparison of enrollment and 8weeks of exercising was insignificant (p>0.05). All other comparisons were significant (p≤0.05).

o. 10minutes post (between groups) - All comparisons were significant (p≤0.01).

p. 10minutes post (experimental)- Comparison for while trained was insignificant (p>0.05). All other comparisons were significant (p≤0.05).

q. 15minutes post (between groups)- Comparison to 16weeks was insignificantly (p>0.05). All other comparisons were significant (p≤0.05).

r. 15minutes post (experimental)-All other comparisons were significant (p≤0.05).

s. 45minutes post (between groups) - Comparison to 16weeks insignificant (p>0.05). All other comparisons were significant (p≤0.05).

t. 45minutes post (experimental): Comparison for while trained was insignificant (p>0.05). All other comparisons were significant (p≤0.01). All data regarding heart rate are presented in Table 4.

Table 4 heart rate before, during, and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

HR (bpm)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		Exercise intervention	
N	25	25	25	25
Rest†	76.6±5.3	87.4±6.7	81.63±3.11	78.08±4.03
+2min	158.3±6.5	153.1±8.2	147.0±4.41	146.25±5.81
+4min	150.6±7.12	140±11.8	143.0±2.91	144.65±6.23
Immediate-post	160.3±9.1	157.31±8.7	153.31±7.11	156.0±7.4
5min post	92.44±6.81	134.1±4.33	133.04±4.19	129.34±4.4
10min post	76.89±4.61	115.34±3.17	102.66±4.78	101.08±3.26
15min post	76.54±5.4	88.14±5.46	82.06±3.48	78.44±2.61
45min post	76.2±3.31	87.16±2.23	81.08±2.71	78.66±1.92

N, number of subjects; HR, heart rate; bpm, beats per minute; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Systolic blood pressure (SBP; mmHg)

a. Rest to 45minutes post (control) - Immediate-post was significantly higher than all other values (p≤0.05). fiveminutes post was significantly higher than rest, 10minutes post, 15minutes post, and 45minutes post (p≤0.05). Differences between rest, 10minutes post, 15minutes post, and 45minutes post were insignificant (p>0.05).

b. Rest to 45minutes post (experimental; Enrollment) - Immediate-post was significantly higher than all other values (p≤0.05). 5minutes post was significantly higher than all other comparisons excluding immediate-post (p≤0.05). 10minutes post was significantly higher compared to rest, 15minutes post, and 45minutes post (p≤0.05). All other comparisons were insignificant (p>0.05).

c. Rest to 45minutes post (experimental; +8weeks) - Immediate-post was significantly higher than all other values (p≤0.05). 5minutes post was significantly higher than all other comparisons excluding immediate-post (p≤0.05). 10minutes post was significantly higher compared to rest, 15minutes post, and 45minutes post (p≤0.05). 15minutes post was insignificantly higher compared to rest (p>0.05), and insignificantly lower compared to 45minutes post (p>0.05).

d. Rest to 45minutes post (experimental; +16weeks) - Immediate-post was significantly higher than all other values (p≤0.05). 5minutes post was significantly higher than all other comparisons excluding immediate-post (p≤0.05). 10minutes post was significantly higher compared to rest, 15minutes post, and 45minutes post (p≤0.01). 15minutes post was insignificantly higher compared to rest (p>0.05), and insignificantly lower compared to 45minutes post (p>0.05).

e. Rest (between groups) – Comparison to eight weeks was insignificant (p>0.05). All other comparisons were significant (p≤0.05).

f. Rest (experimental) – Comparison for while trained was insignificant (p>0.05). All other comparisons were significant (p≤0.05).

g. Immediate-post (between groups) - Control group's value was significantly lower compared to eight and sixteen weeks (p≤0.05), and significantly higher enrollment (p≤0.05).

h. Immediate-post (experimental) – All comparisons were significant (p≤0.05).

i. 5minutes post (between groups) – All comparisons were significant (p≤0.05).

j. 5minutes post (experimental) - All comparisons were insignificant (p>0.05).

k. 10minutes post (between groups) - All comparisons were significant (p≤0.01).

l. 10minutes post (experimental) – All comparisons were significant (p≤0.05).

m. 15minutes post (between groups) – Comparison was insignificantly lower compared to while trained (p>0.05).

n. 15minutes post (experimental) - Enrollment was significantly higher compared to all other values (p≤0.05). Difference while trained was insignificant (p>0.05).

o. 45minutes post (between groups) – All comparisons were significant (p≤0.05).

p. 45minutes post (experimental) – Comparison between enrollment and while exercised was significant (p≤0.05). Comparison while exercised was insignificant (p>0.05). All data regarding systolic blood pressure are presented in Table 5.

Table 5 systolic blood before and after the Six Minute Walk Test pressure according to visit and timing of measurement (Mean±SD)

SBP (mmHg)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
N	25	25	25	25
Rest†	125.1±1.6	133.3±3.6	126.5±2.0	125.37±2.41
Immediate-post	182.3±5.53	175.61±7.32	183.13±5.1	187.0±9.11
5min post	141.6±4.73	165.2±3.54	166.45±5.78	164.33±3.79
10min post	126.11±2.01	150.66±4.07	141.33±4.24	133.44±4.96
15min post	125.22±1.54	134.42±3.37	128.43±3.39	126.37±4.14
45min post	125.13±1.64	137.7±2.72	130.0±2.03	129.54±1.9

N, number of subjects; SBP, systolic blood pressure; mmHg, millimeter of Mercury; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Diastolic blood pressure (DBP; mmHg)

a. Rest to 45minutes post (control) – Immediate-post was significantly higher than all other values (p≤0.05). All other comparisons were insignificant (P>0.05).

