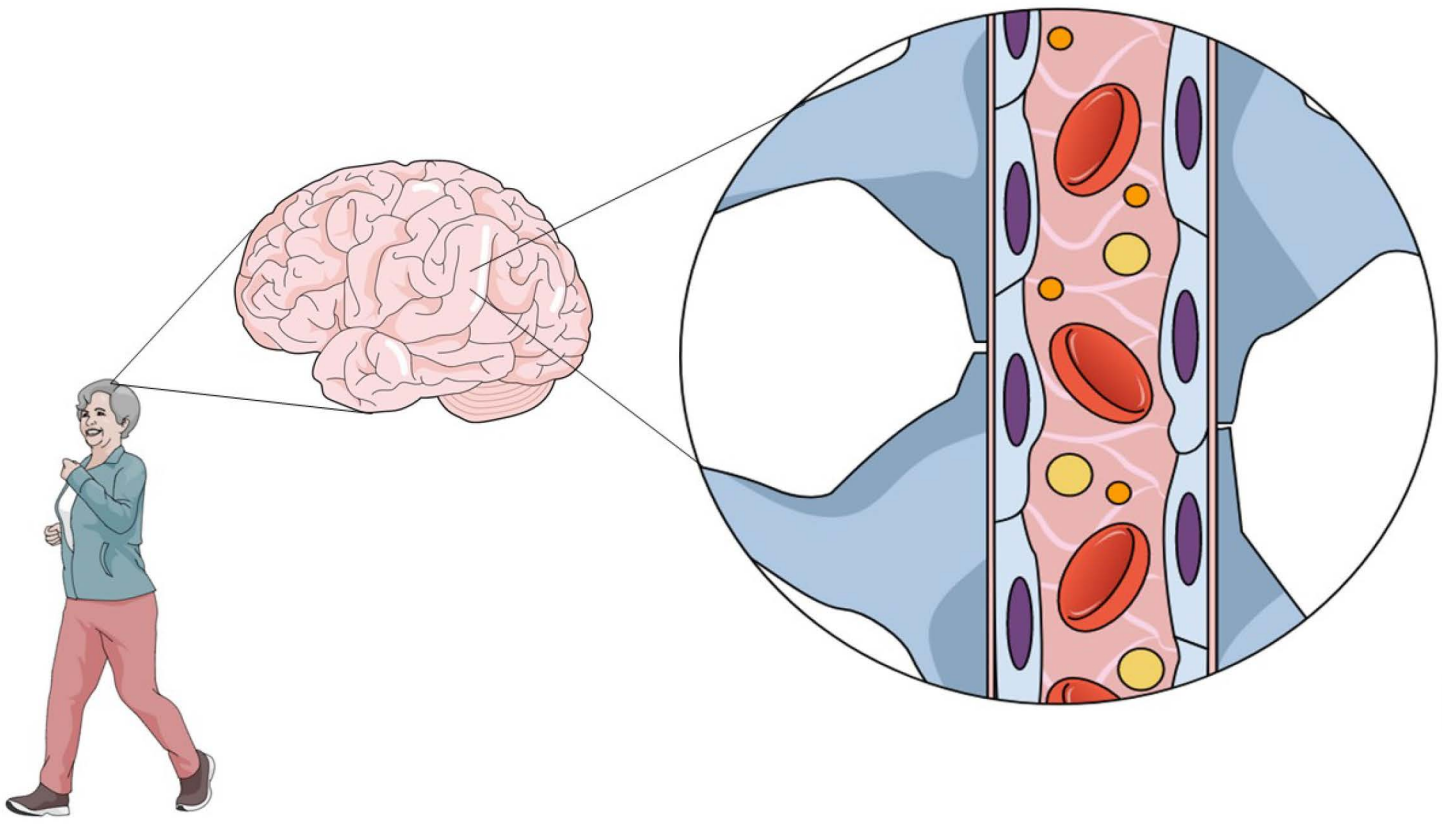

Matheus Uba Chupel

EXERCISE AND SUPPLEMENTATION WITH TAURINE IN THE ELDERLY: EFFECTS ON IMMUNITY AND BLOOD-BRAIN BARRIER INTEGRITY

Tese de Doutoramento em Ciências do Desporto, ramo de Atividade Física e Saúde,
orientada por Professora Doutora Ana Maria Miranda Botelho Teixeira e por Doutora Edith Filaire
e apresentada à Faculdade de Ciências do Desporto e Educação Física da Universidade de Coimbra

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Universidade de Coimbra

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EXERCISE AND SUPPLEMENTATION WITH TAURINE IN THE ELDERLY:

EFFECTS ON IMMUNITY AND BLOOD-BRAIN BARRIER INTEGRITY

Submit in a partial fulfillment of the requirements for the degree of Doctor of Philosophy under the executive committee of Faculty of Sport Science and Physical Education at the University of Coimbra, Portugal.

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FCDEF FACULDADE DE CIÊNCIAS DO DESPORTO E EDUCAÇÃO FÍSICA UNIVERSIDADE DE COIMBRA

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Certa vez perguntaram-me: o que você quer "ser" na vida?
Respondi: quero "ser" aquilo que Deus quiser...
... assim, "sou" feliz!

GENERAL CONTENT

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ABBREVIATIONS

A
AD: Alzheimer Disease

B
BBB: Blood-Brain Barrier

C
CET: Combined Exercise Training
CET+TAU: Combined Exercise Training + Taurine
CG: Control Group
CNS: Central Nervous System
CSF: Cerebral Spinal Fluid
CCI: Charlson Comorbidiy Index
CSHS: Center of Social and Health Support

D
DOMS: Delayed Onset Muscle Soreness

I
IL: Interleukin

M
MMSE: Mini Mental State Examination
MoCA: Montreal Cognitive Assessment
MPO: Mieloperoxidase
MMP: Matrix Metalloproteinase
MCI: Mild Cognitive Impairment

N
NO: Nitric Oxide
NSE: Neuronal Specific Enolase

R
RONS: Reactive Oxygen and Nitrogen Species
RBC: Red Blood Cell Count

T
TBI: Traumatic Brain Injury
TAU: Taurine
TauCl: Taurine Chloramine
TauBr: Taurine Bromamine
TJ: Tight Junctions
TNF: tumor necrosis factor

W
WBC: White Blood Cell Count

ABSTRACT (English and Portuguese)

ABSTRACT (English)

BACKGROUND: The blood-brain barrier (BBB) does not allow any bulk flow of substances between the blood and the brain, and acts as a "gate" that protects the neurons. Dysfunctions in this structure are directly associated with the appearance of neurodegenerative diseases, mainly in the elderly. The widening of inflammation and oxidative processes that occur with aging decrease the BBB integrity and contribute to increased degeneration. Both exercise and nutritional interventions have proven to be effective in promoting health benefits. However, their effects on the integrity of the BBB are still unknown in humans. The objectives of this work were: to study the effect of exercise and supplementation with taurine on pro-and inflammatory cytokines and oxidative stress enzymes (such as IL-1β, IL-1ra, TNF-α, IL-10, IL-17, myeloperoxidase and matrix metalloproteinase-9), peripheral markers of blood-brain barrier leakage and neuronal damage (S100β and neuronal specific enolase - NSE), global cognition, and levels of physical fitness in elderly women.

METHODS: A total of forty-eight (n=48) institutionalized elderly women (age 83,58±6,9 years) participated in the study and were divided into four groups: combined exercise training (CET: n=13), taurine supplementation (TAU: n=12), exercise training in association with taurine (CET+TAU: n=11) and a control group (CG: n=12). The combined exercise training (done by participants of CET and CET+TAU) was apply 2 times per week, in non-consecutive days, and consisted of strength training with elastic bands, aerobic and stretching exercises. The supplementation with taurine (done in TAU and CET+TAU) was given (1,5g/once a day) during 14 weeks. All interventions lasted 14 weeks and all subjects were evaluated before and after this period. The CG did not undergo exercise or supplementation programs, but received care as usual in the nursing home. Plasma and serum concentrations were used to analyze the biological markers by enzyme linked immunosorbent assay (ELISA). Physical fitness was assessed using the senior Physical Fitness battery test, and the assessment of global cognition using the Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) tests.

RESULTS: repeated measures ANOVA revealed that was a treatment*group effect on S100β levels. Afterwards, univariate analysis demonstrated that, despite non-significant, this protein decreased in all interventions and increase in the CG. No changes were observed in NSE levels, except for an increase in TAU group. For the CET group reductions of TNF-α, IL-1β/IL-1ra and TNF-α/IL-10 ratios were observed (p<0.05). In

the TAU group decreases the IL-1β/IL-1ra ratio, MPO and MMP-9 were observed after the intervention (p<0.05). No significant changes were observed in CET+TAU group for any of the biological parameters studied, however, it was the only group to significantly increase the MMSE score, while the CG presented decrease in both MMSE and MoCA (p<0.05). Levels of physical fitness were improved in CET+TAU in two tests (8-foot-up and go test, and 2 minutes Step test, p<0.05), and no significant changes were observed in the other groups. Multiple regression analysis showed that group membership influenced the changes in S100β, together with a trend for an impact of baseline comorbidity index and changes in IL-1β observed for S100β (p=0.054).

CONCLUSION: the practice of exercise or supplementation with taurine can decrease markers of inflammation and oxidative stress, and maintain the BBB integrity in institutionalized elderly women. Exercise also maintain/improve cognition and physical fitness in this sample. It seems that the baseline comorbidity index influences the magnitude of effects of both (exercise and supplementation) interventions. The exercise (alone) presented the greater magnitude of effect in maintaining the BBB integrity, showing that it is an important tool to improve brain health even when started at advanced ages.

