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Effect of Oxyjun™ on Adipose Tissue Inflammation - A Randomized, Placebo-Controlled Clinical Study

Shalini Srivastava [a], **Robert Girandola** [b], **Ankul Suresh Kokate** [c,*]

[a] Department of Clinical development, Enovate Biolife, Mumbai-400053, Maharashtra, India
[b] Department of Human Biology, University of Southern California, Los Angeles, CA 90089, USA
[c] Department of Clinical research, Vedic Lifesciences, Mumbai-400053, Maharashtra, India
*Corresponding author Cell: +91 98908 55330; Email: ankul.k@vediclifesciences.com
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Abstract: The aim of the study was to evaluate the effect of Oxyjun™ on cardiovascular fitness of overweight individuals by reducing obesity induced systemic inflammation. Male participants between the ages of 18 - 35 years and body mass index of 25 - 34.9 kg/m^2 were recruited in the study. Change in neutrophil lymphocyte ratio (NLR), high density lipoprotein (HDL-c) and quality of life using 36-item Short form survey (SF-36) was assessed over a period of 8-weeks. Results demonstrated that NLR was reduced by 0.71 in Oxyjun™ and by 0.42 in the placebo group at the end of study period. Also, within group comparison was significant for Oxyjun™ group when compared from baseline; $p<0.001$. Further, HDL-c levels were increased in the Oxyjun™ group by 4.04 mg/dL and reduced for the placebo group by 1.22 mg/dL when compared from baseline; $p=0.09$. For SF-36 quality of life assessments, the health concepts of fatigue, mental health, and social function showed significant improvement and no adverse or serious adverse events were reported for both groups during the course of the study. In conclusion, Oxyjun™ when consumed for 8-weeks reduced NLR of study volunteers thereby demonstrating its potential for lowering obesity induced systemic inflammation. Oxyjun™ also increased HDL levels that could further promote cardiovascular fitness and prevent the risk of cardiovascular events.

Keywords: Obesity, Cardiovascular fitness, Inflammation, SF-36, High density lipoprotein cholesterol, Neutrophil Lymphocyte Ratio

Dr. Shalini Srivastava is a Doctor of Medicine (RSMU, Moscow), with more than 10 years of experience in clinical development. She is a certified clinical research professional (Cranfield, UK) and holding diploma in project management (Adelaide University, Australia). She has been spearheading end to end management of several clinical studies in collaboration with international researchers.

Robert Girandola received his Doctor of Education degree from the University of California at Berkeley in 1970. He has been an Associate Professor in Human Biology at the University of Southern California since 1973. His research interests have been in the areas of: Ergogenic Aids, Nutrition and Performance, Body composition techniques and Obesity.

Ankul Suresh Kokate obtained his Master of Sciences of Pharmacy in the year 2015 and has since been involved in the field of clinical research. He started his career as a research associate and is currently working as a scientific writer. Furthermore, he hopes to keep contributing to the latest research in a manner that is impactful and beneficial to both healthcare professionals and general public.

1. Introduction

Persistent, low-grade inflammation produces a steady inflammatory state throughout the body [1]. In recent years, research has shown that a pro-inflammatory state observed in overweight individuals

is due to abnormal adipose tissue immune-system activation [2,3]. Neutrophil-lymphocyte ratio (NLR) has been considered as a novel biomarker for low grade inflammation and [4] has been constantly linked with persistent fatigue, reduced cardiovascular (CV) fitness and subsequent risk of CV events [5,6].

Reports have linked increased body mass index (BMI) and sedentary lifestyle to persistent inflammation resulting in reduced cardiorespiratory (CResp) fitness [7-9]. A recent cross-sectional study reported that both, dietary patterns and anthropometric measures are positively associated with persistent inflammation. These findings were not only prevalent in population with metabolic syndrome but also for otherwise healthy individuals. Additionally, the study also suggested that obese people reportedly had a higher NLR as compared to their normal weight peers [10]. In a separate study, Wang and associates observed that diet and exercise significantly influence obesity-induced inflammatory markers such as NLR [11]. Studies on overweight individuals also have negatively correlated diminished peak oxygenation capacity (VO_2 peak) with elevated total neutrophil and leukocyte counts [12, 13]. In a recent Japanese study, elevated NLR was linked to dyspnea, airway obstruction, and impaired exercise capacity [14]. Similarly, an inverse relationship has also been shown to exist between higher NLR, poor functional and exercise capacity, metabolic equivalents and left ventricular ejection fraction (LVEF) [15]. Additionally, the results of a study by Paliogiannis and associates stated that an increase in NLR values is associated with a proportionate decrease in exercise capacity of an individual [16]. Research is hence conclusive that the accumulation of excessive adipose tissue is characterized by low-grade inflammation that can negatively influence exercise capacity and cause a delayed cardiac recovery. As exercise has been shown to lower the markers of systemic inflammation [10], it would not be wrong to propose that a reduced exercise capacity could further be improved by reducing this persistent inflammation.

One of the central mechanisms attributed to endothelial dysfunction (EDF) is obesity-induced systemic inflammation [17]. Altered adipose tissue and adipocyte function negatively influence the ability of the endothelium to produce nitric oxide and prostacyclin. This causes depletion of vasodilator, antithrombotic and anti-atherogenic properties affecting CV fitness [18] Atherosclerotic plaques having activated macrophages and T-cell lymphocytes multiply and spawn an augmented inflammatory response [19] further increasing the CV risk [20]. EDF has also been linked to the fatigued state of a person. Therefore in a state of disruption due to pro-inflammation, it can lead to diminished quality of life (QoL) and cardiac endurance of an individual [21, 22]. It is also worth mentioning, long term inflammation coincides with abnormally low levels of high density lipoproteincholesterol (HDL-c) in overweight individuals [23, 24]. In chronic illnesses (eg Diabetes mellitus) characterized by inflammation and oxidative stress, HDL-c acts as an anti-inflammatory molecule. As levels decline, its cholesterol efflux promoting effect and LDL oxidation preventive functions are restricted [25]. This dysfunction has a significant impact on an individual's physical fitness levels and also contributes to the risk of developing coronary heart disease [26]. Research indicates that increased lipid transfer to HDL-c by lipoprotein lipase and reduced HDL-c clearance by hepatic triglyceride lipase results in higher HDL-c levels. This can be indicative of increased exercise time in obese or overweight people [27]. Therefore it would be desirable to increase HDL-c level to improve the CResp fitness and promote primary or secondary prevention of cardiac events.

