v. 2, n. 65, 2022

International Journal of Health Science

THE EFFECT OF LIPOIC ACID AND PHYSICAL EXERCISE ON SUPEROXIDE DISMUTASE ACTIVITY AND POSTMENOPAUSAL SYMPTOMS

Libne Lidianne da Rocha and Nóbrega
ORCID 0000-0001-7323-8931

Leandro Vinicius Fernandes de Morais
ORCID 0000-0002-4737-331X

Isabelle Cantídio Fernandes Diogenes
ORCID 0000-0002-5293-8733

Rejane Maria de Oliveira Holland
ORCID 0000-0003-4165-7634

Hyderaldo Bezerra dos Santos
ORCID 0000-0002-5196-0250

Adriana Augusto de Rezende
ORCID 0000-0003-2452-4047

Maria das Graças Almeida
ORCID 0000-0002-5587-0922

Abstract: The present study aimed to evaluate the effect of lipoic acid supplementation and physical exercise on the activity of the enzyme Superoxide Dismutase (SOD) and on signs and symptoms of post-menopause. Thirty-three postmenopausal participants were selected to participate in a double-blind, randomized, controlled clinical trial. The women were distributed among the groups: Control - C (9), Lipoic Acid - AL (13), Physical Exercise - E (5) and Lipoic Acid + Exercise - ALE (6). AL and ALE groups performed daily supplementation with lipoic acid at a dose of 600mg orally. Groups E and ALE performed walks 3 times a week, 1 hour a day. A blood sample was collected before and after the 4-month intervention for hormonal evaluation and Superoxide Dismutase activity. Anthropometry and assessment of climacteric symptoms were performed before the first blood collection and monthly. A 2x2 factorial design was used in this test, where the multiple linear regression model was used (analysis of covariance) or the generalized estimation equations model. No evidence was found on the effect of lipoic acid and exercise on SOD. However, lipoic acid improved sexual symptoms and exercise increased psychological, somatic, anxiety, depression and vasomotor symptoms on the Greene scale. The results deserve further studies to clarify the relationships found.

Keywords: Post-menopause; Acid lipoic; Physical exercise; Oxidative stress; Antioxidants.

INTRODUCTION

The enzyme Superoxide Dismutase (SOD) is the main line of antioxidant defense[1.] SOD is an essential enzyme and scavenges superoxide radicals and therefore helps protect cells against by-products of aerobic metabolism [2.] It is the first cellular enzyme in the antioxidant system that catalyzes the dismutation of the superoxide radical anion (O_2^-) into Hydrogen Peroxide (H_2O_2) and oxygen molecules[2-4] and is a sensitive biomarker of antioxidant capacity for related changes. at age.[5.6]

Studies indicate that estrogen has antioxidant properties.[3,7-9] However, menopause, a phase in which there is a progressive decline in the concentrations of this hormone, a condition that affects many body tissues and produces a variety of signs and symptoms,[8] is related to a decrease in antioxidant defense [10] and oxidative stress[5,9] hypoestrogenism interferes with Superoxide Dismutase[5] activity. There are reports that the expression and function of the SOD enzyme can be regulated by estrogen [6,] more specifically, by 17β-estradiol [11.] SOD can be negatively correlated with E_2 [10] status.

However, although the oxidative stress attributed to the drop in estrogen concentrations in menopause is recognized by science, there is a need for evidence based on clinical studies in menopause that point to new strategies to stimulate antioxidant defenses or clarify existing inconsistencies.

Generally, the study of oxidative stress in menopause has been carried out with subjects using hormone replacement therapy (HRT) [12.] However, HRT is already recognized by researchers as being complex and controversial[6.]

In turn, apart from the research of our group, the amount of investigative work that seeks answers to the effect of lipoic acid (LA) alone or associated with physical exercise on oxidative stress in menopause is very discreet, even though LA is considered a good antioxidant[13,] with an effective role in the regeneration of other antioxidants, such as vitamin C, directly, and vitamin E, indirectly, a scavenger of reactive species inside and outside cells[14] and with effects also on antioxidants such as SOD and glutathione.[15- 16]

The study of lipoic acid is often implicated with its effect on oxidative stress in the context of diseases such as hypertension, metabolic syndrome, diabetic neuropathy and brain function, including Alzheimer's disease, among others,[16-17] and is still frequently performed, in animal models, as seen in recent studies.[18-19] In addition, there are still inconclusive answers about the type, duration and intensity of physical exercise and its impact on antioxidant defenses.[19-20]

Therefore, the present study aims to evaluate the effect of lipoic acid supplementation and physical exercise on the activity of the enzyme Superoxide Dismutase and on signs and symptoms of post-menopause. In addition, the effect of lipoic acid and physical exercise on estradiol and follicle stimulating hormones (FSH) was evaluated.