b. Rest to 45minutes post (experimental; Enrollment) – Immediate-post value was significantly higher than all other values (p≤0.05). 5minutes post was significantly higher than all other possible comparisons excluding immediate-post (p≤0.05). Differences between rest, 10minutes post, 15minutes post, and 45minutes post were insignificant (p>0.05).

c. Rest to 45minutes post (experimental; +8weeks) – Immediate-post value was significantly higher than all other values (p≤0.05). 5minutes post was significantly higher than all other comparisons excluding immediate-post (p≤0.05). Differences between rest, 10minutes post, 15minutes post, and 45minutes post were insignificant (p>0.05).

d. Rest to 45minutes post (experimental; +16weeks) – Immediate-post value was significantly higher than all other values (p≤0.05). All other comparisons were insignificant (p>0.05).

e. Rest (between groups) – Comparison to sixteen weeks was significant (p≤0.05). All other comparisons were insignificant (p>0.05).

f. Rest (experimental) – All comparisons were insignificant (p>0.05).

g. Immediate-post (between groups) – All comparisons were significant (p≤0.05).

h. Immediate-post (experimental) – All comparisons were significant (p≤0.05).

i. 5minutes post (between groups) – All comparisons were significant (p≤0.05) excluding sixteen weeks (p>0.05).

j. 5minutes post (experimental) – All possible comparisons were insignificant (p>0.05).

k. 10minutes post (between groups) – All other comparisons were insignificant (p>0.05).

l. 10minutes post (experimental) – All comparisons were insignificant (p>0.05).

m. 15minutes post (between groups) – All comparisons insignificant (p>0.05).

n. 15minutes post (experimental) –All comparisons were insignificant (p>0.05).

o. 45minutes post (between groups) – All comparisons were insignificant (p>0.05).

p. 45minutes post (experimental) – All comparisons were insignificant (p>0.05). All data regarding diastolic blood pressure are presented in Table 6.

Table 6 Diastolic blood before and after the Six Minute Walk Test pressure according to visit and timing of measurement (Mean±SD)

DBP (mmHg)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
N	25	25	25	25
Rest†	83.1±13.6	86.5±12.3	84.1±8.9	84.17±5.21
Immediate-post	91.6±4.7	98.1±5.6	94.45±4.9	92.1±5.2
5min post	86.5±4.25	98.31±8.2	89.42±3.91	84.27±2.2
10min post	83.11±7.2	85.78±10.12	84.0±9.91	85.06±6.2
15min post	83.3±10.1	86.11±7.55	83.56±8.54	84.77±5.64
45min post	83.98±9.5	85.77±4.25	84.4±8.2	84.06±4.91

N, number of subjects; DBP, diastolic blood pressure; mmHg, millimeter of Mercury; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Oxygen saturation (O2sat; %)

Rest to 45minutes post (control) – Multiple comparisons were insignificant (p>0.05) including rest vs 2minutes; rest vs 4minutes; rest vs 5minutes post; rest vs 10minutes post; rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs immediate-post; 2minutes vs 5minutes post; 2minutes vs 10minutes post; 4minutes vs 5minutes post; 4minutes vs 10minutes post; 4minutes vs 15minutes post; 4minutes vs 45minutes post; immediate-post vs 5minutes post; 5minutes post vs 10minutes post; 10minutes post vs 15minutes post; 10minutes post vs 45minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; Enrollment) - Multiple comparisons were insignificant (p>0.05) including rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs 10minutes post; 4minutes vs 5minutes post; immediate-post vs 5minutes post; 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; +8weeks) - Multiple comparisons were insignificant (p>0.05) including rest vs 10minutes post; rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs 5minutes post; 5minutes post vs 10minutes post; 5minutes post vs 15minutes post; 5minutes post vs 45minutes post; 10minutes post vs 15minutes post; 10minutes post vs 45minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; +16weeks) - Multiple comparisons were insignificant ($p>0.05$) including rest vs 10minutes post; rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs 5minutes post; 4minutes vs immediate-post; 10minutes post vs 15minutes post; 10minutes post vs 45minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant ($p\leq0.05$).

Rest (between groups) – All comparisons were significant ($p\leq0.05$).

Rest (experimental) – Comparisons while trained compared to untrained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

2minutes within (between groups) – All comparisons were significant ($p\leq0.05$).

2minutes within (experimental) – Comparisons between enrollment and while trained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

4minutes within (between groups) – All comparisons were significant ($p\leq0.05$).

4minutes within (experimental) – Comparisons between enrollment and while trained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

Immediate-post (between groups) – All comparisons were significant ($p\leq0.05$).

Immediate-post (experimental) – All comparisons were significant ($p\leq0.05$).

5minutes post (between groups) – All comparisons were significant ($p\leq0.05$).

5minutes post (experimental) – All comparisons between while trained and untrained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

10minutes post (between groups) – All comparisons were significant ($p\leq0.05$).

10minutes post (experimental) – All comparisons between while trained and untrained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

15minutes post (between groups) –All comparisons were significant ($p\leq0.05$).

15minutes post (experimental) – All comparisons between while trained and untrained were significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$).

45minutes post (between groups) – All comparisons were significant ($p\leq0.05$).

45minutes post (experimental) – All comparisons between while trained and untrained was significant ($p\leq0.05$). All other comparisons were insignificant ($p>0.05$). All data regarding oxygen saturation are presented in Table 7.