Globally, low CResp fitness and physical functional capacity are leading causes of disease and disability [28-30]. Clinical trials have repeatedly reported adverse CV outcomes in individuals with sedentary behaviour and chronic inflammation [31]. Therefore, this "residual inflammatory risk" has increasingly become a viable therapeutic target [32]. Presently, therapies for enhancing cardiac fitness or endurance include weight loss strategies, exercises and certain interventional therapies [33]. However, the last few decades have seen a surge in the investigation of bioactive compounds for promoting CV fitness. *Terminalia arjuna*, a well-known cardiotonic has been developed as a proprietary extract (Oxyjun™) by Enovate Biolife to harness its potential as an ergogenic aid [34]. The Arjuna tree bark contains a host of bio-actives such as saponins and flavonoids that are known to improve CV fitness [35-37]. It has proven therapeutic potential in hypertension, congestive heart failure and ischaemic heart diseases. Its antioxidant, anti-ischemic, antihypertensive, anti-atherogenic and anti-hypertrophic effects, advocate its use as a potential cardiac health enhancer [33, 38-42]. In our previously published study, Oxyjun™ was able to improve the LVEF; $p<0.001$ of non-overweight young adults, that was also accompanied by a decrease in right ventricular myocardial performance index (MPI);

p<0.001 [43]. Therefore, the present study was designed to explore the effect of Oxyjun™ on the CV fitness of overweight people by decreasing obesity-induced systemic inflammation. We would like to mention the study was initially intended to explore the effect of Oxyjun™ on aerobic fitness (maximal oxygen consumption - VO2Max) of recruited individuals using an incremental exercise test protocol. However, due to the emergence of coronavirus disease of 2019 (COVID-19), we were unable to evaluate the same.

2. Methods

2.1 Ethical considerations

The study was approved by an independent ethics committee - ACEAS, registered with the Office for Human Research Protections in the U.S. Department of Health and Human Services (IRB00006475). Written informed consents were voluntarily obtained from all participants and the study was registered on the public clinical trials registry of the U.S. National Library of Medicine (clinicaltrials.gov; NCT No: NCT03854786). The study was performed in compliance with the Declaration of Helsinki and with the International Conference on Harmonization – Good Clinical Practice guidelines for clinical research.

2.2 Participants

Male participants between 18-35 years and BMI 25-34.9 kg/m^2 were recruited through a participant database. Study volunteers were non-smokers having waist circumference (WC) > 80 cm and fasting blood sugar <125 mg/dL. Participants with a history or presence of cardiac, vascular, endocrine, gastrointestinal, pancreatic or neurological disorders were not included in the present study. Recruited participants needed to abstain from any form of physical exertion and caffeine consumption 48 hours before assessment visits.

2.3 Intervention

The study interventions included - 1) Investigational product (IP) - Oxyjun™: *Terminalia arjuna* extract 2) Placebo: Microcrystalline cellulose. Study products were manufactured in the form of size 0 capsules and packed in duly labeled high-density polyethylene bottles. For preserving the study blinding, identical placebo capsules were manufactured and matched for size, shape, colour, texture, and packaging. The participants took a single capsule (400 mg/day) after breakfast for a period of 56 days.

2.4 Study conduct

The present study was an 8-week, double blind, randomized, placebo-controlled study for the effect of Oxyjun™ in overweight but otherwise healthy individuals seeking cardiac fitness. The first participant was enrolled in January 2020 and the last participant assessment was completed in April 2020. Participants were randomized in blocks of 4 using Stats Direct software (version 3.1.17) to either receive Oxyjun™ or placebo. The blinding codes were secured in tamper-evident, sealed envelopes and access was limited to authorized personnel as per Vedic Lifesciences standard operating procedures. In view of COVID-19 emergence, the study was conducted virtually by utilizing a study specific digital diary. All blood specimens were collected by the central laboratory personnel by performing home based collections and IP adherence or compliance of recruited participants was ascertained digitally. In the event of any discomfort experienced, participants were instructed to record the event starting on the day it happened and also indicate in the diary when the event ended. The same was reviewed by the clinical investigator to obtain as much information as possible related to the events telephonically.

2.5 Exploratory Outcomes

The present study evaluated NLR for assessing obesity induced systemic inflammation, High-density lipoprotein levels which is one of the major biochemical risk markers for CV events and participant QoL standards using a validated and widely used SF-36 health survey questionnaire [44].

Neutrophil-Lymphocyte ratio

In overweight and obese individuals, neutrophils and lymphocytes are established markers for adipose tissue associated subclinical inflammation [45, 46]. Normal NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.53 [47]. In the present study, NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The NLR was calculated from the full blood count performed on day 0 (baseline visit) and end of study visit (day 56) as per standard procedures. There were no signs of clinical infection observed on the day of blood collection for any of the study participants.

High-Density Lipoprotein

Several large-scale studies have repeatedly demonstrated that HDL-c is a strong and inverse predictor of CV risk in individuals [48]. As a result, increasing HDL-c has emerged as an attractive tool for CV prevention [49]. In a recent study, *Terminalia arjuna* was shown to increase HDL-c levels from 42.34 ± 9.27 to 46.78 ± 6.52 ($p < 0.001$) suggesting its cardioprotective benefits in participants with dyslipidaemia [50]. In the present study, blood samples of participants in fasting state were collected on day 0 (baseline visit) and end of study visit (day 56) as per standard procedures. As per literature, levels above 40 mg/dL are considered desirable and more than 60 mg/dL is considered to be high [51].

Short form 36 health survey questionnaire

SF-36 is one of the extensively validated health survey instrument for appraising QoL [44]. In the present study, it was used to assess 8 health concepts: Physical Functioning, Role–Physical, Bodily Pain, Fatigue, Role–Emotional, Social Functioning, Mental Health, and General Health. Scores for each dimension range from 0 (poor health) to 100 (good health) with higher scores indicating better health related QoL. The SF-36 questionnaire was completed by the study participants using a study specific digital diary on day 0 (baseline visit) and end of study visit (day 56).

2.6 Safety assessments

Safety was assessed in terms of AEs or serious adverse events (SAE) occurrences reported by the participants throughout the study duration.

2.7 Quality assurance

The study was conducted in compliance with the ICH-GCP guidelines laid down in E6 (R2) as per pre-approved monitoring and auditing plan by a Vedic Lifesciences team, independent of the clinical operational team.

3. Statistical analysis

The sample size for the present pilot study was chosen based on previous research [45]. A total of 46 participants were planned to be recruited for completing 40 participants; estimating a drop-out rate of 20%. The normality and homogeneity of data distribution were evaluated using the Shapiro–Wilk test. A descriptive and exploratory analysis of the variables was conducted, where their distribution, outliers and missing data were evaluated. The summary (mean, standard deviation, minimum and maximum) and analysis of change (mean difference, standard deviation) of exploratory parameters was compiled using Analysis of Variance (ANOVA) and Paired Sample T test. Due to the COVID-19 outbreak, only 15 participants could be recruited (1 participant dropped out). Haematological data of 11 participants was analyzed for NLR and HDL-c parameters whereas, SF-36 QoL questionnaire data was analysed for 14 participants. All the statistical procedures were performed using the Statistical Package for the Social Sciences program (SPSS Inc., Chicago, United States), version 20.0. The level of statistical significance was set at $p<0.05$.

4. Results

A total of 22 participants were screened, 2 participants not satisfying the inclusion/exclusion criteria were deemed as screening failures. The number of enrolled participants was 15 as 5 participants could not visit the site for randomization visits. Participants were segregated as per the availability of data. Eleven participants (Oxyjun™: 5; Placebo: 6) were assessed for haematological parameters and data for 14 participants (Oxyjun™: 7; Placebo: 7) was analysed for SF-36 health survey questionnaire. **Figure 1** provides the study participant disposition. During the study, one participant dropped out due to personal reasons and we could not perform blood sample collection for 3 participants due to countrywide Covid-19 lockdown.