RESUMO (em português)

INTRODUÇÃO: A barreira hematoencefálica (BHE) não permite o fluxo em massa de substâncias entre a circulação sanguínea periférica e o cérebro, protegendo assim os neurônios. As disfunções nesta estrutura estão diretamente associadas com o aparecimento de doenças neurodegenerativas, principalmente em idosos. O aumento da inflamação crônica e do stress oxidativo, que ocorrem com o envelhecimento, diminuem a integridade da BHE e contribuem para a sua degeneração. Ambas as práticas, exercício e intervenção nutricional, tem demonstrado eficácia em promover benefícios para a saúde, no entanto, seus efeitos na integridade da BHE são ainda desconhecidos em humanos. Os objetivos deste trabalho foram: estudar os efeitos do exercício e da suplementação com taurina em citocinas pró e anti-inflamatórias e enzimas oxidativas (tais como IL-1β, IL-1ra, TNF-α, IL-10, IL-17, mieloperoxidase – MPO e metaloproteinase de matrix-9 – MMP-9), marcadores periféricos de lesão na barreira hematoencefálica (BBB) e lesão neuronal (S100β e enolase neuronal específica – NSE), cognição global (Mini Exame do Estado Mental – MMSE e MoCA), e níveis de aptidão física em mulheres idosas.

MÉTODOS: um total de quarenta e oito (n=48) idosas institucionalizadas (média de idade 83,58±6,9 anos) participaram do estudo e foram divididas em quatro grupos: treino com exercício combinado (CET: n=13), suplementação com taurina (TAU: n=12), treino com exercício combinado com a suplementação (CET+TAU: n=11) e grupo controlo (CG: n=12). O treinamento de exercício combinado (realizado pelos indivíduos dos grupos CET e CET+TAU), ocorreu duas vezes por semana, com intervalo de pelo menos um dia entre as sessões, e envolveu atividades de treino de força com bandas elásticas, exercícios aeróbios e de flexibilidade. A suplementação com taurina (ingerida pelos indivíduos dos grupos TAU e CET+TAU) foi administrada (1,5g/dia) todos os dias, durante 14 semanas. Todas as intervenções duraram 14 semanas e todos os sujeitos foram avaliados antes e após esse período. Os indivíduos do CG não estiveram envolvidos em nenhum programa de atividade física ou de suplementação, mas continuaram recebendo os cuidados usuais no lar. Amostras de soro e plasma foram utilizadas para quantificar a concentração dos marcadores biológicos propostos para o trabalho através de ELISA. A bateria de testes de aptidão física para idosos (*Senior Physical Fitness test*), e a aplicação de questionário para recolha de dados de cognição global (Mini Exame do Estado Mental – MMSE, e

Montreal Cognitive Assessment – MoCA), também foram administrados em ambos os momentos.

RESULTADOS: a aplicação de ANOVA de medidas repetidas mostrou um efeito significativo para a interação ente tratamento*grupo nos níveis de S100β. A análise univariada mostrou que, apesar de não significativo, os níveis dessa proteína caíram em todos os grupos de intervenção, e um aumento foi observado no CG. Além disso, não foram observadas mudanças nos índices de NSE em todos os grupos, exceto por um aumento no grupo TAU. O grupo CET reduziu significativamente os índices de TNF-α, e os rácios de IL-1β/IL-1ra e TNF-α/IL-10 (p<0.05). O grupo TAU apresentou um decréscimo no rácio IL-1β/IL-1ra, bem como na MPO e MMP-9 (p<0.05). Não foram observadas mudanças significativas no grupo CET+TAU para os parâmetros biológicos avaliados, entretanto, este foi o único grupo que apresentou significativo incremento nos valores de MMSE, enquanto que o CG apresentou uma ligeira queda neste teste e nos índices do MoCA (p<0.05). Além disso, os níveis de aptidão física melhoraram no grupo CET+TAU em dois testes (*8-foot-up and go test*, e *2 minutes Step test*, p<0.05), e não foram observadas mudanças significativas nos outros grupos. A regressão linear múltipla mostrou que o grupo influencia as mudanças observadas na S100β, entretanto, existiu também uma tendência para um impacto do índice de comorbidade e a variação da IL-1β interferirem nessas mudanças (p=0.054).

CONCLUSÃO: a prática de exercício físico ou suplementação com taurina podem diminuir a concentração de citocinas inflamatórias e de enzimas oxidativas, além de manter a integridade da BBB em idosas institucionalizadas. O exercício ainda manteve/melhorou a cognição e a aptidão física dessa amostra. Parece ainda haver uma influência do índice de comorbidade na magnitude dos efeitos mediados por ambas (exercício e suplementação) intervenções. O exercício (sozinho) apresentou as maiores magnitudes de efeito na manutenção da integridade da BBB, mostrando que este é uma importante ferramenta para promover a saúde do cérebro, mesmo quando iniciado em idades avançadas.

KEY-WORDS/PALAVRAS CHAVE

Keywords: *Exercise; taurine; aging; blood-brain barrier; inflammation; oxidative stress; cognition.*

Palavras Chave: *Exercício; taurina; envelhecimento; barreira hematoencefálica; inflamação; stress oxidativo; cognição.*

1. INTRODUCTION

Aging is an irreversible process that all individuals undergo, and the existence of a relationship between chronological age and the appearance of decreased cognition or neurodegenerative diseases points to the need to create programs that prevent and/or attenuate these symptoms and promote health aging. The global costs of Alzheimer Disease, for example, increased from 604 billions of dollars in 2010 to 818 billions of dollars in 2015, growing 35,4% (Wimo *et al.*, 2017). Almost all current epidemiologic projections of dementia assume that the prevalence of this condition will not vary over time, but the growing expectancy of life alone drives this projection to increase. Attention should be drawn to Brazil, which, like the rest of Latin America will follow this trend and will have its costs increased in a very significant way, especially in the more advanced stages (*https://www.alz.co.uk/research/world-report-2015*). In Europe, it currently costs approximately 130 billion of euros per year to care for people with dementia, highlighting age-related neurodegenerative disease as one of the leading medical and societal challenges faced by EU society *(www.neurodegenerationresearch.eu*).

There are no doubts regarding the existing relationship between aging and neurodegenerative conditions, and the mechanism that feed this relation is supported in part by immunosenescence. The aging of the immune system increase the onset of several illness and, in some cases, those related to cognitive impairment and brain pathologies are associated with the increase in blood-brain barrier permeability (BBB).

The BBB is a lipophilic structure located between the cerebral endothelial cells connected by tight junctions that do not allow any bulk flow of water and other solutes between blood and neurons, acting as a "gate" that protects the central nervous system. Several evidences indicate that the genesis and worsening of several brain diseases related to cognitive dysfunction are associated with increased BBB permeability, showing that the maintenance of this structure integrity is important to brain health.

The development of immunosenescence is one of the main biological factors involved in cognitive dysfunction, and is precisely against this frame that emerged in the last years, several non-pharmacological therapies, such as exercise and nutritional supplementation, aiming to improve immunity and promote better physical function. Among these tools, exercise has been stablished to be efficient in reducing the risk of developing neurodegenerative disease, ameliorating cognition even in advanced ages. The effects of exercise in brain are exhaustively studied, especially in animal models, and

showed that exercise interventions induce neurogenesis and attenuate neuroinflammation related to aging.

Different to the exercise practice, there are a great number of pharmacological designs to reduce systemic inflammation, however, most of them act when the inflammatory process is already installed. Also, it is recognized that the nutritional therapy can improve several biological mechanisms by which the body fights against inflammation and oxidative stress, and towards this aims, in the last decades started to emerge a great number of studies involving supplementation with vitamins and amino acids to combat low grade chronic inflammation. Between the nutrients studied, the amino acid taurine is said to be capable of decreasing inflammation by acting directly and indirectly in the suppression of production of pro-inflammatory cytokines, and to have a role on neuroprotection. At the same time, the antioxidant role of taurine was widely explored in animal models, suggesting beneficial effects by diminishing endothelial oxidation in a plethora of pathological conditions such as hypertension and arteriosclerosis.

Although the recognition that exercise and administration of amino acids can promote benefits in the immune system and promote antioxidant capacity, there were no evidence to support the involvement of these therapies in improving the BBB integrity in humans.

Knowing that the genesis of several neurodegenerative process (such as Alzheimer Disease and Multiple Sclerosis), is related to permeability of the BBB, the integrity maintenance of this structure can mediate better protection to the brain and consequently decrease the risk of neurological disturbances appearance, representing an important issue to public health.

As these hypotheses were never studied systematically, this work objective is to verify the effects of exercise, alone or in association with taurine supplementation, on BBB integrity by looking at the leakage markers like S100β in elderly women, together with their effects on production of pro and anti-inflammatory cytokines and levels of oxidative stress markers. Correlations between these biological variables and cognitive status will also be analyzed.

1.1. Objectives

The objectives of the present study are:

1.1.1. Main Objective

To verify the effect of combined exercise training, with and without taurine supplementation, on markers of blood-brain barrier permeability in institutionalized elderly women

1.1.2. Secondary's Objectives

- To analyze the influence of 14 weeks of combined exercise training, alone and in association with taurine, on levels of pro and anti-inflammatory cytokines, oxidative enzymes, physical fitness parameters and global cognition of elderly women;

- To verify the correlations between markers of blood-brain barrier permeability, cytokines and cognition, as well the existing association between changes in these parameters over time;

- To examine if exercise and taurine supplementation, when administrated together, have an added effect in modulating changes in blood-brain barrier permeability, inflammatory balance, physical fitness and cognitive profile of the elderly, compared to the isolated interventions;

2. LITERATURE REVIEW

2.1. Aging

The recognition that aging is a process that affects many functions, including the cognitive, biological or physical functions of every person is not new. Even in the Bible there are passages wrote in 1.400 b.C. which says that aging affects everybody (*The measure of our life is seventy years; and if through strength it may be eighty years, its pride is only trouble and sorrow, for it comes to an end and we are quickly gone*, Psalm 90:10). Although a universal process the quality of aging, more specifically the factors that affect health, tend to be traced differently to each person.