MATERIALS AND METHODS

CHARACTERISTICS OF PARTICIPANTS AND STUDY DESIGN

Thirty-three participants who completed between 1 and 8 years of natural amenorrhea, confirming early post-menopause according to *Stages of reproductive Aging Workshop* [21], were selected from an initial sample of 457 women from the Basic Health Units – UBS in the city of Mossoró, RN, Brazil, to participate in a double-blind, randomized and controlled clinical study.

All women were non-practitioners of physical activity, non-smokers or had not smoked up to 6 months before, did not consume moderate amounts of alcohol (more than 15 g of alcohol/day or more than one alcoholic drink/day), nor used psychotropic substances, had no personal history of cancer, diabetes, cardiovascular disease, Acute Myocardial Infarction - AMI, Cerebrovascular Accident - CVA, Chronic Renal Failure - CRF and clinical thyroid, hepatic and renal pathologies, were non-users of hormone replacement therapy, and did not have long-term medical treatment or use of drug substances and supplements that interfere with endogenous antioxidants [10,22-24].

The participants were randomly distributed among the Control - C (9), Lipoic Acid - AL (13), Physical Exercise - E (5) and Lipoic Acid + Exercise - EF (6) groups, and were instructed to inform about the practice of physical activity. any type of physical exercise outside the research, changes in dietary habits or diagnosis of a chronic clinical condition with or without prolonged drug treatment.

The research protocol presents CAAE 15697813.3.0000.5292 and was approved under n. 293,506 by the Research Ethics Committee - CEP of Onofre Lopes University Hospital - HUOL on June 5, 2013. All subjects gave written informed consent.

INTERVENTION

Supplementation with Lipoic Acid

Lipoic Acid group received supplementation with Lipoic Acid (Standard excipient: 78% starch, 10% talc, 10% microcrystalline cellulose, 1% magnesium stearate and 1% aerosil), two 300 mg capsules (600 mg dose), once a day orally for 4 months. Lipoic acid and placebo were masterfully produced by a regulated establishment.

Exercise Program

The Physical Exercise and Lipoic Acid and Physical Exercise groups performed 3 weekly walking sessions, on non-consecutive days, lasting 60 minutes, in a public square, for 4 months and under the supervision of a physical educator. The Subjective Perception of Effort Scale, Borg Scale[25] was the instrument used to control the walking speed, daily and individually. The subjective perception of effort was maintained at a moderate level (between Relatively Easy and Slightly Tired).

The exercise program had an initial 10-minute warm-up plus stretching, a 40-minute walking session, and a further 10-minute cool-down and final stretch.

TECHNICAL PROCEDURES

Anthropometric Data

Anthropometric measurements, Height, Weight, Body Mass Index (BMI) and Waist Circumference (WC) were evaluated at the time of the first blood collection and monthly for 4 months.

The women were instructed to climb without shoes on a digital scale with a glass platform, G-Tech Glass PRO. Height was measured using a stadiometer (Sanny brand) graduated in millimeters. The BMI value was calculated using the quotient of weight in kilograms, by the square of height in centimeters (BMI = Weight (Kg) / Height (m^2), according to the World Health Organization.[26]

Waist circumference was measured with a non-elastic measuring tape to the nearest 0.1 cm, with a total length of 150 cm.

Post-Menopause Symptoms

The gynecologists evaluated the climacteric symptoms of the participants before the first blood collection and monthly, during the consultations, for 4 months, using the Greene Scale.[27]

The Greene Scale consists of 21 questions about heartbeat, tension or nervousness, difficulty sleeping, excitability, panic attacks, difficulty concentrating, tiredness or lack of energy, loss of interest, feelings of unhappiness, crying spells, irritability, dizziness, heaviness in the head, tingling in the body, headache, muscle and joint pain, loss of sensation in the hands or feet, difficulty breathing, hot flashes, night sweats and loss of sexual interest.