4.1 Demographics and screening characteristics

At screening, the mean (SD) age for participants in Oxyjun™ and placebo group was 26.38 (5.63) and 22.43 (5.03) years. The mean BMI (SD) was 29.32 (1.00) and 28.86 (1.84) kg/m^2 for the Oxyjun™ and Placebo groups respectively. Similarly, waist circumference for Oxyjun™ and placebo was 97.92 ± 4.13 cm and 96.45 ± 6.09 cm. Furthermore, baseline assessments of pulse rate and blood pressure were within normal levels for both groups and HDL-c levels in Oxyjun™ had a mean value of 37.46 mg/dL whereas the placebo group levels were on the higher side with a mean of 40.79 mg/dL. Other than absolute lymphocyte count ($p=0.03$) and NLR ($p=0.05$) the two groups were comparable in terms of baseline characteristics. **Table 1** provides the screening and baseline characteristics for the randomized population.

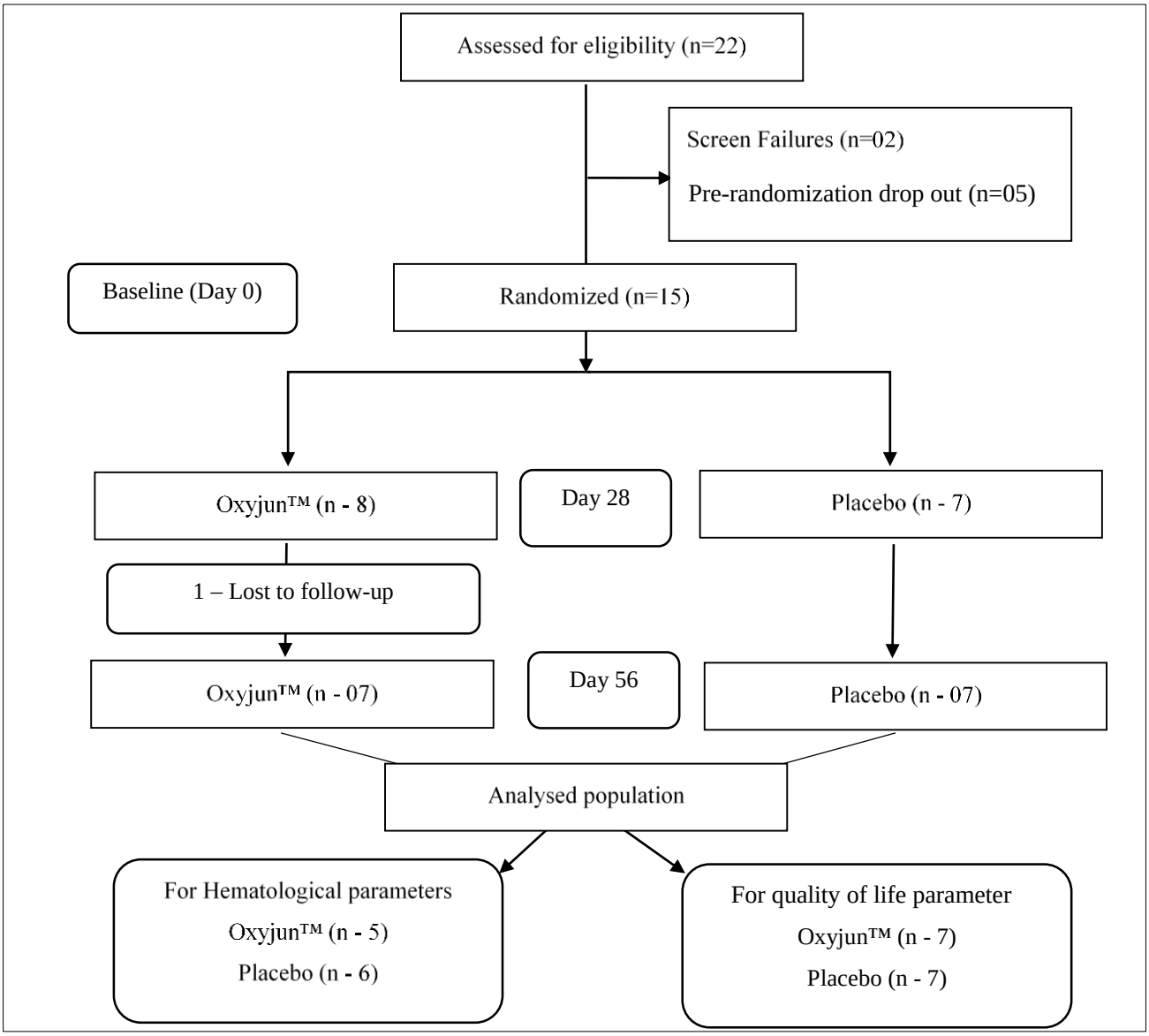

Figure 1 Flow of study participants

4.2 Adipose tissue inflammation - Neutrophil to lymphocyte ratio

For the NLR ratio, values were higher at baseline in Oxyjun™ group as compared to placebo; p=0.07. After 56 days of IP administration, the NLR was reduced by 0.71 in the Oxyjun™ group and by 0.42 in the placebo group; p=0.32. The within group comparison for NLR of Oxyjun™ was statistically significant when compared from day 0 to 56; p<0.01 and the observed reduction in NLR for the placebo arm was approximately 50% lower than that of Oxyjun™; p=0.11. However, the between group comparison did not achieve significant difference at the end of day 56; p=0.28 **Table 2** provides summary of NLR as compared from day 0 to 56.

4.3 Lipid profile - High Density Lipoprotein

The HDL-c levels although lower in the Oxyjun™ group at baseline, increased by 4.04 mg/dL at day 56, comparatively, the HDL-c level reduced by 1.22 mg/dL in the placebo group. The change when compared between both groups was nearing significance at the end of 56 days; p=0.09. **Table 3** provides a summary and change in HDL-c levels as compared from day 0 to 56.