Ways of promoting healthy aging and longevity remain the focus of research challenges in the field of biomedicine (Brooks-Wilson, 2013). In the last decades the discoveries in "*geroscience*", which aims to explain biological mechanisms of aging, have provided insights into molecular and physiological processes that generate biological aging and, more importantly, the potential interventions to delay aging and promote healthy longevity (Kaeberlei, M., Rabinovitch, P.S. Martin, 2015). The increase in longevity, and hence the growth of the world elderly population, makes it important to develop aging-related research in these individuals, especially those over 80 years old. Due to the morphophysiological, psychological and socioeconomic characteristics, this type of population has different features from the "young old" (60-65 years old). In this sense, the older a group of people is, the greater the variability of physical, mental, and social functions relative to other ages (Plouffe, 2003; Charles and Carstensen, 2010; Jaspers *et al.*, 2017).

An increase in the elderly population brings with it the increase of, at least, one or more types of chronic diseases. However, this does not mean an increase in limitation or physical dependence *per se*, although the control of these and other variables can be determinant to promote quality of life of this population (Juster, 2001; Paúl, Ribeiro and Teixeira, 2012). This is understandable, when it beneficiates not only the prolonged life and longevity, but also the increase in health in the remaining years of life of these older persons (Jaspers *et al.*, 2017). There is a wide range of risk factors that compromise the quality and lifespan of these individuals and, even with a large number of cross-sectional studies addressing the relationship between disease biomarkers and aging, it is still very difficult to clearly establish the relationship between them (Kaeberlei, M., Rabinovitch, P.S. Martin, 2015), because aging is not a phenomenon that occurs in isolation, but is accompanied by a series of biological, psychological, social and economic changes. Even

under this complexity, it is consensual that an healthy life-style and physical exercise are powerful components to promote health aging, mainly due to improvements on multiple structures of the organism, even in advanced ages (Chedraui and Pérez-López, 2013).

At older ages, the concepts of health-related quality of life are strongly determined by early life-styles, which mainly include family history of diseases, eating habits, levels of physical activity and sports practice, exposure to chemical agents or psychological stress, among other factors (Table 02). Due the interaction between these processes, quality of aging is far from a simple consequence. In fact, aging quality is a complex network of intrinsic and extrinsic interactions, and it is impossible to determine a context of "health" or "disease" in the elderly based in just one factor.

Table 2.0. Determinants of health and illness during aging

Domain	Measurable Component
Genetic	Genetic predispositions/family history of disease
Life-long	Levels of physical activity Sports practice
	Nutritional habits Tobacco and alcohol use
	Chemical exposure/climate
	Psychological stress Family relationship/leisure activities

Senescence is characterized by an accumulation of metabolic byproducts, are individualized, and lead to a progressive and deleterious loss of several bodily systems, ultimately resulting in loss of reproductive potential and increased probability of death (Arking, 2006). Different from “aging”, senescence now is viewed as age-independent and is not time-dependent, although the changes involved accumulate over a life span making it age-related (Crews, 2007).

2.2. The Aging Immune System - Immunosenescence

As mentioned above, senescence is a complex mechanism that involves molecular, cellular, tissue, and organismal changes (Lipsky and King, 2015). Among these life-time alterations, changes in immune system are some of the most determinant susceptible modifications by which the individual “ages” (Fülöp *et al.*, 2016). The human

immune response acts in two different, but even closely and interrelated pathways: the innate response and the adaptive response (Solana *et al.*, 2012; Male *et al.*, 2013).

From an immunologic point of view, the influence of aging in immune response is widely affected by the rate at which the naïve B and T cells are produced, beyond (and not excluded), the arrangement and quality of the mature lymphocyte pool (Weiskopf, Weinberger and Grubeck-Loebenstein, 2009; Montecino-Rodriguez, Berent-Maoz and Dorshkind, 2013). In a cascade of events, these changes in an aged immune system lead to a decline of the immune response in the elderly. An increase of differentiation from CD4+ Th cells into Th17 cells occurs, which lead to an increased low grade systemic inflammation related to chronic diseases (van der Geest *et al.*, 2014).

The innate response represents the first line of defense against pathogens. The aged immune system is commonly linked with a decreased function of epithelial barriers of the skin, as well as of the lung, and gastrointestinal tract, allowing pathogenic agents to invade the mucosal tissues, leading to an amplified challenge for the elderly body (Gomez, Boehmer and Kovacs, 2005; Nomellini, Gomez and Kovacs, 2008).

Beyond the phagocytic cells such as macrophages and monocytes, and the natural killer cells (NK), several soluble mediators are important for the innate immune system, including cytokines, chemokines and reactive oxygen and nitrogen species (RONS) (Weiskopf, Weinberger and Grubeck-Loebenstein, 2009). An elevation in blood levels of interleukins such as interleukin 1-beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are well known and exhaustively described in the literature to be predictive markers of functional disability, frailty and mortality in elderly individuals (O'Mahony *et al.*, 1998; Ershler and Keller, 2000; Bruunsgaard *et al.*, 2003; Weinstein *et al.*, 2017). It is suggested that the mechanisms by which an age-related increase in cytokines occurs, contribute significantly to a repeated stimulus of the immune response, and lead to a subclinical inflammatory status known as "*inflammaging*" (Franceschi *et al.*, 2006).

Together, these changes in an aging immune system result in a decreased immune function (or immune suppression) in the elderly. This framework proposes that there is a risk factor related to *inflammaging* on the development of several pathological conditions such as, and not only, neurodegenerative (Van Eldik *et al.*, 2016; Schwab and McGeer, 2017), and cardiovascular (Libby, 2002; Lowe, 2005) diseases.

While most studies concerning *inflammaging* are devoted to understand the mechanism by which a decline in immunological function occur, there is a growing number of studies focusing on behavioral patterns and its role in modulation of the immune system in the elderly, like regular exercise, for example, and it's potential to induce beneficial changes in immune system (Forti *et al.*, 2014, 2016; Chupel *et al.*, 2017).

2.2.1. The role of the inflammatory response

The inflammatory process is a part of the complex biological responses that occur after cellular damage, which can be mediated by intrinsic or extrinsic processes. In an equilibrium context, inflammation is generally beneficial to the body since it may act by limiting the survival and proliferation of invading pathogens, or by increasing tissue survival and promoting repair (Abbas and Janeway, 2000).

Inflammation is (generally speaking) the body's immediate response to a stimulus that causes damage to tissues and cells by pathogens. The acute form known as "acute inflammation" is a short-term response that usually results in repair of injury, when leukocytes penetrate the damaged region and remove the stimulus to heal the tissue. This stimulus can be promoted by an external agent like a virus or bacteria, or even caused by physical or mental stress. On the other hand, "chronic inflammation" is a prolonged and dysregulated response that involves active or repeated inflammatory processes, resulting in tissue destruction after efforts of tissue repair. As described earlier, such persistent inflammation is linked to many chronic human conditions of disease. Several neurodegenerative diseases are also related to the quiescent chronic and systemic inflammation, playing an important role on the genesis of Alzheimer, Parkinson and other central nervous system (CNS) related diseases (Rossi *et al.*, 2014; Schwab and McGeer, 2017; Tiwari and Pal, 2017).

The immune responses are mediated by a variety of cells, and the soluble molecules which they secrete against the stimulus. Although the leucocytes are central to all immune responses, other cells in the tissues also participate in this process by signaling to the lymphocytes and responding to the cytokines released by T lymphocytes and macrophages (Male *et al.*, 2013).

Inflammatory processes are developed and sustained by the release of chemical mediators such as vasoactive amines, peptides, cytokines, platelet activation factors, superoxide radicals and arachidonic acid derivatives. In these, cytokines deserve special attention, since they are essential to the functions of macrophages (Duque and Descoteaux, 2014). As inflammatory mediators, cytokines link innate and adaptive immunity and influence the macrophage microenvironment (Unanue *et al.*, 1976; Huynh *et al.*, 2007). There are several subclasses of macrophages depending on their origin, location and activation site. They may also differ on the cytokines that they secrete, and hence, their functions (Biswas and Mantovani, 2010; Duque and Descoteaux, 2014).

2.2.2. Inflammation and Cognition

The organic basis of age-related cognitive impairment is not completely understood, in part because aging in humans relates to several age-related diseases conditions which complicate the attribution of causality. However, extensive and prolonged or unregulated inflammation is highly harmful, and can severely affect endocrine, metabolic, and cognitive functions.

As mentioned above, *inflammaging* is frequently used to describe the organic responses resulting from an imbalance in the immune system that results in an over inflamed environment mediated by high levels of pro-inflammatory cytokines secretion during aging. It is precisely the triggering of these inflammatory cascades that play a key role in the appearance of neuronal damage in the neurodegenerative process (Song *et al.*, 2009). Evidences from large-scale, observational epidemiological studies point to a rather consistent relationship between systemic inflammatory cytokines and dementia or cognitive impairment. A recent review from Gorelick (Gorelick, 2010) highlights several epidemiologic and clinical trials demonstrating the effect of age-related inflammation on cognition.