Table 7 Oxygen saturation before, during, and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

O_2sat (%)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
No intervention		Exercise intervention		
N	25	25	25	25
Rest†	96.89±1.4	88.5±9.6	91.5±6.51	92.65±6.12
+2min	95.29±2.8	85.12±7.72	87.22±6.13	88.0±5.5
+4min	96.07±3.63	84.62±6.89	86.77±6.3	87.3±5.01
Immediate-post	94.88±4.98	82.5±8.7	84.22±6.13	86.6±7.3
5min post	95.91±2.64	83.25±6.66	88.57±8.43	89.03±5.76
10min post	96.75±1.55	86.37±5.41	91.02±4.75	92.3±6.5
15min post	97.04±1.47	88.63±4.97	91.76±5.86	92.21±4.33
45min post	97.49±2.01	88.85±6.76	91.36±5.33	92.16±6.1

N, number of subjects; O_2sat, oxygen saturation; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Rate of perceived exertion (RPE; scale)

Rest to 45minutes post (control) – Multiple comparisons were insignificant ($p>0.05$) including rest vs 10minutes post; rest vs 15minutes post; rest vs 45minutes post; 4minutes vs immediate-post; 10minutes post vs 15minutes post; 10minutes post vs 45minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant ($p\leq0.05$).

Rest to 45minutes post (experimental; Enrollment) – Multiple comparisons were insignificant ($p>0.05$) including rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs 5minutes post; and 4minutes vs 5minutes post. All other comparisons were significant ($p\leq0.05$).

Rest to 45minutes post (experimental; +8weeks) – Multiple comparisons were insignificant ($p>0.05$) including rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; and 15minutes post vs forty-five minutes post. All other comparisons were significant ($p\leq0.05$).

Rest to 45minutes post (experimental; +16weeks) – Multiple comparisons were insignificant ($p>0.05$) including rest vs 15minutes post; rest vs 45minutes post; 2minutes vs 4minutes; 2minutes vs 5minutes post; 4minutes vs 5minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant ($p\leq0.05$).

Rest (between groups) – All comparisons were significant ($p\leq0.05$).

Rest (experimental) –All comparisons were insignificant ($p>0.05$).

2minutes within (between groups) – All comparisons were significant ($p\leq0.05$).

2minutes within (experimental) –All comparisons were insignificant ($p>0.05$).

4minutes within (between groups) – All comparisons were significant excluding enrollment ($p\leq0.05$).

4minutes within (experimental) – Enrollment was significantly different than all other values (p≤0.05). All other comparisons were insignificant (p>0.05).

Immediate-post (between groups) – All comparisons were significant (p≤0.05).

Immediate-post (experimental) – All comparisons were insignificant (p>0.05).

5minutes post (between groups) –All comparisons were significant (p≤0.05).

5minutes post (experimental) – Sixteen weeks was significantly different from all other values. All other comparisons were insignificant (p>0.05).

10minutes post (between groups) – All comparisons were significant (p≤0.05).

10minutes post (experimental) – All comparisons were significant (p≤0.05).

15minutes post (between groups) – All comparisons were insignificant (p>0.05).

15minutes post (experimental) – Comparisons between enrollment and while trained were significant (p≤0.05). Differences while trained were insignificant (p>0.05).

45minutes post (between groups) – All comparisons were insignificant (p>0.05).

45minutes post (experimental) – All comparisons were insignificant (p>0.05). All data regarding rate of perceived exertion are presented in table 8.

Table 8 rate of perceived exertion before, during, and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

RPE[a] (scale)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		Exercise intervention	
N	25	25	25	25
Rest†	6.08±0.27	6.92±0.57	6.7±0.5	6.63±0.22
+2min	9.28±0.78	13.5±1.63	12.08±2.09	12.1±1.98
+4min	13.18±1.23	14.12±1.5	12.08±2.09	12.1±1.98
Immediate-post	13.79±1.68	16.96±0.98	16.46±2.08	16.3±1.35
5min post	9.24±0.64	14.16±0.58	14.26±0.99	13.94±1.15
10min post	6.59±0.28	11.08±0.78	9.16±0.79	8.64±0.63
15min post	6.07±0.21	8.76±0.6	6.87±0.57	6.69±0.61
45min post	6.0±0.34	6.95±0.62	6.66±0.42	6.71±0.44

N, number of subjects; RPE, rate of perceived exertion; SD, standard deviation; †, values obtained while sitting; a, scale of 6-20; EXS, exercise; Wk, weeks;

Lactate (mmol·L-1)

Rest to 45minutes post (control) – Multiple comparisons were insignificant (p>0.05) including rest vs 10minutes post; rest vs 15minutes post; rest vs 45minutes post; 10minutes post vs 15minutes post; 10minutes post vs 15minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; Enrollment) – Multiple comparisons were insignificant (p>0.05) including rest vs 45minutes post; immediate-post vs 5minutes post; and 10minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; +8weeks) – Multiple comparisons were insignificant (p>0.05) including rest vs 15minutes post; rest vs 45minutes post; immediate-post vs 5minutes post; 5minutes post vs 10minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest to 45minutes post (experimental; +16weeks) - Multiple comparisons were insignificant (p>0.05) including rest vs 15minutes post; rest vs 45minutes post; immediate-post vs 5minutes post; and 15minutes post vs 45minutes post. All other comparisons were significant (p≤0.05).

Rest (between groups) – All comparisons were insignificant excluding after sixteen weeks (p>0.05).

Rest (experimental) –All comparisons were insignificant (p>0.05).

Immediate-post (between groups) – All comparisons were significant (p≤0.05).

Immediate-post (experimental) – All comparisons were insignificant (p>0.05).

5minutes post (between groups) – All comparisons were significant (p≤0.05).