Table 1 Screening and demographic characteristics

Groups	Oxyjun™ (n=8)					Placebo (n=7)					p value
Variables	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
Screening Characteristics											
Age (Years)	26.38	5.63	27.00	20.00	34.00	22.43	5.03	20.00	18.00	30.00	0.18
BMI (kg/m²)	29.32	1.00	29.33	28.10	30.90	28.86	1.84	28.56	26.96	31.60	0.55
Waist (cm)	97.92	4.13	98.92	91.50	102.67	96.45	6.09	95.67	87.00	105.50	0.59
Pulse Rate (beats per minute)	73.00	7.75	72.50	64.00	83.00	80.57	5.03	78.00	75.00	87.00	0.05
Resting Systolic BP (mmHg)	126.67	5.40	128.00	116.00	132.67	123.00	8.79	126.00	111.00	134.00	0.34
Resting diastolic BP (mmHg)	81.29	6.42	82.33	70.00	90.00	77.14	7.03	76.00	68.00	87.00	0.25
FBG (mg/dL)	89.18	7.69	91.25	73.10	98.00	86.80	6.39	86.00	75.40	93.90	0.53
Haemoglobin (g/dL)	14.25	1.24	14.40	12.50	15.70	14.39	1.32	14.60	12.20	15.70	0.84
Baseline Characteristics											
Waist (cm)	98.02	4.22	98.75	91.75	102.75	96.44	6.07	96.50	86.50	105.50	0.57
Pulse Rate (Beats / minute)	75.50	8.72	73.50	62.00	91.00	74.57	8.96	76.00	63.00	89.00	0.84
BP Systolic (mmHg)	117.50	10.41	114.00	110.00	140.00	112.29	7.25	112.00	102.00	122.00	0.29
BP Diastolic (mmHg)	78.50	8.60	80.00	64.00	90.00	72.57	9.00	70.00	60.00	84.00	0.22
HDL (mg/dL)	37.46	4.17	38.50	30.00	42.30	40.79	8.10	44.00	28.90	50.60	0.33
WBC (/cmm)	6892.50	1760.49	6540.00	4480.00	9960.00	7545.71	2469.62	6790.00	4660.00	12600.00	0.56
Abs. Lymphocytes (/cmm)	1767.16	296.89	1852.85	1291.30	2099.30	2480.01	743.82	2562.10	1360.70	3641.40	0.03
Abs. Neutrophils (/cmm)	4213.75	1443.56	4129.95	2400.00	6840.00	4099.60	1526.13	3560.00	2651.50	6993.00	0.88
NLR	2.39	0.74	2.34	1.40	3.48	1.68	0.46	1.76	1.02	2.30	0.05

n – number of participants, SD – Standard deviation, Min – minimum, max – maximum, /ccm - per cubic millimetre, HDL – High density lipoprotein, WBC – White blood cells, Abs. – Absolute, BP- Blood pressure, NLR - neutrophils lymphocytes ratio, BMI – Body mass index.
Values are presented as mean (SD).

Table 2 Summary of Neutrophil to lymphocyte ratio

Variables	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	p value**
	Day 0				Day 56				Change in NLR				
Oxyjun™ (n=5)	2.31	0.62	1.70	3.25	1.60	0.46	1.12	2.33	-0.71	0.17	-0.92	-0.53	< 0.01
Placebo (n=6)	1.64	0.49	1.02	2.30	1.22	0.68	0.60	2.40	-0.42	0.54	-1.09	0.48	0.11
p value*	**0.07**				**0.32**				**0.28**				

n – number of participants, SD – Standard deviation, Min – minimum, Max – maximum.
p* – ANOVA (Inter-group) and p - Paired sample T test (Intra group).**
Values are presented as mean (SD).

Table 3 Summary of High Density Lipoprotein

Variables	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	p value**
	Day 0				Day 56				Change in HDL-c				
Oxyjun™ (n=5)	38.24	3.67	33.20	42.30	42.28	6.69	31.40	49.10	4.04	4.11	-1.80	8.80	0.09
Placebo (n=6)	40.25	8.73	28.90	50.60	39.03	7.24	27.50	47.10	-1.22	4.85	-5.80	5.30	0.57
p value*	**0.64**				**0.46**				**0.09**				

n – number of participants, SD – Standard deviation, Min – minimum, Max – maximum.
p* – ANOVA (Inter-group) and p - Paired sample T test (Intra group).**
Values are presented as mean (SD).

Table 4 Summary of SF-36 Health Survey Questionnaire

SF – 36 Parameters	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	p value*
Physical function	**Day 0**				**Day 56**				**Change in Physical function score**				
Oxyjun™ (n=7)	55.00	20.00	30.00	85.00	49.29	33.59	10.00	100.00	-5.71	51.43	-75	70	0.78
Placebo (n=7)	65.71	10.97	50.00	75.00	60.00	25.50	25.00	100.00	-5.71	30.34	-45.00	35.00	0.64
p value*	**0.24**				**0.51**				**1.00**				
Role – Physical health	**Day 0**				**Day 56**				**Change in Role limitation due to Physical health**				
Oxyjun™ (n=7)	46.43	33.63	0.00	100.00	42.86	27.82	0.00	75.00	-3.57	46.61	-75.00	75.00	0.85
Placebo (n=7)	46.43	36.60	0.00	100.00	53.57	41.90	0.00	100.00	7.14	27.82	-25.00	50.00	0.52
p value*	**1.00**				**0.58**				**0.61**				
Role – Emotional	**Day 0**				**Day 56**				**Change in Role limitation due to Emotional problem**				
Oxyjun™ (n=7)	61.90	29.99	33.33	100.00	47.62	57.14	37.09	0.00	100.00	57.14	-4.76	35.64	0.74
Placebo (n=7)	47.62	42.41	0.00	100.00	57.14	37.09	0.00	100.00	9.52	41.79	-33.34	66.67	0.57

p value	**0.48**				**1.00**				**0.50**				
Fatigue	**Day 0**				**Day 56**				**Change in Fatigue**				
Oxyjun™ (n=7)	56.43	15.74	40.00	85.00	74.29	14.84	50.00	90.00	17.86	12.20	5.00	35.00	0.01
Placebo (n=7)	56.43	14.06	30.00	70.00	57.86	8.09	45.00	70.00	1.43	20.15	-20.00	40.00	0.86
p value*	**1.00**				**0.02**				**0.09**				
Mental Health	**Day 0**				**Day 56**				**Change in Mental health**				
Oxyjun™ (n=7)	66.29	15.12	44.00	84.00	78.29	16.63	48.00	96.00	12.00	12.65	0.00	32.00	0.05
Placebo (n=7)	69.14	14.37	44.00	84.00	68.57	13.15	52.00	88.00	-0.57	17.04	-28.00	20.00	0.93
p value*	**0.72**				**0.25**				**0.14**				
Social function	**Day 0**				**Day 56**				**Change in Social functioning**				
Oxyjun™ (n=7)	66.07	17.25	50.00	100.00	82.14	14.17	62.50	100.00	16.07	13.91	0.00	37.50	0.02
Placebo (n=7)	80.36	20.23	50.00	100.00	71.43	23.62	25.00	100.00	-8.93	37.99	-75.00	50.00	0.56
p value*	**0.18**				**0.32**				**0.13**				
Pain	**Day 0**				**Day 56**				**Change in Pain**				
Oxyjun™ (n=7)	65.71	19.13	45.00	100.00	81.07	18.87	55.00	100.00	15.36	23.91	-10.00	52.50	0.14
Placebo (n=7)	72.50	23.67	45.00	100.00	79.29	25.93	47.50	100.00	6.79	21.39	-27.50	42.50	0.43
p value*	**0.57**				**0.89**				**0.49**				
General Health	**Day 0**				**Day 56**				**Change in General health**				
Oxyjun™ (n=7)	65.00	14.14	50.00	90.00	62.86	5.67	55.00	70.00	-2.14	15.24	-35.00	10.00	0.24
Placebo (n=7)	65.71	18.80	35.00	85.00	73.57	14.06	50.00	90.00	7.86	16.04	-10.00	30.00	0.72
p value*	**0.94**				**0.09**				**0.26**				

n – number of participants, min – minimum, max – maximum, SD – standard deviation.
p* – ANOVA (Inter-group) and p - Paired sample T test (Intra group).**
Values are presented as mean (SD).