In Alzheimer's disease, for example, the formation of beta-amyloid plaques and the neurofibrillary webs in the cerebral cortex are the main events related to the neurodegenerative process. These circumstances alone are already capable of activating a pro-inflammatory response by microglia and astrocytes (Wyss-coray and Rogers, 2012), where the activation of glia often results in overproduction of pro-inflammatory cytokines (Van Eldik *et al.*, 2016), further contributing to increased neurotoxicity and enhancing

the neurodegenerative condition (Takeda, Sato and Morishita, 2014). Evidence suggests that the neurodegeneration mediated by inflammation involves primarily the activation of macrophages. This process induces the production of cytokines and free radicals who promote tissue damage (Jou *et al.*, 2013).

Literature describes with particular attention the increased expression of IL-1β, IL-6, and TNF-α cytokines as mediators of a neuroinflammatory process, and their role in neuronal and brain endothelial cells injury are important in the development of cognitive impairment and neurodegeneration (Wang *et al.*, 2015). The promotion of this inflammatory environment in the brain occurs not only by the microglia-released cytokines (Smith *et al.*, 2012), but is also facilitated by the "open door" of the blood-brain barrier (BBB) breakdown mediated by circulating pro-inflammatory mediators (Argaw *et al.*, 2006; Förster *et al.*, 2008).

An increasing number of clinical and cross-sectional evidences suggests that age-related inflammatory mediation contribute directly and indirectly to cognitive changes (Gimeno *et al.*, 2008; Simen *et al.*, 2011; Narasimhalu *et al.*, 2015), since increased peripheral levels of IL-6 and TNF-α, in association with elevation of circulating cortisol, were described recently as inducers of smaller hippocampal volume in the elderly (Sudheimer D. *et al.*, 2014). Immune cascades could be repeatedly activating by cytokines, which then induce increases in unbound cortisol. This unbound cortisol can cross the BBB and affect the hippocampus (Sudheimer D. *et al.*, 2014).

Regardless of a limited ability to cross BBB, several evidences show the negative role of peripheral cytokines in the neuronal environment, either by promoting BBB injury or by the activation of cytokines in the CNS via neural signals mediated by endothelial, astrocytes and glial cells (Quan and Banks, 2007; Yirmiya and Goshen, 2011).

2.3. The Blood-Brain Barrier: Historical concerns, Structure and Function

For a proper functioning of the brain, the neural signaling inside the central nervous system (CNS) requires an extremely controlled environment, and one of the key interfaces that is responsible for this control between the blood and the CNS is the blood–brain barrier (BBB) (Abbott *et al.*, 2010). The term "barrier" was coined by Lewandowsky, who noted that neurotoxic compounds led to neuronal cell death only if

applied directly to the brain, but not after systemic injection on vascular circulation (Liebner, Czupalla and Wolburg, 2011).

The BBB is a lipophilic and delicate structure formed by endothelial cells that control trafficking of substances between the blood and the brain, and: 1) act as a "shield" of brain from potential blood-borne toxins; 2) meet the metabolic demands of the brain; 3) regulate the CNS environment for neuronal function (Andreone, Lacoste and Gu, 2015).

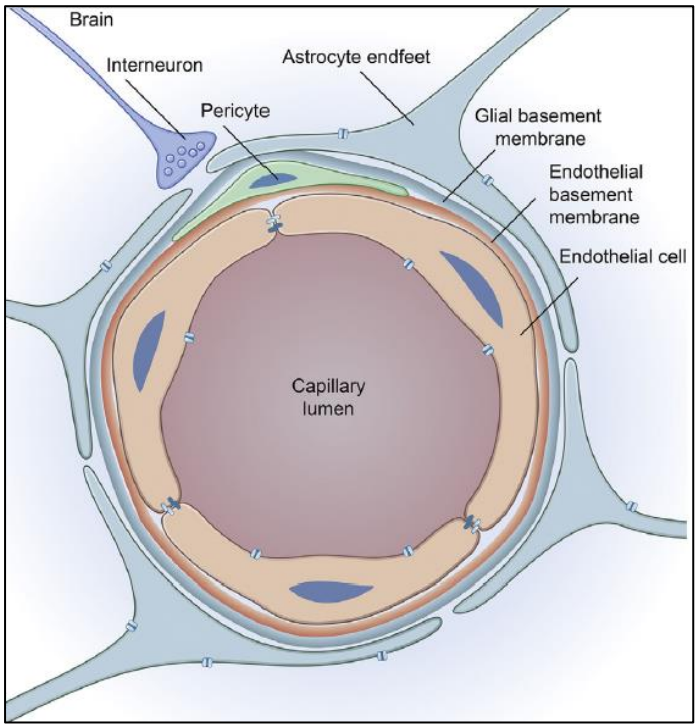

Figure 2.0. Structural representation of the Blood-Brain Barrier.
The BBB is composed by endothelial cells connected by tight junctions (TJ), surrounded by basement membrane and pericytes, with astrocytic end-feet forming internal layer. Adapted from (de Wit *et al.*, 2017).

The BBB cells are connect by tight junctions (TJ), that do not allow mass flow of water and solutes (Paulson, 2002). These structures are essentially responsible for the restriction and control of the paracellular flux between the endothelial and epithelial cells (Liebner, Czupalla and Wolburg, 2011). Recently, the importance of crosstalk among TJ proteins has been showed and pointed out as a regulatory mechanism to the restrictive barrier junction (Tietz and Engelhardt, 2015). The proteins component of TJ such as occludin, claudin, tricellulin and junctional adhesion molecules not only perform a role on cell-cell adhesion structure, but integrates several signaling pathways that involves

cell proliferation, cytoskeletal rearrangement, and transcriptional control as well (Chiba *et al.*, 2008; Bauer *et al.*, 2014; Bauer and Traweger, 2016).

The functioning of the BBB is mediated by a combined working of three interfaces (the endothelial cells that form the "wall" of capillaries, the epithelial cells of choroid plexus, and by the avascular arachnoid epithelium). All these interfaces act simultaneously in providing a proper function of the BBB, forming physical, transport and metabolic barriers (Abbott *et al.*, 2010). Thus, the CNS capillaries are comprised by a single and non-fenestrated continuous endothelial cell layer (Chow and Gu, 2015). The CNS endothelial cells, pericytes, astrocytes and neurons collectively form a functional neurovascular unit (NVU), the functional structure of the BBB (Obermeier, Daneman and Ransohoff, 2013).

2.3.1. The BBB delivery system

Different from the peripheral endothelial cells, the CNS endothelium displays minimal vesicular trafficking between the luminal and abluminal plasma membrane - or transcytosis (Tuma and Hubbard, 2003) however, although limited, it remains the ideal pathway for the selective transport of macromolecules in plasma such as albumin and low density lipoproteins (Xiao and Gan, 2013). The restrictive transcytosis also allows the BBB to use highly polarized cellular transporters to regulate the influx of necessary nutrients and efflux of metabolic waste and toxins (Chow and Gu, 2015). The BBB has specific transport systems for essential nutrients and metabolites to the brain, since it has structurally low passive permeability to many water-soluble molecules (Abbott *et al.*, 2010). In this way, the transport of substances between the blood and the brain includes not only transcytosis but also involves solute carriers (ex. glucose, amino acids transporters and small peptides (Smith, 2000), passive diffusion and ATP-binding cassete transporter efflux (lipid soluble and non-polar molecules and conjugates), and mononuclear cell migration (leukocytes, monocytes, and macrophages) (Banks, 2009). The transports mechanisms across the BBB are very well described in Begley's review study (Begley, 1996).

The synthesis of catecholamines and serotonin (5-HT) in the brain is dependent on specific amino acids entrance across specific channels of the BBB. Examples of these include the amino acids tryptophan and tyrosine, where the first is the precursor of 5-HT and the last one is involved in the synthesis of noradrenaline, adrenaline and dopamine

(Upadhyay, 2014). Evidence shows that changes in the proper delivery of amino acids are related to the genesis of some pathological conditions in the brain, such as depression (Steiner *et al.*, 2012). Dysfunctions of the BBB delivery system are not only related to depression, but also, the appearance of several neurodegenerative conditions is associated with deterioration, leakage or malfunctioning of this structure. In Alzheimer Disease (AD) for example, the deterioration on the BBB are related to the increased accumulation of plaque amyloid-beta in the brain (Kook *et al.*, 2013; Deo *et al.*, 2014). Also, in Parkinson Disease, the malfunctioning on the BBB increases endotoxin entrance in the brain which aggravates the symptoms (Lange, Niehaus and Cegolon, 2016; Thiollier *et al.*, 2016). Likewise, cognitive dysfunction such as mild cognitive impairment (MCI) were recently related to the appearance of BBB lesions (Taheri *et al.*, 2011; Stranahan *et al.*, 2016). BBB permeability increases in normal aging and further increases in patients with dementia (Farrall and Wardlaw, 2009). As occurs with many organs in the human body, there are biological, physiological and mechanical mechanisms that affect the operation and integrity of them. When this "interference" is harmful, the onset of several diseases related to malfunction of the organ may occur. In the brain, the malfunctioning of the BBB is thought to be involved in the genesis of the various pathologies listed above. However, an important question remains: which mechanisms are involved in BBB dysfunction?