5minutes post (experimental) – All comparisons were insignificant (p>0.05).

10minutes post (between groups) – All comparisons were significant (p≤0.05).

10minutes post (experimental) – All comparisons were insignificant (p>0.05).

15minutes post (between groups) – All comparisons were significant (p≤0.05).

15minutes post (experimental) – All comparisons were insignificant (p>0.05).

45minutes post (between groups) –All comparisons were insignificant (p>0.05).

45minutes post (experimental) – All comparisons were insignificant (p>0.05). All data regarding rate of lactate are presented in Table 9.

Table 9 Lactate before and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

Lactate (mmol L^{-1})	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		Exercise intervention	
N	25	25	25	25
Rest†	1.73±0.41	2.01±0.5	1.95±0.53	1.96±0.56
Immediate-post	5.15±0.87	2.93±0.79	3.03±0.66	3.21±0.92
5min post	3.7±0.53	2.85±0.63	2.9±0.75	2.95±0.8

Table continued

Lactate (mmol Ŀ-1)	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		**Exercise intervention**	
10min post	1.89±0.47	2.44±0.71	2.57±0.58	2.56±0.66
15min post	1.69±0.32	2.38±0.41	1.97±0.46	1.96±0.33
45min post	1.75±0.45	1.98±0.37	1.96±0.39	1.95±0.41

N, number of subjects; mmol, millimole; L, liter; SD, standard deviation; †, values obtained while sitting; EXS, exercise; Wk, weeks

Angina (scale)

No angina events were noted for the control group upon enrollment while five events occurred throughout the study in the experimental group. Number of events for experimental group was significantly higher compared to control group (2 vs 0 events·session^{-1}, respectively, p≤0.05). All angina events throughout the study occurred within four minutes and/or immediate-post; the number of events within four minutes was significantly lower while compared to immediate-post (1 vs 4 events; 20% vs 80% of events, respectively, p≤0.05). Angina events were almost completely equally distributed between data collection sessions with an insignificant difference (2 vs 1 vs 1 vs 1 events·session^{-1}, respectively; p>0.05).

Dyspnea (scale)

No dyspnea events were noted for the control group upon enrollment while ten events occurred throughout the study in the experimental group. Number of events for experimental group was significantly higher compared to control group (10 vs 0 events·study^{-1}, respectively, p≤0.01). The most events occurred immediate-post, while an equal number of events occurred at rest and within four minutes (6 vs 2 vs 2 events, respectively). The most events occurred upon enrollment, while events decreased as time passed by (4 vs 3 vs 2 vs 1 events·session^{-1}, respectively). Number of events were significantly higher while untrained compared to while trained (7 vs 3 events·session^{-1}, respectively; p≤0.05). Within the untrained and trained weeks, no significant differences were noted (p>0.05). While comparing the number of events according to the timing within the sessions, only one comparisons was insignificant. The number of events at rest was the same as that within four minutes (2 vs 2 events, respectively; p>0.05). All other comparisons were significant (p≤0.05).

Angina vs Dyspnea

Total number of events throughout the study was significantly higher for dyspnea compared to angina (10 vs 5 events·study^{-1}, respectively; p≤0.05). Total number of events upon enrollment was insignificantly higher for dyspnea compared to angina (4 vs 2 events·session^{-1}, respectively; p>0.05). Total number of events at sixteen weeks was insignificantly higher for dyspnea compared to angina (3 vs 1 events·session^{-1}, respectively; p>0.05). Total number of events after eight weeks of exercise was insignificantly higher for dyspnea compared to angina (2 vs 1 events·session^{-1}, respectively; p>0.05). Total number of events after sixteen weeks of exercise was identical for dyspnea and angina (1 vs 1 events·session^{-1}, respectively; p>0.05). All data regarding rate of angina and dyspnea events are presented in Table 10.

Table 10 number of Angina and dyspnea eventsa, b before, during, and after the Six Minute Walk Test according to visit and timing of measurement (Mean±SD)

Timing of events	Enroll healthy		Enroll OSA		EXS+8 Wk		EXS+16 Wk		Sum Ang	Sum Dys
	No intervention				**Exercise intervention**					
N	**25**		**25**		**25**		**25**			
Events†	**Ang**	**Dys**	**Ang**	**Dys**	**Ang**	**Dys**	**Ang**	**Dys**		
Rest†	0	0	0	1	0	0	0	0	**0**	**2**
+2min	0	0	0	0	0	0	0	0	**0**	**0**
+4min	0	0	1	1	0	1	0	0	**1**	**2**
Immediate-post	0	0	1	2	1	1	1	1	**4**	**6**
5min post	0	0	0	0	0	0	0	0	**0**	**0**
10min post	0	0	0	0	0	0	0	0	**0**	**0**
15min post	0	0	0	0	0	0	0	0	**0**	**0**
45min post	0	0	0	0	0	0	0	0	**0**	**0**
Sum	**0**	**0**	**2**	**4**	**1**	**2**	**1**	**1**	**5**	**10**

N, number of subjects; SD, standard deviation; †, values obtained while sitting; a, grading of 3 at least on the Angina scale; b, grading of 4 on the modified Borg dyspnea scale; Ang, Angina; Dys, dyspnea; †, in absolute cases; EXS, exercise; Wk, weeks;

Citation: Saghiv M, Sawhney M, Welch L, et al. Sixteen weeks of aerobic training influence spirometry, s-klotho, and hemodynamic responses to sub-maximal exercise testing in obese men with severe obstructive sleep apnea. *Sleep Med Dis Int J.* 2018;2(4):76‒91. DOI: 10.15406/smdij.2018.02.00048

The 6MWT

6MWT distance (m; Ft): The control group achieved a significantly greater distance compared to the experimental group's distances in all sessions ($p \leq 0.05$). A significant difference was noted for the distance achieved within the experimental group after sixteen weeks of exercise compared to all other sessions ($p \leq 0.05$). All other comparisons within the experimental group were insignificant ($p > 0.05$).