4.4 Quality of life by SF-36 Health Survey

Participants in the Oxyjun™ group reported reduced fatigue levels as indicated by a significant increase in Fatigue score as compared from baseline; p=0.02. In comparison, the scores in the placebo group remained more or less the same. Furthermore, body pain scores for Oxyjun™ and placebo group at baseline were 65.71 (19.13) and 72.50 (23.67) which at day 56 increased to 81.07 (18.87) and 79.29 (25.93) respectively. This indicates there was optimum relief from pain experienced by the Oxyjun™ group of participants at the end of day 56. Similar improvement was observed in mental health, social function and general health parameters of SF-36 in the Oxyjun™ group of participants. Comparatively, the mean (SD) physical function score for Oxyjun™ and placebo was 55.00 (20.00) and 65.71 (10.97) and on day 56 scores were reduced to 49.29 (33.59) & 60.00 (25.50) respectively. **Table 4** provides the summary and change in the SF-36 questionnaire as compared from day 0 to 56.

4.5 Adverse event reporting and IP compliance

None of the exposed participants reported AE or SAE during the entire course of the study. The treatment compliance was measured as >95% in Oxyjun™ and placebo groups respectively. None of the study participants dropped out due to non-compliance in the present study.

5. Discussion

CResp fitness has been strongly linked to sustained inflammation which is a pivotal risk factor for cardiac dysfunction [52]. Obese or overweight individuals are predisposed to a pro-inflammatory state via increased inflammatory mediators. They show reduced levels of adiponectin that have an anti-inflammatory effect under homeostatic conditions [53]. Consequently, high adiposity-linked chronic inflammation has been described as a major contributor to cardiorespiratory fitness [54, 55]. In a study by Lewis et al, effect of rice bran arabinoxylan compound was evaluated on NLR and other biomarkers in adults with non-alcoholic fatty liver disease. After 90 days the NLR reduced to 1.4 ± 0.7 from baseline levels of 1.5 ± 0.6; $p>0.05$ [56]. In a separate study, the effect of Omega fatty acid was assessed on platelet lymphocyte ratio (PLC) and NLR in patients with percutaneous coronary intervention. Results indicated that PLC was significantly reduced after consumption of high dose Omega-3. However, there was no reduction observed in NLR of study participants [57]. In the present study, we evaluated systemic inflammation using NLR parameter, a routinely available non-invasive diagnostic marker. The values were on a higher side on baseline (2.31) and after 56 days of Oxyjun™ administration, the NLR was reduced by 0.71 in the Oxyjun™ group and the within group comparison for Oxyjun™ was also significant; $p<0.01$. Literature suggests that NLR shares an intimate relationship with cardiac performance and an increase in its levels has been conclusively linked to fatigue, exhaustion or stress [58]. In previous studies, elevated levels of neutrophils and lymphocytes have been linked with low levels of physical activity and cardiac endurance. Thus, NLR, though being a ratio of two different yet complementary immune pathways [59] could serve as an excellent candidate for improving Cresp fitness and endurance [60]. Furthermore, an increase in NLR has also been associated with the pathophysiological mechanism of EDF [61]. Low cardiorespiratory fitness contributes to EDF and atherosclerosis in overweight individuals as opposed to their normal weight peers. Thus, an early reduction in NLR could promote its anti-inflammatory effect thereby improving CResp fitness and endothelial function in overweight individuals.

Several studies have investigated the influence of eccentric exercises, such as downhill running and resistance exercise on CV recovery [62, 63]. Research indicates that neutrophils infiltration into tissues causes inflammation and oxidative stress, and is also involved in muscle damage and delayed muscle soreness [64, 65]. Therefore, inflammation-related biomarkers (eg cytokines, leukocyte counts and NLR) are used as physiological measures for the same [65]. Results of a study published in 2014 suggested that the development of stress-related neuromuscular fatigue is accelerated in overweight-obese individuals that correlate with autonomic dysfunction [66]. In the present study, the NLR levels were significantly reduced which may have had an effect on the cardiac recovery potential of participants. This also correlates with a significant reduction in the fatigue parameter of the SF-36 questionnaire [67]. Our findings are also in line with the results of our previous study where significant improvement was shown in LVEF and the right MPI of participants was reduced; $p<0.001$ [45]. As low LVEF and MPI are important determinants of fatigue and exercise capacity, [68] our results further justify the relationship between inflammation, fatigue and CResp fitness thereby strengthening our study findings. However, it is recommended that the association of these factors is intricately investigated in future studies.

HDL-c has known for its anti-atherogenic and anti-inflammatory activity as it inhibits cholesterol transport and LDL-c oxidation [69-71]. It reduces inflammation, promotes nitric oxide production in endothelial cells and also has a role in platelet activation and expression of adhesion molecules [72-74]. There also exists a direct relationship between maximal exercise or work intensity and the concentration of HDL-c [75]. Therefore, raising HDL-c levels provides an important strategy for addressing CResp fitness. A study by Cooke et al reported that CoenzymeQ10 increased baseline HDL level of 53 ± 12 mg/dL to 54 ± 10 mg/dL after 2-weeks [76]. A separate study that evaluated the antilipidemic properties of Vitamin K reported an increase of 1.5 mg/dL post 56 days consumption [77]. Comparatively, for the present study the baseline HDL-c levels were on a lower side (<40) for the Oxyjun™ arm when

compared to placebo. Even so, after 56 days HDL-c levels in Oxyjun™ group were increased by 4.04 mg/dL (↑10.56%) and in the placebo group reduced by 1.22 mg/dL (↓-3.03%). Raising HDL-c levels is a daunting proposition. Even the most widely used statin therapy with lifestyle and dietary changes accounts for a 5 - 10% increase in HDL-c levels [78]. Hence, our findings are particularly important as Oxyjun™ induced an increase of >10% in HDL-c levels for overweight and physically inactive study participants with no dietary and lifestyle changes.

With regards to safety assessments, none of the participants reported AEs or SAEs in the present study. This validates the excellent safety profile and tolerability of Oxyjun™ over 56 days in study participants. Despite of the present study confirming previous findings and contributing to additional evidence, it does have a few limitations. The SF-36 health concepts of fatigue, mental health, and social function showed significant improvement and even the pain scores were improved. However, some parameters displayed no change which can be attributed to sudden lifestyle changes due to the emergence of COVID-19. Additionally, we were not able to evaluate the effect of Oxyjun™ on VO2Max due to COVID-19 pandemic which could have further reinforced and substantiated the present study findings.

6. Conclusion

In conclusion, the present findings serve as a basis for the potential of Oxyjun™ in improving exercise capacity by the virtue of reducing adipose tissue induced inflammation. Oxyjun™ with its proven role in enhancing LVEF and MPI along with improved exercise capacity can further synergize the endurance enhancer and cardiovascular remodelling in exercising adults. It is recommended that the association of these factors is further investigated in future studies.