2.3.2. BBB Dysfunction: how and why occurs?

BBB dysfunction is the result of acute or chronic events that may range from factors like impacts and concussion (Chodobski, Zink and Szmydynger-Chodobska, 2011) to the imbalance of physiological processes mediated by inflammation and over formation of free radicals (Abbott, 2000; Freeman and Keller, 2012; Enciu, Gherghiceanu and Popescu, 2013). Age appears to be an important factor in the increased dysfunction of the BBB, since there is evidence that points to a relationship between aging and permeability of the BBB (Mooradian, 1988; Takechi *et al.*, 2013; Montagne *et al.*, 2015). Accordingly, the onset of neurodegenerative disorders such as AD and Parkinson's disease is mostly observed in the elderly. At the same time, the cognitive deficits present in this population also raises the suspicion that the deterioration of the BBB and brain illness have a very close relationship (Erickson and Banks, 2013; van de Haar *et al.*, 2016).

Due the difficult to access the integrity of this structure *in vivo*, several peripheral biomarkers in the last decades, such as S100β and neuronal specific enolase (NSE), have been proposed as indicators of the extent of BBB damage. The protein S100β being proposed to be a putative marker for this evaluation in humans (Marchi *et al.*, 2004).

About 80 to 90% of S100β is expressed by astrocytes and oligodendrocytes, and located in the brain where it is distributed specially around the white matter structure (Streitbürger *et al.*, 2012). Some extracranial sources of S100β were also found in adipocytes and skeletal myoblast cells (Michetti *et al.*, 1983; Tubaro *et al.*, 2010). Quantitative measures of S100β can be established in biological fluids such as peripheral blood (plasma and serum), urine, cerebrospinal fluid and breast milk (Chong *et al.*, 2016). In blood, S100β has been related to BBB permeability, leading to its use as a peripheral marker for BBB dysfunction (A. a Kanner *et al.*, 2003; Marchi *et al.*, 2003, 2013; Blyth *et al.*, 2009; Takechi *et al.*, 2010; Dadas *et al.*, 2016). When the BBB is intact increases in CSF S100β do not result in increased levels in serum, however, a leakage in BBB lead to a rise of S100β levels in blood due to its extravasation to the peripheral circulation (Marchi *et al.*, 2004). Furthermore, despite the existence of S100β expression by other tissues, Pham and co-workers (Pham *et al.*, 2010) induced intraarterial mannitol to disrupt the BBB and used western blot techniques to quantify the blood levels of this protein, concluding that the extracranial sources of S100β do not influence serum levels. Imaging analysis also showed a correlation between serum S100β levels and disruption of BBB in humans (Marchi *et al.*, 2013), leading to use of this protein as a relatively non-invasive and easy peripheral method to monitoring BBB permeability in clinical and research practice (Blyth *et al.*, 2009).

The recognition that dysregulation of the immune system can cause structural damage to the tissues, lead to the hypothesis that there was a relationship between the increased inflammatory levels with injuries on brain endothelial cells (Argaw *et al.*, 2006; Cheng *et al.*, 2016; Dash *et al.*, 2016; Elwood *et al.*, 2017). At the same time, the increased production of reactive nitrogen and oxygen species (RONS) related to immunosenescence lead many researchers to study the possibility that both, inflammation and oxidative stress, could lead to BBB damage and their consequences in brain health (Barichello *et al.*, 2011; Al Ahmad, Gassmann and Ogunshola, 2012).

2.3.3. Inflammation and Blood-Brain Barrier permeability

The brain was considered as an “immune-privileged” organ, since it was thought to be isolated from the peripheral immune system. However, now it is known that the CNS is an active surveillance site, with bi-directional communication between the brain and the peripheral immune system (Holmes and Butchart, 2011). The way such communication is established is through the BBB, and the contact with several pro and anti-inflammatory cytokines produced by the immune cells in the peripheral circulation draws attention to its role in brain illness during chronic systemic inflammation. The recognition that the BBB dysfunction is involved with the immune system imbalance is evidenced by the BBB dysfunction in several disease conditions, such as Alzheimer Disease, Multiple Sclerosis and other CNS disorders, that are immune suppressed-related diseases (Zlokovic, 2008).

During pathologic processes, the affected BBB may not have the same response to inflammation compared to the healthy one, since even subtle BBB alterations in the initial stages of illness could make it more susceptible to systemic inflammation, and particularly may predispose to dysfunction (Varatharaj and Galea, 2016).

Monocytes and inflammatory mediators such as prostaglandins can directly entry through the BBB and are recognized to be important communication pathways between the brain and the peripheral immune system. This explains why alterations in peripheral immune activity can affect several immunological responses in the brain (Takeda, Sato and Morishita, 2014).

Cytokines and other immune modulators (e.g., lipopolysaccharide and prostaglandins) play several roles in BBB functions. The interactions between BBB and interleukins, interferons, neurotrophic factors, smaller neurotrophic peptides, and adipokines have been studied in neuropathology (Banks, 2005). Cytokines and other mediators of inflammation can disrupt the BBB structure, but at the same time can modulate BBB saturable transport systems. Even those transport mechanisms that carry immune-active and neurotrophic substances can be affected by injuries in BBB mediated by inflammation (Banks and Erickson, 2010). The process by which immune cells can cross the brain endothelial barrier is called ‘diapedesis’. The diapedesis is more transcellular rather than paracellular for certain types of cells, whereas some evidence suggest that other cell types may use paracellular route. The paracelluar pathway involves

the passage of immune cells through the epithelium, between the endothelial barrier (across the TJ). On the other hand, in the transcellular pathway the immune substances travel through the endothelial cell of the BBB. (Engelhardt and Wolburg, 2004).

A great number of peripherally produced cytokines, including those that play a role on neurotrophic activity, are transported through the BBB in amounts that affect proper CNS function. These transporters suffer complex changes in response to CNS injury (Pan and Kastin, 2008), specially because the regulation of transport in pathophysiological conditions affects the extent of neuroinflammation and result in neurodegeneration (Pan and Kastin, 2016).

In this context, conditions such as inflammation, autoimmunity, trauma, tumor, hypoxia and other processes altering the cerebral blood flow and metabolism are able to promote changes in transport sites of substances through the BBB (Engelhardt and Ransohoff, 2005).

The endothelial cells of the BBB secrete a host of neuroimmune substances, including cytokines, chemokines and nitric oxide (Fabry *et al.*, 1993; Vadeboncoeur *et al.*, 2003). The release of these substances can, depending on the physiological environment, be constitutive or induced by substances such as lipopolysaccharide. Since the BBB provides a polarized cross-point between CNS and blood, polarized responses may occur (Verma *et al.*, 2006). In this sense, the BBB can respond to a neuroimmune stimulus received from one compartment by secreting into the other, thus forming a communication pathway between the peripheral and CNS tissues (Banks and Erickson, 2010).

Inflammatory mediators are involved in the genesis of several pathologies, but their production is not always related to negative effects. Cytokines are expressed in many ways, and can play an important role during infections, allergies and even cancers. However, one of the most complex examples of molecular networking is seen in infections associated with acute systemic inflammation. While it signals the immune system in the battle against the stressor agent, a continuous and permanent acute inflammation can involve several systems and some structures are threatened by the evolution of the process to systemic inflammation, which can cause severe damage and eventually death (Deutschman and Tracey, 2014). It is, in this scenario, that some cytokines play a damaging role in the BBB structure, because the molecular composition

of BBB tight junctions is changed during CNS inflammation, which is generally accompanied by BBB leakiness (Wolburg *et al.*, 2003).

Among the cytokines who play a role in BBB integrity are the IL-1β and IL-1α. Both are examples of cytokines from a family of 11 know members that are ligands for receptors within the IL-1R-family (Garlanda, Dinarello and Mantovani, 2013). Although acting in different pathological processes and sharing less than half of protein sequence identity, IL-1α and IL-1β induce similar responses since they bind to the same receptors.

However, the expression of both are different: while IL-1α is expressed in epithelial, endothelial, and astroglia cells, IL-1β is mainly expressed and released by monocytes and phagocytes in response to danger associated molecular patterns, immune complexes, and pro-inflammatory cytokines such as TNF-α and IL-6 (Schroder and Tschopp, 2010). Its function is controlled at various levels, and the activation occurs as a two-step process: first, in unstimulated cells, IL-1β is expressed as a pro-peptide, but at very low levels and as an inactive form. Un upregulation and transcription of IL-1β mRNA is induced and after translated as the IL-1 precursor protein. In case of infection this process can occur after activation of pattern recognition receptors such as Toll-like receptors (Schroder and Tschopp, 2010). Second, intracellular enzymes cleave the pro-IL-1β into a biologically active 17kD molecule. Then, IL-1β in mature form is secreted and binds to the IL-1 receptor to exerts its biological function (Schett, Dayer and Manger, 2016).

The chronic expression of IL-1β is one of the factors responsible for the loss of integrity of the BBB, because it can act as an inducer of neutrophil recruitment (Ferrari *et al.*, 2004), or by reactivating the hypoxia-angiogenesis axis (Zhang *et al.*, 2000; Argaw *et al.*, 2006). In both animal and human models, it is shown that a high proinflammatory activity is directly associated to the increase in BBB permeability. IL-1β has been suggested to play an important role in upregulating the expression of several proinflammatory mediators, including adhesion molecules and many chemokines (Gibson, Rothwell and Le Feuvre, 2004). Since IL-1β acts through the IL-1 receptor 1, their activity can be blocked by interleukin 1 receptor antagonist (IL-1ra), which reduces the BBB dysfunction mediated by IL-1β (Boutin *et al.*, 2003; Mina *et al.*, 2014). More precisely in humans, recent evidence shows that the inflammatory balance, in this case mediated by IL-1ra levels, plays an important role in maintaining a good inflammatory

balance in the brain, accompanied by an attenuation of the loss of BBB integrity (Michael *et al.*, 2016).