Walking speed (kph; mph): The control group achieved a significantly greater walking speed compared to that achieved by the experimental group in all sessions ($p \leq 0.05$). A significant difference was noted for the walking speed achieved within the experimental group after sixteen weeks of exercise compared to all other sessions ($p \leq 0.05$). All other comparisons within the experimental group were insignificant ($p > 0.05$).

Test terminations (number): No tests were terminated at all upon enrollment of the control group. Thus, all comparisons between groups for the number of terminations per study were significant (15 vs 0 terminations·study^{-1}; $p \leq 0.05$). The number of tests terminated by the research team was significantly greater compared to those by the subjects (13 vs 2 terminations·study^{-1}; $p \leq 0.05$). The number of tests terminated by the research team was significantly greater while subjects were untrained compared to while trained (10 vs 3 terminations·study^{-1}, respectively, $p \leq 0.05$). The number of terminations by the researchers was insignificantly lower after eight weeks of exercise compared to after sixteen weeks of exercise (1 vs 2 terminations·session^{-1}, respectively, $p > 0.05$). The number of terminations by the researchers upon enrollment was significantly higher in comparison to both sessions while exercised (6 vs 1 and 6 vs 2, terminations·session^{-1}, respectively; $p \leq 0.05$). The number of terminations by the researchers after sixteen weeks was insignificantly higher in comparison to both sessions while exercised (4 vs 1 and 4 vs 2 terminations·session^{-1}, respectively; $p > 0.05$). All other comparisons were insignificant ($p > 0.05$). No significant difference in the number of terminations per session by subjects was found (0 vs 0 vs 2 vs 0 terminations·session^{-1}; $p > 0.05$). The number of terminations between researchers and subjects upon enrollment was significantly greater for the researchers (6 vs 0 terminations·session^{-1}, respectively; $p \leq 0.05$). The number of terminations between researchers and subjects after sixteen weeks was significantly greater for the researchers (4 vs 0 terminations·session^{-1}, respectively; $p \leq 0.05$). The number of terminations between researchers and subjects after eight weeks of exercise was insignificantly lower for the researchers (1 vs 2 terminations·session^{-1}, respectively; $p > 0.05$). The number of terminations between researchers and subjects after sixteen weeks of exercise was insignificantly higher for the researchers (2 vs 0 terminations·session^{-1}, respectively; $p > 0.05$).

Sitting down (number): The average amount of times subjects sat down during the test was significantly lower for the control group compared to the experimental group ($p \leq 0.01$) since none of the control subjects sat down during the test. All other comparisons were found to be significant ($p \leq 0.05$).

Duration of sitting down (seconds): The average duration of sitting down during the test was significantly lower for the control group compared to the experimental group ($p \leq 0.01$) since none of the control subjects sat down during the test. The duration of sitting down during the test (for each time a subject sat down) was significantly higher while untrained compared to while trained within the experimental group. Differences in sitting down duration while untrained and while trained were insignificant ($p > 0.05$). All data regarding indices of the 6MWT are presented in table 11.

Table 11 Six Minute Walk Test related variables according to visit and timing of measurement (Mean±SD)

Distance	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		Exercise intervention	
N	25	25	25	25
Distance (m)	579.6±98.41p	319.53±44.13p	345.6±82.4p	388.79±75.5p
Distance (Ft)[a]	1901.57±322.86p	1048.32±144.78p	1133.85±270.34p	1275.55±247.7p
Improvement (m)‡	N/A	N/A	26.07±63.7n	69.26±58.42p
Improvement (Ft)‡	N/A	N/A	85.53±208.6n	227.23±192.2p
Walking speed (kmph)	5.8±0.98	3.2±0.44	3.45±0.82	3.88±0.75
Walking speed (mph)	3.6±0.61	1.99±0.27	2.15±0.51	2.42±0.47
Number of test terminated by research team; %	0†	6 (100%)†	1 (33%)†	2 (100%)†
Number of test terminated by subjects; %	0†	0 (0%)†	2 (67%)†	0 (0%)†
Number of times subjects sat down during the test[b]	0†	0.98±0.23	0.82±0.07	0.78±0.3
Duration of sitting down during the test (seconds)[c]	0†	31.6±5.78	22.39±3	24.0±3.4

Table Continued

Distance	Enroll healthy	Enroll OSA	EXS+8Wk	EXS+16Wk
	No intervention		Exercise intervention	
N	25	25	25	25
Walking distance lost ($m \cdot test^{-1}$)	0	8.36	4.95	5.05
Walking distance lost ($ft \cdot test^{-1}$)	0	27.42	16.24	16.56

N, number of subjects; SD, standard deviation; a, calculated as the distance in meters divided by 30.48; b, average per subject, per test; c, average per subject, per occurrence; p, positive prognosis; n, negative prognosis; m, meters; Ft, feet; †, absolute number of occurrence; ‡, improvement from distance achieved at enrollment; N/A, non-applicable; kmph, kilometer per hour; mph, miles per hour; EXS, exercise; Wk, weeks;

Spirometry

FEV1 predicted (%): FEV1 predicted at rest was significantly higher in the control group compared to all measurements of the experimental group ($p \leq 0.01$). A significant difference was noted for the comparison of values at rest between sixteen weeks of exercising vs enrollment within the experimental group ($p \leq 0.05$). All other comparisons at rest were insignificant ($p > 0.05$) table 12.