References

[1] M.M. Bosma-den Boer, M.L. van Wetten, L, Pruimboom, Chronic inflammatory diseases are stimulated by current lifestyle: how diet, stress levels and medication prevent our body from recovering, Nutrition & metabolism, 9(1) (2012) 32. DOI | PubMed

[2] G. Ghigliotti, C. Barisione, S. Garibaldi, P. Fabbi, C. Brunelli, P. Spallarossa, P. Altieri, G. Rosa, G. Spinella, D. Palombo, R. Arsenescu, V. Arsenescu, Adipose tissue immune response: novel triggers and consequences for chronic inflammatory conditions, Inflammation, 34(4) (2014) 1337-1353. DOI | PubMed

[3] M.S. Burhans, D.K. Hagman, J.N. Kuzma, K.A. Schmidt, M. Kratz, Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus, Comprehesive Physiology, 9(1) (2018) 1-58. DOI | PubMed

[4] L. Venkatraghavan, T.P. Tan, J. Mehta, A. Arekapudi, A. Govindarajulu, E. Siu, Neutrophil Lymphocyte Ratio as a predictor of systemic inflammation - A cross-sectional study in a pre-admission setting, F1000Res, 4(123) (2015). DOI | PubMed

[5] E. Yu, V.S. Malik, F.B. Hu, Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series, Journal of the American College of Cardiology, 72(8) (2018) 914-926. DOI | PubMed

[6] R. Zahorec, Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill, Bratislavske lekarske listy, 102(1) (2001) 5-14. PubMed

[7] K.M, Beavers, T.E. Brinkley, B.J. Nicklas, Effect of exercise training on chronic inflammation, Clinica Chimica Acta; International Journal of Clinical Chemistry, 411(11-12) (2010) 785-793. DOI | PubMed

[8] A.S. Wedell-Neergaard, R. Krogh-Madsen, G.L. Petersen, A.M. Hansen, B.K. Pedersen, R. Lund, H. Bruunsgaard, Cardiorespiratory fitness and the metabolic syndrome: Roles of inflammation and abdominal obesity, PLoS One, 13(3) (2018) e0194991. DOI | PubMed

[9] M. E. Piché, A. Tchernof, J.P. Després, Obesity Phenotypes, Diabetes, and Cardiovascular Diseases, Circulation research, 126(11) (2020) 1477–1500. DOI

[10] A. Syauqy, C.Y. Hsu, H.H. Rau, J.C. Chao, Association of dietary patterns, anthropometric measurements, and metabolic parameters with C-reactive protein and neutrophil-to-lymphocyte ratio in middle-aged and older adults with metabolic syndrome in Taiwan: a cross-sectional study, Nutrition Journal, 17(1) (2018) 106. DOI | PubMed

[11] R. Wang, P.J. Chen, W.H. Chen, Diet and exercise improve neutrophil to lymphocyte ratio in overweight adolescents, International Journal of Sports Medicine, 32(12) (2011) 982-986. DOI | PubMed

[12] I.J. Kullo, M. Khaleghi, D.D. Hensrud, Markers of inflammation are inversely associated with VO2 max in asymptomatic men, Journal of Applied Physiology (1985), 102(4) (2007) 1374-1379. DOI | PubMed

[13] R. Michishita, N. Shono, T. Inoue, T. Tsuruta, K. Node, Associations of monocytes, neutrophil count, and C-reactive protein with maximal oxygen uptake in overweight women, Journal of Cardiology, 52(3) (2008) 247-253. DOI | PubMed

[14] R. Furutate, T. Ishii, T. Motegi, K. Hattori, Y. Kusunoki, A. Gemma, K. Kida, The Neutrophil to Lymphocyte Ratio Is Related to Disease Severity and Exacerbation in Patients with Chronic Obstructive Pulmonary Disease, Internal Medicine, 55(3) (2016) 223-229. DOI | PubMed

[15] A. Yıldız, M. Yüksel, M. Oylumlu, N. Polat, M.A. Akıl, H. Acet, The association between the neutrophil/lymphocyte ratio and functional capacity in patients with idiopathic dilated cardiomyopathy, The Anatolian Journal of Cardiology, 15(1) (2015) 13-17. DOI | PubMed

[16] P. Paliogiannis, A.G. Fois, S. Sotgia, A.A. Mangoni, E. Zinellu, P. Pirina, C. Carru, A. Zinellu, The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: A systematic review and meta-analysis, European Journal of Clinical Investigation, 48(8) (2018) e12984. DOI | PubMed

[17] I.K. Kwaifa, H. Bahari, Y.K. Yong, S.M. Noor, Endothelial Dysfunction in Obesity-Induced Inflammation: Molecular Mechanisms and Clinical Implications, Biomolecules, 10(2) (2020) 291. DOI | PubMed

[18] P. Rajendran, T. Rengarajan, J. Thangavel, Y. Nishigaki, D. Sakthisekaran, G. Sethi, I. Nishigaki, The vascular endothelium and human diseases. International Journal of Biological Sciences, 9(10) (2013) 1057-1069. DOI | PubMed

[19] E. Galkina, K. Ley, Immune and inflammatory mechanisms of atherosclerosis (*), Annual Review of Immunology, 27 (2009) 165-197. DOI | PubMed

[20] H.O. Santos, L.F.M. Izidoro, Neutrophil-Lymphocyte Ratio in Cardiovascular Disease Risk Assessment, International Journal of Cardiovascular Sciences, 31(5) (2018) 532-537. DOI

[21] Y. Ohno, T. Hashiguchi, R. Maenosono, H. Yamashita, Y. Taira, K. Minowa, Y. Yamashita, Y. Kato, K. Kawahara, I. Maruyama, The diagnostic value of endothelial function as a potential sensor of fatigue in health. Vascular Health and Risk Management, 6 (2010) 135-144. DOI | PubMed

[22] G.D. Florida-James, R. Simpson, G. Davison, G. Close, Exercise, Free Radical Metabolism, and Aging: Cellular and Molecular Processes, Oxidative Medicine and Cellular Longevity, 2016 (2016) 3813680. DOI | PubMed

[23] D.C. Lee, X. Sui, T.S. Church, C.J. Lavie, A.S. Jackson, S.N. Blair, Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia, Journal of the American College of Cardiology, 57(7) (2012) 665-672. DOI | PubMed

[24] I. Raz, H. Rosenblit, J.D. Kark, Effect of moderate exercise on serum lipids in young men with low high density lipoprotein cholesterol, Arteriosclerosis, 8(3) (1988) 245-251. DOI

[25] H.B. G, V.S. Rao, V.V Kakkar, Friend Turns Foe: Transformation of Anti-Inflammatory HDL to Proinflammatory HDL during Acute-Phase Response, Cholesterol, 2011 (2011) 274629. DOI | PubMed

[26] P.P Toth, High-density lipoprotein and cardiovascular risk, Circulation, 109,15 (2004) 1809-1812. DOI | PubMed

[27] S. Rashid, J. Genest, Effect of obesity on high-density lipoprotein metabolism, Obesity (Silver Spring), 15(12) (2007) 2875-2888. DOI | PubMed