Not only IL-1β but also TNF-α is part of a group of cytokines capable of causing tumor cells apoptosis and, at the same time, has a wide range of pro-inflammatory actions. TNF-α production is primarily performed by macrophages, however, T lymphocytes, mast cells, natural killer (NK) cells, endothelial cells and astrocytes can also produce it. A variety of stimuli, such as endotoxins, viruses and lipopolysaccharides can cause exacerbated production of TNF-α by macrophages, contributing to the amplification of the inflammatory process (Male *et al.*, 2013).

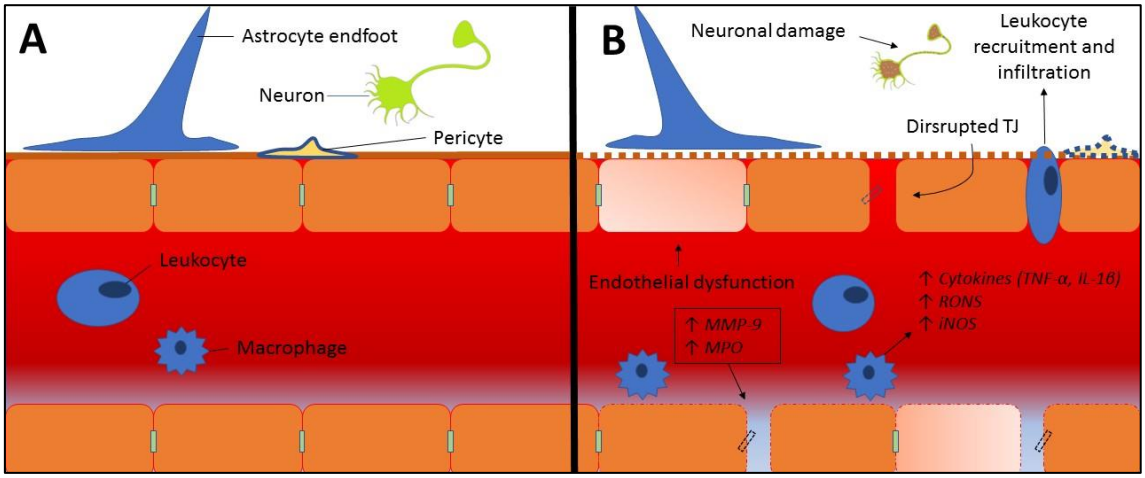

Figure 2.1. The Blood-Brain Barrier in "normal state" (A), and during systemic inflammation (B).

The BBB is primarily composed of endothelial cells connected by tight junctions (TJ), and a thin pericyte layer. A basement membrane and a layer of astrocytes endfoots surround the barrier. During systemic inflammation (B), an increase in circulating cytokines (such as IL-1β and TNF-α), chemokines, and reactive oxygen and nitrogen species (RONS), increase the BBB lesions and hence it permeability. An increase in matrix metalloproteinase-9 (MMP-9) and myeloperoxidase (MPO) contribute to the TJ disruption and barrier dysfunction. The macrophage induction of cytokines release deteriorates protein components of the BBB, which also contributes to the leukocyte infiltration and neuronal damage. In the figure, relative proportions are not intended to be realistic. Taken together, these inflammatory and oxidative events lead to the increased toxic components entering in the brain and contributing to the neurodegeneration.

The peripheral elevated production of TNF-α can affect the BBB structure by several mechanisms, like changing the TJ cellular distribution and disrupting the endothelial cells, or upregulating the NF-kB expression, and inducing the transcription of myosin light chain kinase, a factor that is known to induce internalization of TJ proteins

(Alvarez, Cayrol and Prat, 2011; Wu *et al.*, 2016). Beyond disruption of TJs, another way by which the elevated levels of TNF-α in blood can affect the BBB permeability is through loss of the TJ-associated protein occludin (Lv *et al.*, 2010) and by decreasing the components of the basal lamina (Reyes *et al.*, 2009). In addition to the involvement of TNF-α on inflammatory amplification, it also acts as a regulator to the generation of reactive oxygen and nitrogen species (RONS) (Blaser *et al.*, 2016), which in turn contribute to increase BBB susceptibility to breakdown. Proof of this is the fact that elevated levels of TNF-α in the blood induce the activation of matrix metalloproteinanse-9 (MMP-9), an oxidative enzyme involved in the degradation of the BBB (Tsuge *et al.*, 2010).

Interestingly, the microenvironment created by TNF-α together with RONS alters cytokine response by terminally differentiated cells, targeting the Th17 cells in autoimmune disorders (Wang *et al.*, 2013; Abimannan *et al.*, 2016). In fact, Th17 cells which are defined by the production of IL-17, are associated with chronic inflammatory disease, being overexpressed in patients with chronic obstructive pulmonary disease (Cazzola and Matera, 2012; Tan and Rosenthal, 2013), rheumatoid arthritis (Lee and Bae, 2017) and lupus (Abdel Galil, Ezzeldin and El-Boshy, 2015). This cytokine acts together with other cytokines like TNF-α, IL-6 and IL-8 (Miossec, 2017).

Controlling the extent of neuroinflammatory responses in disease may be beneficial, since brain endothelial inflammation has been associated with adverse outcomes in the elderly. To do that, the right balance between pro and anti-inflammatory secretion is critical in maintaining a normal immune homeostasis. In fact, considering the existing immune-communication between periphery and brain (Engelhardt and Ransohoff, 2012), it is important to suppress the excessive expression of blood circulating pro-inflammatory cytokines namely by the secretion of anti-inflammatory ones. Involved in these process is the anti-inflammatory cytokine interleukin 10 (IL-10).

Actions mediated by IL-10 in the brain include the inhibition of expression of pro-inflammatory cytokines in microglia, and induction of TGF-β production by the astrocytes (Norden *et al.*, 2014). Since its identification over two decades ago (Fiorentino, Bond and Mosmann, 1989), IL-10 has been described as able to suppress several inflammatory events such as production of pro-inflammatory cytokines like interferon-γ (IFN-γ), IL-1, IL-6 and TNF-α by macrophages and lymphocytes (Mittal and Roche, 2015; Lobo-Silva *et al.*, 2016). Furthermore, IL-10 inhibits the leukocytes adhesion to the

endothelium and the increased production of free radicals and nitric oxide by macrophages (Krakauer, 1995; Csuka *et al.*, 1999). In fact, recent evidence shows that IL-10 mediated several immune regulatory mechanisms in brain, suppressing the astrocyte inflammatory transcriptional program and stabilization of the BBB leakiness (Mayo *et al.*, 2016).

As briefly mentioned above, the peripheral formation of pro-inflammatory cytokines has a close relationship with the formation of RONS, leading to oxidative stress. This event is intimately related with the increase in BBB permeability, leading to brain endothelial and neuronal dysfunctions (Mariani *et al.*, 2005). This phenomenon is more frequently related to be age-dependent, since *inflammaging* is associated with increased RONS production. Moreover, age-related impairment in several body structures has been characterized by an increase in intracellular free radicals resulting in oxidative stress, due to the progressive reduction in intracellular RONS scavenging (Minelli *et al.*, 2009).

2.3.4. Oxidative Stress and BBB dysfunction

A great number of studies, in a variety of designs, show that the production of RONS is involved in several (if not all) neurodegenerative diseases. An equally large number of studies show that oxidative stress occurs in the early stages of the disease, and is closely related to the impairment of cognitive and motor functions that often accompanies many CNS pathologies. In these and other pathological processes, BBB plays an important role in controlling the brain environment, and the oxidative events that lead to increased permeability/dysfunction of this structure have been studied in recent years in animal model (Takemori *et al.*, 2013; Banks *et al.*, 2015), humans (Duits *et al.*, 2015), *in vitro* techniques (Zehendner *et al.*, 2013) and was object of several scientific based reviews (Freeman and Keller, 2012; Dias, Polidori and Griffiths, 2014).

Regarding the structure of BBB, the endothelial cells that form the protective layers of the CNS are different from those found in the rest of the body. Even so, they are equipped with a defense against oxidative stress that includes enzymatic and non-enzymatic antioxidants, such as GSH, glutathione peroxidase, glutathione reductase and catalase. Particularly, GSH plays an important role in maintain the BBB integrity against oxidative threats (Agarwal and Shukla, 1999). However, the increased activity of enzymes such as myeloperoxidase (MPO) and matrix metalloproteinases (MMPs) may

contribute to exceed the normal condition and surpass the antioxidant defense, leading to BBB dysfunction.

2.3.5. Myeloperoxidase and Matrix-Metalloproteinase-9 – an oxidative pathway

Myeloperoxidase (MPO) is a myeloid-lineage enzyme with strong antibacterial properties, is largely expressed by neutrophils and is the most toxic enzyme found in the azurophilic granules of this cells (Strzepa, Pritchard and Dittel, 2017). MPO is also produced by macrophages/microglia in pathological conditions (Nagra *et al.*, 1997). The major role of MPO is to catalyze the formation of hypochlorous acid (HOCl), a powerful chlorinating oxidant which is suggested to be critically involved on microbicidal properties and host defence (Eiserich *et al.*, 1998; Kettle *et al.*, 2007).

MPO is involved in pathophysiological mechanisms of cardiovascular disease (Nicholls and Hazen, 2005; Heslop, Frohlich and Hill, 2010; Anatoliotakis and Deftereos, 2013), diabetes (Gómez García *et al.*, 2015), chronic kidney disease (Kisic *et al.*, 2016), and neurodegenerative conditions (Green *et al.*, 2004; Ray and Katyal, 2016; Gellhaar *et al.*, 2017). In coronary dysfunction, MPO has been used in clinical practice as a marker to predict mortality (Mocatta *et al.*, 2007; Heslop, Frohlich and Hill, 2010).