Table 12 spirometry related variables according to visit (Mean±SD)

Variable	Enroll healthy	Enroll OSA	EXS+8 Wk	EXS+16 Wk
	No intervention		Exercise intervention	
N	25	25	25	25
FEV1 predictedR (%)†	101.96±4.3	63.42±4.51	67.5±5.23	69.88±4.49
FEV1 predictedIP (%)†	97.3±2.7	75.3±3.3	76.37±5.16	79.11±4.18
FVC predictedR (%)†	102.63±4.78	68.23±4.09	71.03±3.79	74.63±3.61
FVC predictedIP (%)†	98.23±1.68	76.44±6.5	80.67±4.35	84.22±3.67
FEV1/FVCR ratio	0.753±0.78	0.657±0.9	0.693±0.71	0.719±0.8
FEV1/FVCIP ratio	0.84±0.54	0.79±1.5	0.81±1.97	0.82±3.51

N, number of subjects; SD, standard deviation; FEV, forced expiratory volume; FVC, forced vital capacity; R, at rest; IP, immediate-post; EXS, exercise; Wk, weeks; †, compared for the predicted value of an age and sex matching healthy person

FEV1 predicted immediate-post was significantly higher in the control group compared to all measurements of the experimental group ($p \leq 0.05$). A significant difference was noted for the comparison of values immediate-post between sixteen weeks of exercising vs sixteen weeks within the experimental group ($p \leq 0.05$). All other comparisons at rest were insignificant ($p > 0.05$). In the transition from rest to immediate-post, FEV1 predicted was insignificantly higher at rest compared to immediate-post within the control group ($p > 0.05$).

All comparisons within the experimental group were significant while comparing values at rest with values immediate-post ($p \leq 0.05$), whereas values at rest were lower than immediate-post.

FVC predicted (%): FVC predicted at rest was significantly higher in the control group compared to all measurements of the experimental group ($p \leq 0.05$). A significant difference was noted for the comparison of values at rest between sixteen weeks of exercising vs enrollment within the experimental group ($p \leq 0.05$). All other comparisons at rest were insignificant ($p > 0.05$).

FVC predicted immediate-post was significantly higher in the control group compared to all measurements of the experimental group ($p \leq 0.05$). A significant difference was noted for the comparison of values immediate-post between sixteen weeks of exercising vs sixteen weeks within the experimental group ($p \leq 0.05$). All other comparisons at rest were insignificant ($p > 0.05$). In the transition from rest to immediate-post, FVC predicted was insignificantly higher at rest compared to immediate-post within the control group ($p > 0.05$).

All comparisons within the experimental group were significant while comparing values at rest with values immediate-post ($p \leq 0.05$), whereas values at rest were lower than immediate-post.

FEV1/FVC ratio

FEV1/FVC ratio at rest was significantly higher in the control group compared to all measurements of the experimental group ($p \leq 0.05$) excluding after sixteen weeks of exercise ($p > 0.05$). Significant differences were noted for the comparisons of values at rest between sixteen weeks of exercising vs enrollment and sixteen weeks ($p \leq 0.05$) , and an insignificant difference compared to eight weeks of exercise ($p > 0.05$) within the experimental group. All other comparisons at rest were insignificant ($p > 0.05$).

FEV1/FVC ratio immediate-post was significantly higher in the control group compared ratio upon enrollment and sixteen weeks of the experimental group ($p \leq 0.05$). A significant difference was noted for the comparison of values immediate-post between sixteen weeks of exercising vs enrollment within the experimental group ($p \leq 0.05$). All other comparisons at rest were insignificant ($p > 0.05$). In the transition from rest to immediate-post, FEV1/FVC ratio was significantly higher immediate-post compared to rest within the control group ($p > 0.05$). All comparisons within the experimental group were significant while comparing values at rest with values immediate-post ($p \leq 0.05$), whereas values at rest were lower than immediate-post.

Discussion

In general

The influence of prolonged aerobic exercise on s-klotho levels in people with severe obstructive sleep apnea has never been investigated prior to this study, especially in such length. The present study demonstrates clear and significant influences of sixteen weeks of aerobic training on s-klotho, hemodynamic responses, and spirometry indices before, during, and after the Six Minute Walk Test.

Experimental group's BMI was significantly greater compared to age and sex matching healthy subjects. Obesity (BMI>30kg·m^{-2}) has been previously indicated in countless publications as a risk factor and predictor of future and current sleep apnea.[33–38]

An additional risk factor well established in the literature is a person's neck circumference. Previous data published indicated a neck circumference of sixteen inches or higher as a possible risk factor for obstructive sleep apnea. Furthermore, the neck circumference to height ratio is indicated as better predictor than BMI alone.[37–39] As with the OSA subjects of this study, previous studies have shown little to no difference in Weight and BMI following exercise and/or stretching.[40,41] While the design of the study did not allow full control of diet and adherence to exercise, the lack of improvement in BMI and neck circumference may be explained by possible lack of adherence to instructions throughout the study. Exercise alone has been shown as unable to battle bad nutritional habits.[42,43]

In this current study, exercise had a positive effect on AHI decreasing it by five episodes/hour in average. This data is perfectly aligned with the literature, indicating improvements in AHI of up to 6 episodes/hour.[44,45]

S-klotho

To the best of the researchers' knowledge, no previously published data exist regarding OSA, s-klotho, and/or the effects of exercise, nor the combination of. The data of this study suggest that s-klotho is significantly higher in healthy age and sex matching subject before and after exercise compared to subjects with OSA. Similar findings between healthy and clinical populations have been noted.[46–48]

While resistance training showed no to little effect on s-klotho levels, aerobic training, especially chronic aerobic training has been proven to increase the biomarker's levels.[25,46–48] The current study further suggest that s-klotho levels increase from baseline to immediate-post exercise and then decrease. Levels of s-klotho are higher immediate-post and decrease faster in healthy compared to OSA subjects. No published data exists to compare with in current literature. It is the researchers' suggestion that biomarker's levels remain high in clinical populations in order to better battle high levels of ROSs induced by exercise.