The scores also range from 0 to 3 (0 - no symptoms and 3 - intense) and the symptomatology can be classified according to subscales of psychological symptoms, anxiety, depression, somatic, vasomotor and sexual symptoms.

Laboratory Assessment

The activity of the enzyme Superoxide Dismutase and the hormonal parameters were measured before the beginning of the experiment and at the end of it (after 4 months). Approximately 20 mL of blood was collected from all women through venipuncture in the cubital region, after a 12-hour fast. The blood was divided into two aliquots, one without anticoagulant for hormonal measurements and one with ethylenediamine tetraacetic acid (EDTA - anticoagulant) to evaluate the antioxidant profile.

Biochemical Analysis

FSH and E2 measurements were performed on a Centaur analyzer, Siemens brand, mod. 1 or 4, by the chemiluminescence method.

Obtaining Erythrocytes

For determination of Superoxide Dismutase enzyme activity in erythrocytes, samples were isolated from 5ml of peripheral blood collected in heparinized tubes. First, the plasma was separated by centrifugation at 3000 rpm, 4ºC for 10min. After removing the plasma, the concentrated erythrocytes were washed three times, under the same centrifugation conditions, with 2 mL of pH 7.4 potassium phosphate buffer solution. The erythrocytes were stored in a -80ºC freezer until the beginning of their analysis.

Determination of superoxide dismutase activity

The activity of the enzyme superoxide dismutase was determined in erythrocytes from peripheral blood collected with heparin, according to Woolliams [28], using the Ransod

kit (Randox, Ireland, United Kingdom). The principle of the reaction is based on the inhibition of formazan red formation by capturing the superoxide anion by superoxide dismutase. Activity was measured by spectrophotometry at 505 nm (Shimadzu-1650 PC UV-visible, Tokyo, Japan), reading at 37 ºC, and the result expressed as U/mg of Hb.

STATISTICAL ANALYSIS

For statistical analysis, the Stata 11.0 program (Stata Corporation, College Station, TX, USA). Data were expressed as mean ± standard deviation, simple frequency and percentage. p values < 0.05 were considered significant.

The statistical tests used were the student's t test and the chi - square test to assess the heterogeneity in the distribution of the subjects' characteristics between the groups.

In this test, the 2x2 factorial design was applied. In the analysis of the efficacy of lipoic acid and exercise, analysis of covariance was used. For the variables measured only in the baseline and final evaluation, a multiple linear regression model was used, in which the dependent variable was the difference between the final value and the initial value of this variable. The independent variables were a dummy binary variable encoding whether the subject received lipoic acid, a dummy binary variable encoding whether the subject exercised, the baseline value of the studied variable, and a term representing the interaction between lipoic acid and exercise. When the interaction test was not significant, this term was eliminated and the estimates presented correspond to models without interaction.

For the variables measured at baseline and at 4, 8, 12 and 16 weeks, the generalized estimation equations (GEE) model was used with normal family, link identity and type 1 autoregressive correlation structure, with dummy independent variables, encoding whether the subject used lipoic acid and/or practiced exercise and a term for the interaction of these two.

RESULTS

The thirty-three study participants had the following means± sd for: age, 52.4 ± 4.1 years; time since menopause, 3.5 ± 2.2 years and; age at menopause, 49.0 ± 3.2 years.

Most women do not work outside the home (18 [54.5%]), are not retired (30 [90.9%]), are married (17 [51.5%]), have completed high school (13 [39.4%]), never smoked (19 [57.6%]) and use alcohol (20 [60.6%]) (Table 1).

Regarding the effect of LA and physical exercise on SOD, no evidence was found (Table 2).

In turn, lipoic acid decreased the score in the sexual symptom subscale (p=0.001), and physical exercise resulted in an increase in the score in the subscales psychological symptoms (p=0.007), somatic symptoms (p=0.001), anxiety (p= 0.003), vasomotor symptoms (p=0.002) and symptoms of depression (p=0.028) on the Greene scale (Table 3).