[28] R. Ross, S.N. Blair, R. Arena, T.S. Church, J.P. Després, B.A. Franklin, W.L. Haskell, L.A. Kaminsky, B.D. Levine, C.J. Lavie, J. Myers, J. Niebauer, R. Sallis, S.S. Sawada, X. Sui, U. Wisløff, Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association, Circulation, 134(24) (2016) e653-e699. DOI | PubMed

[29] H. Henriksson, P. Henriksson, P. Tynelius, M. Ekstedt, D. Berglind, I. Labayen, J.R. Ruiz, C.J. Lavie, F.B. Ortega, Cardiorespiratory fitness, muscular strength, and obesity in adolescence and later chronic disability due to

cardiovascular disease: a cohort study of 1 million men, European Heart Journal, 41(15) (2020) 1503-1510. DOI | PubMed

[30] X. Zhang, R.E. Cash, J.K. Bower, B.C. Focht, E.D. Paskett, Physical activity and risk of cardiovascular disease by weight status among U.S adults, PLoS One, 15(5) (2020) e0232893. DOI | PubMed

[31] M.A. Allison, N.E. Jensky, S.J. Marshall, A.G. Bertoni, M. Cushman, Sedentary behavior and adiposity-associated inflammation: the Multi-Ethnic Study of Atherosclerosis, American Journal of Preventive Medicine, 42(1) (2012) 8-13. DOI | PubMed

[32] U.K. Sampson, S. Fazio, M.F. Linton, Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges, Current Atherosclerosis Reports, 14(1) (2012) 1-10. DOI | PubMed

[33] D, Lorber, Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus, Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 7 (2014) 169-183. DOI | PubMed

[34] S. Mandal, A. Patra, A. Samanta, S. Roy, A.Mandal, T.D. Mahapatra, S. Pradhan, K. Das, D.K. Nandi, Analysis of phytochemical profile of Terminalia arjuna bark extract with antioxidative and antimicrobial properties, Asian Pacific Journal of Tropical Biomedicine, 3(12) (2013) 960-966. DOI | PubMed

[35] A. Amalraj, S. Gopi, Medicinal properties of Terminalia arjuna (Roxb.) Wight & Arn.: A review, Journal of Traditional and Complementary Medicine, 7(1) (2016) 65-78. DOI

[36] A. Rees, G.F. Dodd, J.P.E. Spencer, The Effects of Flavonoids on Cardiovascular Health: A Review of Human Intervention Trials and Implications for Cerebrovascular Function, Nutrients, 10(12) (2018) 1852. DOI | PubMed

[37] D. Singh, P.K. Chaudhuri, Structural characteristics, bioavailability and cardioprotective potential of saponins, Integrative Medicine Research, 7(1) (2018) 33-43. DOI

[38] A. Bharani, A. Ganguly, K.D. Bhargava, Salutary effect of Terminalia Arjuna in patients with severe refractory heart failure, International Journal of Cardiology, 49(3) (1995) 191-199. DOI | PubMed

[39] S. Dwivedi, A. Aggarwal, M.P. Agarwal, S. Rajpal, Role of Terminalia arjuna in ischaemic mitral regurgitation, International Journal of Cardiology, 100(3) (2005) 507-508. DOI | PubMed

[40] D. Kapoor, R. Vijayvergiya, V. Dhawan, Terminalia arjuna in coronary artery disease: ethnopharmacology, pre-clinical, clinical & safety evaluation, Journal of Ethnopharmacology, 155(2) (2014) 1029-1045. DOI | PubMed

[41] R. Gupta, S. Singhal, A. Goyle, V.N. Sharma, Antioxidant and hypocholesterolaemic effects of Terminalia arjuna tree-bark powder: a randomised placebo-controlled trial, Journal of the Association of Physicians of India, 49 (2001) 231-235. PubMed

[42] A. Bharani, L.K. Ahirwar, N. Jain, Terminalia arjuna reverses impaired endothelial function in chronic smokers, Indian Heart Journal, 56(2) (2004) 123-128. PubMed

[43] R.N. Girandola, S. Srivastava, Effect of E-OJ-01 on Cardiac Conditioning in Young Exercising Adults: A Randomized Controlled Trial [published correction appears in American Journal of Therapeutics, American Journal of Therapeutics, 24(3) (2017) e298-e307. DOI | PubMed

[44] C.A. McHorney, J.E. Ware Jr, J.F. Lu, C.D. Sherbourne, The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups, Medical Care, 32(1) (1994) 40-66. DOI | PubMed

[45] Tutino VM, Poppenberg KE, Li L, H. Shallwani, K. Jiang, J.N. Jarvis, Y. Sun, K.V. Snyder, E.I. Levy, A.H. Siddiqui, J. Kolega, H. Meng, Biomarkers from circulating neutrophil transcriptomes have potential to detect unruptured intracranial aneurysms, Journal of Translational Medicine, 16(1) (2018) 373. DOI | PubMed

[46] A.R. Dancsok, N. Setsu, D. Gao, J.Y. Blay, D. Thomas, R.G. Maki, T.O. Nielsen, E.G. Demicco, Expression of lymphocyte immunoregulatory biomarkers in bone and soft-tissue sarcomas, Modern Pathology, 32,12 (2019) 1772-1785. DOI | PubMed

[47] P. Forget, C. Khalifa, J.P. Defour, D. Latinne, M.C. Van Pel, M. De Kock, What is the normal value of the neutrophil-to-lymphocyte ratio?,

BMC Research Notes, 10,1 (2017) 12. DOI | PubMed

[48] E.J. Whitney, R.A. Krasuski, B.E. Personius, J.E. Michalek, A.M. Maranian, M.W. Kolasa, E. Monick, B.G. Brown, A.M. Gotto Jr, A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events, Annals of Internal Medicine, 142, 2 (2005) 95-104. DOI

[49] R.S. Birjmohun, B.A. Hutten, J.J. Kastelein, E.S. Stroes, Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials, Journal of the American Colege ofl Cardiology, 45,2 (2005) 185-197. DOI

[50] N. Priya, K.C. Mathur, A. Sharma, R.P. Agrawal, V. Agarwal, J. Acharya, Effect of Terminalia Arjuna on total platelet count and lipid profile in patients of coronary artery disease, Advances in Human Biology, 9, (2019) 98-101. DOI

[51] G. Rajagopal, V. Suresh, A. Sachan, High-density lipoprotein cholesterol: How High, Indian Journal of Endocrinology and Metabolism, 16 (Suppl2) (2012) S236-S238. DOI | PubMed

[52] A. Lopez-Candales, P.M. Hernández Burgos, D.F. Hernandez-Suarez, D. Harris, Linking Chronic Inflammation with Cardiovascular Disease: From Normal Aging to the Metabolic Syndrome, Journal of Nature and Science, 3,4 (2017) e341. PubMed

[53] L. Pirola, J.C. Ferraz, Role of pro- and anti-inflammatory phenomena in the physiopathology of type 2 diabetes and obesity, World Journal of Biological Chemistry, 8,2 (2017) 120-128. DOI | PubMed

[54] J. Myers, P. Kokkinos, E. Nyelin, Physical Activity, Cardiorespiratory Fitness, and the Metabolic Syndrome, Nutrients, 11(7) (2019) 1652. DOI | PubMed