Heart rate

Heart rate was higher in the OSA subjects compared to that of the control group. These data are in accordance with the known heart rate for the population.[49] During the 6MWT, healthy subjects were able to move faster and reach a higher heart rate on comparison to subjects with OSA. Furthermore, the decline in heart rate during recovery was slower in subjects with OSA. Such dynamics have been previously reported in regard to comparison of healthy vs clinical, and specifically in regard to people with OSA.[50–55] Sixteen weeks of exercise improved heart at rest and responses during exercise in the subjects with OSA. Such improvement to heart rate were previously noted in the literature.[53,56] As in previous studies, the data of this study suggest a blunt response to exercise and during exercise, preventing people with OSA to function at levels common to age and sex matching healthy people.[53]

Systolic blood pressure

Systolic blood pressure at rest was lower in the control group compared to people with OSA, and has improved in the experimental group as a response to exercise. Such results have been previously reported in regards to people with OSA and exercise.[53,57,58]

Systolic blood pressure seemed to be somewhat lower than previously reported blood pressure values in men with OSA, yet lower than hypertensive men with OSA.[53,57,59] As seen in heart rate's response immediate-post, so was a blunt response seen during exercise and immediate-post exercise regarding systolic blood pressure.[53–55,57,59]

Diastolic blood pressure

Diastolic blood pressure at rest was higher for subjects with OSA ompared to controls, yet within the range of values previously reported for age and sex matching people.[53,54,57–60] Diastolic blood pressure within the experimental group decreased due to exercise. Such a decreased has been previously noted in similar subjects with OSA.[55,58,60,62] Both control and experimental groups' diastolic blood pressure was within resting values within ten minutes post. The reported values during recovery seem to be similar to previously reported.[62] The researchers suggest that the same impairments mentioned and referenced earlier, cause diastolic blood pressure to return to the vicinity of resting values within ten minutes post.

Oxygen saturation

Oxygen saturation was lower in people with OSA compared to the control subjects. Multiple studies have shown oxygen saturation to be lower in people with OSA at rest.[63–65]

Oxygen saturation has improved following the sixteen weeks of exercise. These findings are documented in the literature regarding adaptation to exercise in people with OSA.[66,67] During exercise, oxygen saturation in the OSA subjects declined, and rose gradually post-exercise. Such dynamics have been previously reported.[63–67]

Rate of perceived exertion

RPE was greater in subjects with OSA compared to the control group from rest to recovery measurements and during all data collection sessions. While the researchers were unable to find data equivalent in it extent to that of this study in subjects undergoing the 6MWT, it has been suggested that the perception of dyspnea is increased during and after exercise in people with OSA.[51] Since such a perception is one of perceived stress, it is possible that in people with OSA, nonetheless severe OSA, the perception of dyspnea may be influencing their perception of their rate of exertion. Inconsistency in RPE has been noted in healthy people[68] and in people with COPD, often compared to people with OSA, since people with COPD may be diagnosed as OSA as well, and vice versa, as well as the obstructive aspects.[69–71]

Angina

Angina events during this study were based upon the subjects' rating utilizing the angina scale. Angina events in people with OSA are not surprising. Evidence exists suggesting that people with OSA may perceive themselves as experiencing an angina event, similar to that of cardiac patients.[72] On the other hand, OSA has been associated with CAD.[73,74] Furthermore, OSA has been suggested as a risk marker for CAD.[75] Thus, while few angina events occurred throughout the study, the researchers suggest the "occurrence" of angina events during the study were either real or perceived as real, while such events could have been related to undiagnosed CAD or other cardiac clinical conditions.[76] The angina events were concentrated within four minutes of the start of the 6MWT and/or immediate-post. Angina events occurred in 5% (5/100 test) of the 6MWT within the experimental group. A similar percentage of events was previously reported in a large cohort (n=740) of people with chronic lung disease.[77] The number of angina events decreased while trained compared to while untrained. The ability of exercise to reduce the occurrence of angina in clinical populations has been previously noted.[78,79]

Dyspnea

Ten dyspnea events occurred (or were perceived as occurring) throughout this study. The dyspnea events were concentrated within four minutes of the start of the 6MWT and/or immediate-post. Dyspnea events occurred in 10% (10/100 test) of the 6MWT within the experimental group. In previous studies one-third of the subjects reported experiencing dyspnea during the 6MWT while others did not.[80,81] With that said, the occurrence of dyspnea during exercise in people with OSA is not at all a new finding.[51,80,82] The highest number of events occurred while untrained and immediate-post. Dyspnea upon maximal effort has been previously noted in several studies pertaining to people with OSA.[83,84] Yet, exercise has been indicated as one of several means to reduce dyspnea events in people with obstructive diseases.[55,85–87] These previous findings are a basis for understanding the occurrence of dyspnea in this study and the improvement following weeks of exercise.