The analysis also found no evidence regarding the effect of LA and exercise on hormonal variables, E_2 and FSH (data not shown).

DISCUSSION

When evaluating the influence of LA on the activity of superoxide dismutase in the participants of the present study, no alteration was observed in this enzyme. It is possible that the dose adopted in the experimental protocol (600mg daily) was not enough to stimulate an increase in SOD activity in the population studied, middle-aged women, without the antioxidant protection of E_2.

In a study that evaluated the effect of LA (600mg for 3 months) in elderly people over

Variable	Value*	
	SIM	NÃO
Works	15 (45,5)	18 (54,5)
Outside		
Retired	3 (9,1)	30 (90,9)
Married †	17 (51,5)	16 (48,5)
= 2nd degree	13 (39,4)	20 (60,6)
complete		
Ex smoker	14 (42,4)	19 (57,6)
Alcohol	20 (60,6)	13 (39,4)

	Control (C) N=9		Acid lipoic (AL) N=13		Exercise (E) N=5		Acid Lipoic + Exercise (ALE) N=6		P
	N	%	n	%	n	%	n	%	
works	4	44.4	6	46.1	3	60.0	3	50.0	0.99
outside									
retired	2	22.2	1	7.6	1	20.0	0	0.0	0.53
married[a]	4	44.4	6	46.1	4	80.0	3	50.0	0.66
>=2nd degree complete	3	33.3	4	30.7	3	60.0	3	50.0	0.63
Ex smoker	7	77.7	4	30.7	2	40.0	1	16.6	0.08
Alcohol	4	44.4	9	69.2	1	20.0	6	100.0	0.1

*Values are given in absolute frequency (relative frequency)

** "Casada" (Maried) was the most scored option for "Civil Status".

Table 1. Socio-demographic characteristics of the study population (n33).

Variable	Lipoic acid				Exercise				Integration
	M	IC95%		P	m	IC95%		P	P
SOD	10.14	-94.34	114.62	0.844	-56.21	-165,6	53.13	0.302	0,292

Mothod: Mutiple linear regression with baseline adjustment (analysis of covariance)

Values of $p < 0.05$ were considered significant.

Table 2. Effect of lipoic acid and physical exercise on Superoxide Dismutase (n=33).

Variable	Lipoic Acid				Exercise				Integration
	m	IC95%		P	m	IC95%		P	P
Symptoms	-1.27	-3.95	1.40	0.351	3.89	1.08	6.69	**0.007**	0.805
psychological symptoms	-0.85	-2.17	0.47	0.206	2.44	1.06	3.82	**0.001**	0.791
somatic anxiety	-0.58	-2.00	0.84	0.420	2.29	0.80	3.78	**0.003**	0.690
symptoms vasomotor	-0.42	-1.20	0.37	0.299	1.32	0.49	2.14	**0.002**	0.285
symptoms depression	-0.66	-2.00	0.67	0.330	1.58	0.17	2.98	**0.028**	0.930
symptom sexual	-0.90	-1.43	-0.37	**0.001**	0.47	-0.80	1.03	0.094	0.571

Mothod: Generalized estimating equations.

Values of $p < 0.05$ were considered significant.

Table 3. Effect of lipoic acid and exercise on the Greene scale (n=33).

70 years of age with peripheral arterial disease, there was also no effect on the formation of hydroperoxides. It has been suggested that the dose of LA may have been inadequate and that doses between 200 and 1800mg/day of this supplement have been considered safe in humans, with minimal side effects [29]. In an experiment with animals supplemented with LA to verify if it influences memory, oxidation and lifespan, SOD activity was also not altered.[16]

However, unlike our findings, in a study with 31 healthy adults, supplementation with LA (600mg) for 2 months decreased LDL oxidation and urinary isoprostane, a biomarker of lipid peroxidation.[30] The amount of urinary F2-isoprostane did not increase in patients with DM treated with LA (300mg, 600mg and 1200mg), having increased in the placebo group, although not significantly [31]. SOD activity in kidneys of diabetic rats treated with AL was higher than in those patients and not treated [32], and also increased in rats with hepatic steatosis supplemented with AL [15].