Among several mechanisms by which MPO is implicated in the pathogenesis of cardiovascular disease is the oxidation/modification of LDL and HDL (resulting into uptake by macrophages and perpetuation of foam cell formation), disruption of the atherosclerotic plaque through activation of MMP's, and by consumption of endothelium-derived nitric oxide (NO) leading to reduced bioavailability and dysregulation of its vasodilatory and anti-inflammatory properties (Hazen and Heinecke, 1997; Heslop, Frohlich and Hill, 2010; Nussbaum *et al.*, 2013).

MPO concentration is lower in physically active people rather than sedentary controls, independently of sex, age, body mass index, cholesterol levels and cardiovascular disease risk factors (Autenrieth *et al.*, 2011), suggesting that physical activity may modulate MPO levels. In fact, a large prospective case-control study carried out in the European population showed that MPO were positively correlated with waist circumference and offered a prognostic value for the risk of developing cardiovascular disease over a 10-year follow up in sedentary women (Rana *et al.*, 2011).

These studies suggest the importance of exercise inducing the anti-oxidant and anti-inflammatory mechanisms that might contribute to inhibit MPO activity and decrease disease risk.

The effects of MPO in the brain are emerging in the literature, however, data in humans is still scarce. In the murine model, for example, MPO-generated oxidants play detrimental roles by causing brain damage after stroke (Yu *et al.*, 2016). The inhibition of MPO activity also restores the BBB integrity in mice models of multiple sclerosis (Zhang *et al.*, 2016). In fact, Üllen and co-workers (Üllen *et al.*, 2013) showed that a significant reduction of HOCl (MPO derivate oxidant) improves the BBB integrity, and an induction of MPO-pathway induces BBB dysfunction under inflammatory conditions.

In general, the steps of immune regulation such as repair and defence, depend on the cell types involved and requires simultaneous inflammatory responses. As mentioned earlier, some oxidative enzymes act in several phases during inflammation and, more specifically, the matrix metalloproteinases (MMPs) regulates various inflammatory and repair processes. Consequently, they might represent an initial step in the evolution of the immune system (Parks, Wilson and López-Boado, 2004).

Metalloproteinases represent the main class of proteases with catalytic properties and, as their names imply, they are responsible for turnover and degradation of the extracellular matrix (Parks, Wilson and López-Boado, 2004; Rivera *et al.*, 2010). Normally, MMPs are not expressed in healthy human tissues, however, they can be highly detected in repair or remodeling processes of disease and inflamed tissues (Gozdzialska *et al.*, 2016; Gao *et al.*, 2017). Members of MMP family are upregulated in several inflammatory disorders, playing a particular role in inflammation (Nathan, 2002; Parks, Wilson and López-Boado, 2004).

Specifically, the MMP-9, for example, have been pointed to act directly and indirectly to induce the expression of various cytokines with proinflammatory function, such as IL-1β (Schonbeck, Mach and Libby, 1998) and TNF-α (Gearing *et al.*, 1994). The up-regulation of this enzyme has long been suggested to be involved in several neurodegenerative disorders (Vafadari, Salamian and Kaczmarek, 2016), and the link with neuroinflammation being generated by an imbalance between two processes – the proteases formation and inhibition, tending towards the first one (Vandooren, Van Damme and Opdenakker, 2014).

MMP-9 can impair the BBB integrity by contributing to the release of cytokines and free radicals, or by cleaving TJs between the neurovascular unit (Reijerkerk *et al.*, 2006; Candelario-Jalil, Yang and Rosenberg, 2009), hence contributing to the inflammation of the CNS. In fact, there is some evidence in animal and humans linking the involvement of MMP-9 in increased BBB permeability, caused by T cells and monocytes migration into the CNS and induction of proteolysis (Ludewig *et al.*, 2013; Ljubisavljevic *et al.*, 2015).

2.4. The antioxidant/anti-inflammatory therapy – potential role of taurine

The proposed above frame evokes the importance for anti-inflammatory and antioxidant therapies in the combat of low-grade chronic inflammation related to disease progression. There are emerging attempts to study the role of non-pharmacological therapy for treatment of systemic inflammation and oxidative stress in humans. In this case, exercise is pointed as a potential mechanism to ameliorate health conditions in the presence of clinical pathology, and their association with supplementation have been formed a basis against immunosuppression-related diseases (Pedersen and Hoffman-Goetz, 2000; Kohut and Senchina, 2004; Bjelakovic *et al.*, 2012; Conti *et al.*, 2016).

One amino acid that has received increased attention in recent years is taurine, since it has been linked to anti-inflammatory, antioxidant and hypothetical ergogenic effects (Lee, Paik and Park, 2003; Marcinkiewicz and Kontny, 2014). In animal and human models, taurine has been proposed to upregulate the anti-inflammatory balance in cardiac disease (Lu *et al.*, 2017), to decrease adiposity (Caetano *et al.*, 2017), and to protect the body against the cardiovascular complications of diabetes (Zhang *et al.*, 2004; Ito, Schaffer and Azuma, 2012; Imae, Asano and Murakami, 2014; Sun *et al.*, 2016). Supplementation with taurine has been studied in humans undergoing exercise (where the hypothetical effect on improving performance is suggested), and in patients with inflammatory diseases (where it is suggested as co-adjuvant in the treatment).

A brief description about the role of taurine in health will be given. For a complete comprehension of this topic please see the review paper submitted for publishing in Annex 3.

2.4.1. Taurine – history, structure and function

Taurine (2-aminoethanesulfonic acid, shown in Figure 1) is a β-amino acid, with a sulphonic acid group replacing the characteristic carboxylic group of amino-acids, which is considered semi-essential (Stapleton *et al.*, 1997). Taurine is the most abundant free amino acid in humans and plays an important role in several essential biological processes (Marcinkiewicz and Kontny, 2014). Taurine was discovered by Leopold Gmelin and Friedrich Tiedemann which isolated the compound from the bile of the ox, which in latin is *Bos taurus*, giving the name to the amino acid (Demarçay, 1838; Huxtable, 1992).

The ability of biosynthesis of taurine in humans is limited in newborns, and decreases with aging and in some pathological conditions. The main source of taurine in humans is the diet (Redmond *et al.*, 1998) and the estimated intake is 40-400mg per day (Wójcik *et al.*, 2010). The highest amounts of taurine in food can be found in shellfish, especially scallops, mussels and clams. High amounts can also be found in the dark meat of turkey and chicken, and turkey bologna (Wójcik *et al.*, 2010).

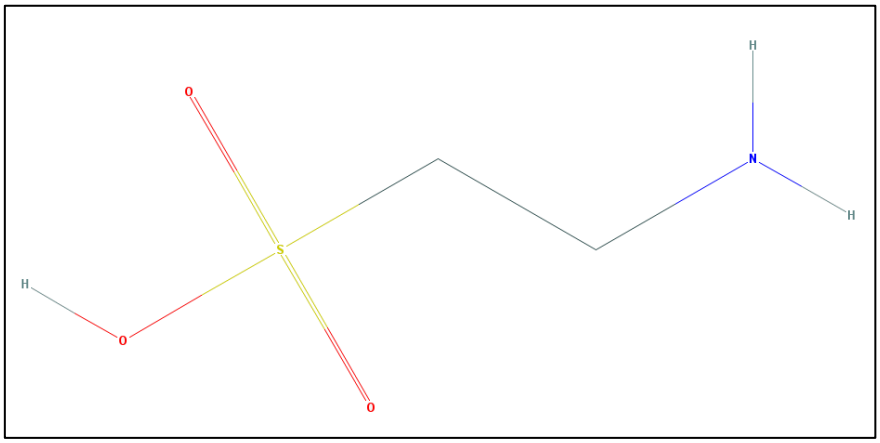

Figure 2.2 Taurine Structure
Source: PubChem, URL: *https://pubchem.ncbi.nlm.nih.gov*

Taurine is kept at an intracellular concentration of 5-20umol/g wet weight (Chesney, 1985), and enters in cells across its transporter TauT, which belongs to a similar class of sodium-chloride dependent transporters of creatine, named as SLC6a6; this

transporter is mostly expressed by mammalian tissue (Uchida *et al.*, 1992). In pathological conditions, it is observed that taurine content in cell is depleted and this event is observed when the cellular transporter is either suppressed by a competitive inhibitor (Jong *et al.*, 2010) or completely depleted (Ito *et al.*, 2010). The explanations for this depletion is that synthesis of taurine in tissues (such as heart and skeletal muscle) is limited, and cells appear to be dependent of the taurine uptake from the extracellular space. Since the average of the concentration in serum seems to be up to 100-fold less than cells (20-100uM), the active transport of taurine (through TauT) uptake works against a concentration gradient (Ito *et al.*, 2010).

In animal model of species that cannot naturally synthesize taurine, this amino acid is classified as an essential amino acid (eg: felines). In these animals, the deficit in taurine intake results in physiological changes that lead to myocardial failure, ocular and skeletal muscle impairment (Son, Kim and H Kwon, 2007; Wójcik *et al.*, 2010; De Luca, Pierno and Camerino, 2015a). Although this level of deficiency is unlikely to occur in humans, these manifestations caused by lack of dietary taurine intake demonstrate that this amino acid plays an important role in controlling various bodily functions. Despite its classification as a semi-essential amino acid in humans, the functional deficiency of taurine in the body can be induced by increasing the intake of beta alanine or guanidininoethanesulfanate (GES), since both compete at the level of the same cellular transporter due to structural similarity (Lake, 1993; Pansani *et al.*, 2012).