Distance achieved in the 6MWT

The distance achieved by both groups of this study were within previously reported ranges for healthy vs people with OSA.[51,88] Furthermore, both the fact that healthy people achieve better distance compared to people with clinical conditions, and that exercise improves the distance achieved during the 6MWT have been reposted before.[51,88–90] The effect of exercise on the distance achieved during the 6MWT has also been noted in people with OSA.[91–93] Indeed, the results of this current study show clearly that the control groups' distance achieved during the 6MWT was greater than that of the subjects with OSA, and that the distance has improved after exercise within the experimental group.

Subject with OSA have improved their achieved distance by 2.5meters in average while untrained. This improvement, though not substantial, can be the result of better strategy and/or learning from one test to the other, and perhaps even random. Rather or not the prognosis becomes positive or negative has been shown to be dependent on the overall distance achieved during the test, whereas a distance >300meters or more yields a positive prognosis and <300 yields a negative prognosis.[94–96] The improvement (meters) between two tests of the same person has been reported to have prognosis value in several different clinical populations.[97,98] The minimal improvement in the distance, also termed the "minimal clinical important difference (MCID) achieved during the 6MWT in order for the prognosis to be positive is different for different clinical populations yet ranges from 30meters to 80meters between tests of the same person.[94–99] The results of the current study show that while sixteen weeks of aerobic training achieved the minimum improvement needed for a positive prognosis, eight weeks were not a strong enough stimulus, though subjects achieved >300meters distance in all tests.

Walking speed during the 6MWT

Since the duration of movement is fixated during the test to a maximum of 6minutes, and the distance achieved is known as part of the results of this study, mathematically, the average speed is already determined. Thus, the analysis of walking speed between groups and within the experimental group does not differ than that of the distance achieved, nor the minimal distance needed to be achieved to result in a positive prognosis. It has been suggested that walking speed may be affected and regulated according to will to avoid dyspnea, leading to a lower walking speed.[100]

Sitting down duration

While the phenomenon of sitting down during the 6MWT is well known and is addressed in the guidelines for the administration of the test, the researchers were unable to find data pertaining to the average duration of each sitting down episode. The time spent sitting down (average per single sitting down episode) ranged in this study from ≈22 to ≈33seconds. These durations translate to a loss of walking distance of ≈4.95 to ≈9.82 ($m \cdot test^{-1}$). The decrease in distance loss with the onset of training is an additional indication of the positive influences of exercise on functional aspects of people with severe OSA as established previously in this discussion.

FEV1 predicted (%)

Often, obstructive pulmonary diseases are accompanied by sere OSA, and resemble in functional indices and responses to exercise.[101,102] The extent of data pertaining to people with COPD is substantially greater in comparison to that of OSA. Furthermore, the need to define OSA as a disease within itself and a treatment plan of its own has been discussed previously.[103,104] It is for these reasons that the two are often regarded together or as clinical conditions with similar symptoms, as well as risk factor for each other, known as the "overlap syndrome".[101,102] The control group had a higher FEV1 predicted compared to that of the experimental group. Suspected-healthy having a higher FEV1 predicted has been noted in the professional literature before.[105–107] Sixteen weeks of aerobic exercise elevated FEV1 predicted by roughly 6% at rest. The positive effects of exercise on spirometry indices have been reported before whereas adaptation to exercise induced an increase in FEV1 predicted (%).[108] FEV1 predicted (%) was elevated from rest to immediate-post in the experimental group yet was decreased in the control group. Such finding have been reported in people with COPD.[109]

FVC predicted (%)

The fact that FVC predicted (%) was higher in the control group at rest compared to that of the experimental group for all sessions is well in accordance with the literature.[110,111] This variable has also been associated with the distance achieved during the 6MWT whereas shorter distances achieved were highly correlated with lower FVC predicted (%).[88] The same dynamic was observed in the current study. The results of this study indicate that while the control groups FVC predicted (%) values were in the range reported for sex and age matching people, that of the experimental group were significantly lower.[112,113] FVC predicted (%) improved due to exercise and was increased by ≈6% at rest. Such improvement are well established in the literature.[114–116] Value decreased mildly in the healthy subjects while increased in the experimental group's subjects in the transition from rest to immediate-post. Several studies have indicated similar dynamics while comparing healthy and clinical populations.[117–119]

FEV1/FVC ratio

The results of the current study indicate a higher ratio in the control group compared to the experimental group at rest. These results align with previous finding in the literature.[120] Furthermore, the subjects with OSA had a lower ratio at rest and immediate-post exercise while compared to the control group. In both cases, the experimental group's values improved in response to exercise. Previous studies have shown similar dynamics.[121,122] A study from 2015 suggests that there are no differences between obese and obese people with OSA regarding their ratio. A possible conclusion could be that obesity within itself is a strong enough reducer of the ratio, regardless of the existence of OSA.[111,123] Based on this discovery alone and the fact that the OSA subjects of this study were obese, one could anticipate a reduced ratio, actually seen.[111,123]

Conclusions

Severe OSA has similar symptoms, functional capacities, and responses to exercise as people with COPD have. As shown in previous studies, people with severe OSA respond to exercise by improving vital indices of function.

During the study, subject with severe OSA performed at a lower level compared to age and sex matching subjects, presenting with impaired function during and after the 6MWT. As a result, s-klotho were substantially lower at rest, during exercise, and after adaptation to exercise, while compared to suspected healthy age and sex matching people. As seen in other clinical populations, Aerobic exercise is a powerful adaptation inducer, leading to improvement in multiple parameters, including s-klotho. The researchers wish to call upon others to obtaine more data pertaining to the influence of exercise on people with OSA in general, and in more detail throughout exercise testing.

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Conflict of interest

The author declares no conflict of interest.

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