Thus, taking into account the difference between the response to OS of sick elderly and healthy adults in LA supplementation, as seen in the studies above, it is suggested that in future studies, the dose of LA can be reassessed for the use with middle-aged women under conditions of hypoestrogenism. In addition, few studies have evaluated SOD activity in humans supplemented with LA, a fact that justifies the deepening of this aspect.

In continuity, physical exercise also did not influence the activity of superoxide dismutase in the participants of our study. A probable cause for the absence of this effect may have been the intensity of the exercise protocol, which was not sufficient to stimulate the production of superoxide anion and, in turn, induce an increase in SOD activity [33].

A similar finding was verified in a trial with oophorectomized rats that performed

swimming, in which no antioxidant adaptation was observed in the trained rats, unlike the control group, which exhibited a significant increase in superoxide dismutase activity. Ovariectomy may have made adaptation difficult 34, more specifically, hypoestrogenism, an explanation that may also apply to postmenopausal women in our study.

However, although our results did not show changes in SOD with the exercise protocol adopted, the practice with moderate intensity is indicated to maintain health and prevent chronic diseases in old age. Walking is one of the most recommended exercises and has shown positive effects on several biochemical markers, including those related to OS [35].

Thus, unlike our findings, an effect of walking on GPx was verified in a study with the elderly (1 hour of moderate exercise daily for 6 months), however, SOD, total antioxidant status and lipoperoxides behaved better in the tai chi group. [35]. Antioxidant activity of the copper/zinc isoform of SOD was improved in the skeletal muscle of elderly individuals who performed resistance training 3 times a week on non-consecutive days [36]. Healthy middle-aged women who performed resistance exercise and spinning regularly also had better SOD and CAT activity compared to the sedentary group [37].

Therefore, it is suggested that the next studies that evaluate the effect of exercise on the antioxidant status of postmenopausal women, include protocols with more intense activities, either on the walk itself or in another type of physical modality.

In turn, in the evaluation of the influence of LA and exercise on the climacteric symptoms of the participants of this study, it was observed that lipoic acid acts on the sexual symptom of the Greene scale, specifically improving the loss of sexual interest.

Studies indicate that sexual function declines with age, and menopausal symptoms were one of the most significant determinants of sexual dysfunction, defined as a disorder that includes manifestations ranging from unresponsiveness to any variation in the intensity and quality of desire, arousal, and orgasm.[38-39] Postmenopausal women seem to show more decreased sexual desire than those who have not yet reached stage [40-41].

However, in the presence of lipoic acid, the loss of sexual interest symptom scores decreased on the Greene scale. No mention was found in the literature about this relationship.

However, evidence indicates that vulnerability to reduced sexual desire in menopausal women is associated with low concentrations of estrogen and testosterone, aging, worse perceived health, among others [39-40,42].

The association, then, between decreased loss of sexual interest and LA supplementation may be related to the antioxidant power of the latter, reported in the literature [43-44], replacing the role of estrogen in its influence on antioxidant defense, particularly, on SOD [45], although in the present study there was no change in this enzyme in the supplemented women. However, this hypothesis deserves further investigation.

In turn, in the present study, physical exercise caused an increase in scores about the subscale's psychological symptoms, somatic symptoms, anxiety, vasomotor symptoms and symptoms of depression (Greene scale).

Some works differ from ours when they identified that physical activity had a positive impact on the physical and mental health of middle-aged women [46] and menopausal women[47]. Aerobic exercise, as well as resistance exercise, performed 3 times a week for 2 months, had a positive effect on vasomotor, psychosocial, physical and sexual symptoms

in menopausal women, and aerobic exercise proved to be superior in terms of amount of influence [48]. Work that performed a 55-minute aerobic exercise program on 3 days a week for 6 months found significant reductions in hot flashes, sweating, anxiety, irritability, and depressed mood. It has been suggested that the reduction could be associated with the type, duration, intensity and frequency of exercise [49].

Thus, it is suggested that the negative effect of exercise on the psychological, somatic, and vasomotor symptoms of the Greene Scale in the present study is related to the amount of exercise established in the protocol of the present research, considered, therefore, insufficient to cause positive changes in the mentioned symptoms.