[55] Z. Wang, T. Nakayama, Inflammation, a link between obesity and cardiovascular disease, Mediators of Inflammation, 2010 (2010) 535918. DOI | PubMed

[56] J.E. Lewis, S.E. Atlas, O.L. Higuera, A. Fiallo, A. Rasul, A. Farooqi, O. Kromo, L.A. Lantigua, E. Tiozzo, J.M. Woolger, S. Goldberg, A. Mendez, A.E. Rodriguez, J. Konefal, The Effect of a Hydrolyzed Polysaccharide Dietary Supplement on Biomarkers in Adults with Nonalcoholic Fatty Liver Disease, Evidence-Based Complementary and Alternative Medicine, (2018) 1751583. DOI | PubMed Erratum in: Evidence-Based Complementary and Alternative Medicine. 2020 (2020) 9575878. DOI

[57] A. Sut, K. Chiżyński, M. Różalski, J. Golański, Dietary intake of omega fatty acids and polyphenols and its relationship with the levels of inflammatory markers in men with chronic coronary syndrome after percutaneous coronary intervention, Kardiologia Polska, 75(2) (2020) 117-123. DOI | PubMed

[58] K. Matsuo, M. Kubota, H. Sasaki, J. Toyooka, R. Nagatomi, The association of the blood lymphocytes to neutrophils ratio with overtraining in endurance athletes, New Studies in Athletics, 24(4) (2009) 23-29.

[59] M.E. Afari, T. Bhat, Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update, Expert Review of Cardiovascular Therapy, 14,5 (2016) 573-577. DOI | PubMed

[60] N.M. Johannsen, D.L. Swift, W.D. Johnson, V.D. Dixit, C.P. Earnest, S.N. Blair, T.S. Church, Effect of different doses of aerobic exercise on total white blood cell (WBC) and WBC subfraction number in postmenopausal women: results from DREW, PLoS One, 7(2) (2012) e31319. DOI | PubMed

[61] Y. Jiang, N. Qiao, A6326 Correlation between neutrophil/lymphocyte ratio and endothelial dysfunction in essential hypertension, Journal of Hypertension, 36 (2018) 158. DOI

[62] O. Assumpção Cde, L.C. Lima, F.B. Oliveira, C.C. Greco, B.S. Denadai, Exercise-induced muscle damage and running economy in humans, The Scientific World Journal, 2013, (2013) 189149. DOI | PubMed

[63] D.G. Burt, C. Twist, The effects of exercise-induced muscle damage on cycling time-trial performance, The Journal of Strength and Conditioning Research, 25(8) (2011) 2185-2192. DOI | PubMed

[64] T. Kawamura, K. Suzuki, M. Takahashi, M. Tomari, R. Hara, Y. Gando, I. Muraoka, Involvement of Neutrophil Dynamics and Function in Exercise-Induced Muscle Damage and Delayed-Onset Muscle Soreness: Effect of Hydrogen Bath, Antioxidants (Basel), 7(10) (2018) 127. DOI | PubMed

[65] M. Mittal, M.R. Siddiqui, K. Tran, S.P. Reddy, A.B. Malik, Reactive oxygen species in

inflammation and tissue injury, Antioxidants & Redox Signaling, 20(7) (2014) 1126-1167. DOI | PubMed

[66] R.K. Mehta, Impacts of obesity and stress on neuromuscular fatigue development and associated heart rate variability, International Journal of Obesity, 39(2) (2015) 208-213. DOI | PubMed

[67] P.D. Thompson, E.M. Cullinane, S.P. Sady, M.M. Flynn, C.B. Chenevert, P.N. Herbert, High density lipoprotein metabolism in endurance athletes and sedentary men, Circulation, 84(1) (1991) 140-152. DOI

[68] E. Kasikcioglu, H. Oflaz, H. Akhan, A. Kayserilioglu, Right ventricular myocardial performance index and exercise capacity in athletes, Heart Vessels, 20(4) (2005) 147-152. DOI | PubMed

[69] E. Eren, N. Yilmaz, O. Aydin, High Density Lipoprotein and it's Dysfunction, The Open Biochemistry Journal, 6 (2012) 78-93. DOI | PubMed

[70] K.A. Rye, C.A Bursill, G. Lambert, F, P.J. Tabet, The metabolism and anti-atherogenic properties of HDL, Journal of Lipid Research, 50, Suppl(Suppl) (2009) S195-S200. DOI | PubMed

[71] T.D. Filippatos, M.S. Elisaf, High density lipoprotein and cardiovascular diseases, World Journal of Cardiology, 5(7) (2013) 210-214. DOI | PubMed

[72] B.J. Ansell, K.E. Watson, A.M. Fogelman, M. Navab, G.C. Fonarow, High-density lipoprotein function recent advances, Journal of the American College of Cardiology, 45(10) (2005) 1792-1798. DOI | PubMed

[73] P.P. Toth, M.H. Davidson, High-density lipoproteins: marker of cardiovascular risk and therapeutic target, Journal of Clinical Lipidology, 4(5) (2010) 359-64. DOI

[74] K.A. Rye, P.J. Barter, Antiinflammatory actions of HDL: a new insight, Arteriosclerosis, Thrombosis, and Vascular Biology, 28(11) (2008) 1890-1891. DOI | PubMed

[75] S. Leclerc, C. Allard, J. Talbot, R. Gauvin, C. Bouchard, High density lipoprotein cholesterol, habitual physical activity and physical fitness, Atherosclerosis, 57(1) (1985) 43-51. DOI

[76] M. Cooke, M. Iosia, T. Buford, B. Shelmadine, G. Hudson, C. Kerksick, C. Rasmussen, M. Greenwood, B. Leutholtz, D. Willoughby, R. Kreider, Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals, The Journal of the International Society of Sports Nutrition, 5 (2008) 8. DOI | PubMed

[77] S. Kolahi, B. Pourghassem Gargari, M. Mesgari Abbasi, M. Asghari Jafarabadi, Ghamarzad Shishavan, Effects of phylloquinone supplementation on lipid profile in women with rheumatoid arthritis: a double blind placebo controlled study, Nutrition Research and Practice, 9(2) (2015) 186-191. DOI | PubMed

[78] K. Mahdy Ali, A. Wonnerth, K. Huber, J. Wojta, Cardiovascular disease risk reduction by raising HDL cholesterol--current therapies and future opportunities, British Journal of Pharmacology, 167(6) (2012) 1177-1194. DOI | PubMed

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Authors Contribution

Individual contributions are as follows: Study conceptualization, methodology and supervision, Dr. Shalini Srivastava and Ankul Kokate; Manuscript preparation, Ankul Kokate; review and editing, Ankul Kokate; Dr. Shalini Srivastava and Robert Girandola. All authors have read and approved the manuscript.

Conflict of interest

– Dr. Shalini Srivastava and Mr. Ankul Suresh Kokate are affiliated with Enovate Biolife and Vedic Lifesciences. The authors report no other conflicts of interest in this work.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

Informed consent

All participants gave written informed consent to participate in this study.