CONCLUSIONS

Studies with higher doses of LA may be justified in evaluating its effect on SOD enzyme activity in postmenopausal hypoestrogenism. Notwithstanding, there was no effect of LA and physical exercise on the enzyme superoxide dismutase, LA had a positive effect on loss of sexual interest on the Greene Scale. While exercise collaborated with the increase in psychological, somatic, vasomotor, depression and anxiety symptoms in postmenopausal women.

The results deserve further clinical studies to clarify the relationships found between LA and exercise on menopausal symptoms, and it is also plausible to increase exercise intensity or verify its effect at different intensities on antioxidant defense and menopausal symptoms.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Massafra C, Gioia D, Felice CD, Picciolini E, Leo VD, Bonifazi M, et al. Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle. **Journal of Endocrinology** 2000; 167: 447–52.

2. Mansuroglu B, Derman S, Yaba A, Kızılbey K. Protective effect of chemically modified SOD on lipid peroxidationand antioxidant status in diabetic rats. **International Journal of Biological Macromolecules** 2015; 72: 79–87.

3. Bednarek-Tupikowska G, Tworowska U, Jedrychowska I, Radomska B, Tupikowski K, Bidzinska-Speichert B, et al. Effects of oestradiol and oestroprogestin on erythrocyte antioxidative enzyme system activity in postmenopausal women. **Clinical Endocrinology** 2006; 64: 463–8.

4. Zhou Y-H, Tao J, Lv Q-C, Jia W-G, Yun R-R, Cheng Y. Effect of the amide groups on superoxide dismutation catalyzed by copper (II) complexes of adamantine. **Inorganica Chimica Acta** 2015; 426: 211–20.

5. Bogna GG, Justyna M, Adam S, Juliusz P. Nutritional habits and oxidative stress in postmenopausal age. **Polskie archiwum medycyny wewnętrznej** 2014; 124(6): 298-305.

6. Unfer TC, Figueiredo CG, Zanchi MM, Maurer LH, Kemerich DM, Duarte MMF, et al. Estrogen plus progestin increase superoxide dismutase and total antioxidant capacity in postmenopausal women. **Climacteric** 2015; 18: 379-88.

7. Wiecek M, Maciejczyk M, Szymura J, Szygula Z. Changes in Oxidative Stress and Acid-Base Balance in Men and Women Following Maximal-Intensity Physical Exercise. **Physiol. Res.** 2015; 64: 93-102.

8. Bellanti F. Sex hormones modulate circulating antioxidant enzymes: impact of estrogen therapy. **Redox Biology** 2013; 1: 340–6.

9. Kolesnikova L, Semenova N, Madaeva I, Suturina L, Solodova E, Grebenkina L, et al. Antioxidant status in peri- and postmenopausal women. **Maturitas** 2015; 81: 83–7.

10. Campos HH, Brandão LC, Almeida, VD, Grego BHC, Bittencourt LR, Tufik S, Baracat EC. Sleep disturbances, oxidative stress and cardiovascular risk parameters in postmenopausal women complaining of insomnia. **Climacteric** 2006; 9:312–9.

11. Strehlow K, Rotter S, Wassmann S, Adam O, Grohé C, Laufs K, et al. Modulation of antioxidant enzyme expression and function by estrogen. **Circulation research.** 2003; 25: 170-8.

12. Victorino VJ, Panis C, Campos FC, Cayres RC, Colado-Simão NA, Oliveira SR., et al. Decreased oxidant profile and increased antioxidant capacity in naturally postmenopausal women. **Age** 2012; 1-11.

13. Mainini G, Rotondi M, Nola KD, Pezzella MT, Iervolino SA, Seguino E, et al. Oral supplementation with antioxidant agents containing alpha lipoic acid: effects on postmenopausal bone mass. **Clin. Exp. Obst. & Gyn** 2012; 4: 89-93.

14. Rahimifard M, Navaei-Nigjeh M, Baeeri M, Maqbool F, Abdollahi M. Multiple protective mechanisms of alpha-lipoic acid in oxidation, apoptosis and inflammation against hydrogen peroxide induced toxicity in human lymphocytes. **Mol Cell Biochem** 2015; 403:179–86.

15. Stankovic MN, Mladenovic D, Ninkovic M, Đuricic I, Sobajic S, Jorgacevic B, et al. The Effects of a-Lipoic Acid on Liver Oxidative Stress and Free Fatty Acid Composition in Methionine–Choline Deficient Diet-Induced NAFLD. **J Med Food** 2014; 17(2): 254–61.

16. Farr SA, Price TO, Banks WA, Ercal N, Morley JE. Effect of Alpha-Lipoic Acid on Memory, Oxidation, and Lifespan in SAMP8 Mice. **Journal of Alzheimer's Disease** 2012; 32: 447–55.

17. Abdali D, Samson SE, Grover AK. How Effective Are Antioxidant Supplements in Obesity and Diabetes? **Med Princ Pract.** 2015; 1-15.

18. Martins RR, Macedo UBO, Leite LD, Rezende AA, Brandão-Neto J, Almeida MG. Lipoic acid and moderate swimming improves the estrous cycle and oxidative stress in Wistar rats. Appl. **Physiol. Nutr. Metab** 2011; 36:1–5.

19. Zhao R-R, Xu F, Xu X-C, Tan G-J, Liu L-M, Wu N, et al. Effects of alpha-lipoic acid on spatial learning and memory, oxidative stress, and central cholinergic system in a rat model of vascular dementia. **Neuroscience Letters** 2015; 587: 113–9.

20. Palasuwan, A, Suksom D, Margaritis I, Soogarun S, Rousseau A-S. Effects of Tai Chi Training on Antioxidant Capacity in Pre- and Postmenopausal Women. **Journal of Aging Research** 2011: 1-8.

21. Harlow SD, Gass M., Hall JE, Lobo R., Maki P., Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. **Fertility and Sterility** 2012; 97(4): 843-51.

22. Signorelli SS, Sergio Neri S, Sciacchitano S, Pino LD, Pia Costa MP, Marchese G, et al. Behaviour of some indicators of oxidative stress in postmenopausal and fertile women. **Maturitas**. 2006; 57: 77–82.

23. Bobeuf F, Labonte M, Dionne IJ, Khalil A. Combined effect of antioxidant supplementation and resistance training on oxidative stress markers, muscle and body composition in an elderly population. **The Journal of Nutrition, Health & Aging** 2011; 15(10): 883-9.

24. Vassale C, Novembrino C, Maffei S, Sciarrino R, Giuseppe RD, Vigna L, et al. Determinants of oxidative stress related to gender: relevance of age and smoking habit. **Clin Chem Lab Med** 2011; 49(9): 1509-13.

25. Borg GAV Psychophysical bases of perceived exertion. **Medicine and Science in Sports and Exercise** 1982 14(5): 377-81.

26. World Health Organization. Obesity: preventing and managing the global epidemic. 2000. **Report of the WHO consultation on Obesity.** Geneva.

27. Silveira IL, Petronilo PA, Souza MO, Nogueira TD, Silva C, Duarte JMBP, et al. Prevalência de sintomas do climatério em mulheres dos meios rural e urbano do Rio Grande do Norte, Brasil. **Rev Bras Ginecol Obstet.** [internet] 2007 Aug [cited 2015 June 23]; 29(8): 415-22.

28. Woolliams JA, Wiener G, Anderson PH, McMurray CH. Variation in the activities of glutathione peroxidase and superoxide dismutase and in the concentration of copper in the blood in various breed crosses of sheep. **Research in veterinary science.** 1983; 34: 253-6.

29. Vincent HK, Bourguignon CM, Vincent KR, Taylor AG. Effects of Alpha-Lipoic Acid Supplementation in Peripheral Arterial Disease: A Pilot Study. **The Journal of Alternative and Complementary Medicine** 2007; 13(5): 577–84.

30. Marangon K, Devaraj S, Tirosh O, Packer L, Jialal IC. Comparison of the effect of alpha-lipoic acid and alpha-tocopherol supplementation on measures of oxidative stress. **Free Radical Biol. Med** 1999; 27: 1114–21.

31. Porasuphatana S, Suddee S, Nartnampong A, Konsil J, Harnwong B, Santaweesuk A. Glycemic and oxidative status of patients with type 2 diabetes mellitus following oral administration of alph-alipoic acid: a randomized double-blinded placebo controlled study. **Asia Pac J Clin Nutr** 2012; 21(1):12-21.

32. Feng B, Yan X-F, Xue J-L, Xu L, Wang H. The protective effects of **α**-lipoic acid on kidneys in type 2 diabetic goto-kakisaki rats via reducing oxidative stress. **Int. J. Mol. Sci.** 2013; 14: 6746-56.

33. Souza PS, Rocha LGC, Tromm CB, Scheffer DL, Victor EG, Silveira PCL, et al. Therapeutic action of physical exercise on markers of oxidative stress induced by chronic kidney disease. **Life Sciences** 2012; 91: 132–6.

34. Macedo UBO, Martins RR, Freire Neto FP, Oliveira YMC, Medeiros AC, Brandão-Neto J. et al. Oophorectomy hinders antioxidant adaptation promoted by swimming in Wistar rats. **Appl. Physiol. Nutr. Metab.** 2013; 38: 148–53.

35. Rosado-Pérez J, Ortiz R, Santiago-Osorio E, Mendoza-Núñez VM. Effect of Tai Chi versus Walking on Oxidative Stress in Mexican Older Adults. **Oxidative Medicine and Cellular Longevity** 2013; 2013: 1-8.

36. Parise G, Phillips SM, Kaczor JJ, Tarnopolsky MA. Antioxidant enzyme activity is up-regulated after unilateral resistance exercise training in older adults. **Free Radical Biology & Medicine** 2005; 39: 289 – 95.

37. Cardoso AM, Bagatini MD, Roth MA, Martins CC, Rezer JFP, Mello FF et al. Acute effects of resistance exercise and intermittent intense aerobic exercise on blood cell count and oxidative stress in trained middle-aged women. **Brazilian Journal of Medical and Biological Research** 2012; 45: 1172-82.

38. Katz-Bearnot S. Menopause, depression, and loss of sexual desire: a psychodynamic contribution. **Journal of The American Academy of Psychoanalysis and Dynamic Psychiatry** 2010; 38(1): 99–116.

39. Cabral PUL, Canário ACG, Spyrides MHC, Uchôa SAC, Eleutério Jr. J, Gonçalves AK. Determinants of sexual dysfunction among middle-aged women. **International Journal of Gynecology and Obstetrics** 2012; 2-4.

40. Woods NF, RN, Mitchell ES, Julio KS-D. Sexual desire during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. **Journal of Women's Health** 2010; 19(2): 209-18.

41. Gonçalves R, Merighi MAB. Reflexões sobre a sexualidade durante a vivência do climatério. **Rev Latino-am Enfermagem** 2009; 17(2):1-7.

42. Shifren JL, Braustein GD, Simon JA, Casson PR, Buster JE, Redmond JP, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. **The New England Journal of Medicine** 2000; 7: 682-8.

43. Gomes MB, Negrato CA. Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. **Diabetology & Metabolic Syndrome**. 2014; 6: 1-18.

44. Cui J, Xiao Y, Shi Y-H, Wang B, Le G-W. Lipoic acid attenuates high-fat-diet–induced oxidative stress and B-cell–related immune depression. **Nutrition** 2012; 275–80.

45. Pejíc S.A, Kasapovic JD, Todorovic AU, Stojiljkovic VR, Gavrilovic LV, Popovic NN, et al. Antioxidant enzymes in women with endometrial polyps: relation with sex hormones. **European Journal of Obstetrics & Gynecology and Reproductive Biology** 2013; 241-6.

46. Gonçalves AKS, Canário ACG Cabral PUL, Silva RAH, Spyrides MHC, Giraldo PC, et al. Impacto da atividade física na qualidade de vida de mulheres de meia idade: estudo de base populacional. **Rev Bras Ginecol Obstet.** 2011; 33(12): 408-13.

47. Mansikkamäki K, Raitanen J, Malila N, Sarkeala T, Männistö S, Fredman J, et al. Physical activity and menopause-related quality of life – a population-based cross-sectional study. **Maturitas** 2015; 80: 69–74.

48. Agıl A, Abıke F, Daskapan A, Alaca R, Tüzün H. Short-term exercise approaches on menopausal symptoms, psychological health, and quality of life in postmenopausal women. **Obstetrics and Gynecology International** 2010; 1-8.

49. Karacan S. Effects of long-term aerobic exercise on physical fitness and postmenopausal symptoms with menopausal rating scale. **Science & Sports** 2010 25: 39—46.