Taurine is not involved in protein synthesis, and even being the most abundant free amino acid present in the heart, retina, skeletal muscle, brain and white blood cells (Schuller-Levis and Park, 2003), the effects of this amino acid are not yet completely understood. Several beneficial effects have been described in well controlled clinical studies on the role of Taurine in health: prevention of obesity and increase energy expenditure (Tsuboyama-Kasaoka *et al.*, 2006); maintenance of normal glucose metabolism (Ito *et al.*, 2015); treating cardiovascular diseases including hypertension, hypercholesterolemia and atherosclerosis (Murakami, 2014) by acting positively on cardiovascular system by modulation of Ca^{++} and antagonism action on Angiotensin II (Xu *et al.*, 2008). Other benefits recognized are diminishing the adipocyte diameter (Tsuboyama-Kasaoka *et al.*, 2006) and modulation of insulin (De La Puerta *et al.*, 2010).

Because it is present in large amounts in leukocytes, it is suggested that taurine deficiency can affect immune function of cells (Marcinkiewicz and Kontny, 2014). In

human, taurine is found at particularly high concentrations in tissues that are exposed to elevated levels of oxidants. This may suggest a role in the antioxidant system (Jeon *et al.*, 2009; Oliveira *et al.*, 2010). The taurine haloamines (TauCl and TauBr) potentially useful anti-inflammatory and antimicrobial properties are good candidates for clinical use, especially for local treatment of infectious and inflammatory diseases (Gottardi and Nagl, 2010; Marcinkiewicz and Kontny, 2014). However, the evidence involving low levels of taurine with the deficit on immune system in humans still needs to be investigated.

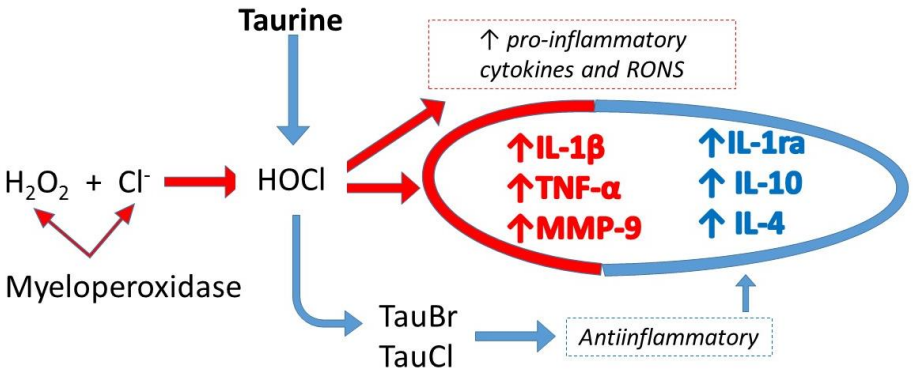

Figure 2.3. Mechanisms by which taurine acts as an anti-inflammatory and antioxidant agent.

The formation of hypoclorous acid by mediation of MPO halide system can be suppressed by taurine reaction with HOCl and formation of taurine bronamine and taurine chloramine, which not react like HOCl but also have anti-inflammatory properties, inducing formation of IL-10, IL-1ra and IL-4. The formation of IL-10, for example, suppress the formation of TNF-α that can be induced by HOCl. The over formation of pro-inflammatory cytokines due to increased MPO activity affect negatively several bodily functions (mechanism indicated by red arrows representing the harmful effect of uncontrolled inflammation and/or oxidative stress). However, the formation of TauBr and TauCl due to supplementation with taurine (and their consequences indicated by blue arrows) can oppose the increased inflammation and act positively in human organism.

As mentioned earlier, myeloperoxidase (MPO) is an enzyme responsible for myeloid-specific generation of hypochlorous acid and other reactive oxygen species (Pattison, Davies and Hawkins, 2012). In this case, nutritional supplementation with taurine may contribute to the local formation of Taurine Chloramine (TauCl) or Taurine Bromamine (TauBr) from reaction with the hypochlorous acid and hypobromous acid (HOBr) (Marcinkiewicz and Kontny, 2014), which in addition to oxidative potential mismatches still have antioxidant properties (Chapman *et al.*, 2009). Both TauCl and TauBr are linked to anti-inflammatory actions, since they act in inhibiting pro-

inflammatory cytokines such as TNF-α, IL-1β and IL-6 (Marcinkiewicz *et al.*, 1995; Barua, Liu and Quinn, 2001; Kim *et al.*, 2011). The action of taurine in inhibition RONS production may be evidenced by enhanced expression of antioxidant enzymes such as Cu/Zn superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), which demonstrate their antioxidant-like effects (Zhou *et al.*, 2011; Marcinkiewicz and Kontny, 2014; Vanitha *et al.*, 2015).

Supplementation with taurine had been demonstrated to play an antioxidant and anti-inflammatory role in treatment of several chronic diseases, such as metabolic syndrome (Xiao, Giacca and Lewis, 2008; Moloney and Casey, 2010; Rosa *et al.*, 2014). Taurine intake also demonstrated positive effects in alleviating symptoms related to hypertension (Kohashi and Katori, 1983).

In brain, taurine plays an important role, not only due to its antioxidant activity, but also because is it recognized to be a neuroprotective amino acid (Saransaari and Oja, 2000). The structural similarity between taurine and γ-aminobutyric acid, as well as the distribution of these amino acids and its precursors and enzymes present abundantly in various regions of the brain, give reasons for taurine to be classified as a neurotransmitter. Moreover, the application of taurine directly to CNS neurons exerts an inhibitory effect on its firing rate (Curtis and Watkins, 1965), which further contributes to the view that it is in fact a neurotransmitter.

Taurine supplementation may alleviate edema and intracranial pressure after traumatic brain injury (TBI) (Wang *et al.*, 2016), that is why some effects in structural brain and neurological functions were also showed after supplementation, supporting its potential administration for clinical implications (Suárez *et al.*, 2016). A dose dependent effect of taurine supplementation was demonstrated in lowering brain edema and BBB permeability, and decreasing activity of superoxide dismutase and malondialdehyde as well, in rats with head injury (Sun *et al.*, 2014; Jamshidzadeh *et al.*, 2017), and may protect brain from neuron damage caused by RONS (Ma *et al.*, 2010).

Regarding exercise practice, taurine has been suggested to play an ergogenic effect in several parameters of performance, ranging from augmenting the exercise time (Lee, Paik and Park, 2003) to decreasing the delayed onset muscle soreness (DOMS) (da Silva *et al.*, 2014). However, the effects of taurine in immune system of exercising elderly were not investigated yet.

2.5. EXERCISE

The prerogative that exercise promotes several benefits has already been exhaustively researched and reviewed, in animal and human models. An increasing number of evidence regarding improvement in cardiovascular health (Jablonski *et al.*, 2015; Alkatan *et al.*, 2016), musculoskeletal (Prior *et al.*, 2014; Chen *et al.*, 2017), and cognitive function (Muscari *et al.*, 2010), is available. The mechanisms by which exercise promotes these benefits are varied, and studies emerged referencing their mediation through – and not only, the improvement of immunity (Chupel *et al.*, 2017), lipid profile metabolism (Veríssimo *et al.*, 2002; Sato *et al.*, 2007), and induction of neurogenesis (Foster, Rosenblatt and Kuljiš, 2011). Comprehensive reviews on this topic are already available (Smith *et al.*, 2011; Coats *et al.*, 2017).

Exercise has a potential to affect the normal functioning of the immune system. It is recognized that larger periods of prolonged exercise can suppress the immunity, meanwhile, regular exercise in moderate intensity is beneficial (Gleeson, 2007). It is suggested that moderate exercise intensities are protective of the human body by stimulating the immune system, namely due to the increased number of NK cells, neutrophils and immunoglobulins seen after an exercise bout (Nieman, 1994; Brolinson and Elliott, 2007).

From a immunologic point of view, the mechanisms by which exercise has an anti-inflammatory effect occurs, at least, in three fronts: a) the reduction in fat mass, b) the increased production and release of cytokines with anti-inflammatory properties from skeletal muscle and, c) a reduction of Toll-like receptors expression on monocytes and macrophages (Flynn and McFarlin, 2006; Pedersen and Febbraio, 2008; Gleeson *et al.*, 2011).

In addition to the mechanisms proposed earlier, animal models have revealed other pathways by which exercise promotes anti-inflammatory effects, these include the suppression of macrophage infiltration and acceleration of phenotypic switching of these cells in the adipose tissue, reduction in the circulating number of inflammatory monocytes in peripheral blood after exercise, and the increase in circulating regulatory T cells are suggested also to be involved (Yeh *et al.*, 2006; Timmerman *et al.*, 2008; Kawanishi *et al.*, 2010; Wang *et al.*, 2012). More importantly, in older people, the repeated bouts of

exercise may contribute significantly to generate an anti-inflammatory environment, maintaining the concentration anti-inflammatory cytokines such as, IL-1ra, IL-2 and IL-10 (Simpson and Guy, 2010; Gleeson *et al.*, 2011), and suppressing the expression of pro-inflammatory mediators.

2.5.1. Exercise and Blood-Brain Barrier

The effects of physical exercise on BBB are relatively recent and need further investigation, especially in humans. Most of the evidences around the effects of exercise on BBB are related to acute effects, and an initial reading lead us to ask about the hypothetical “harmful” effect that exercise may have on the brain. Numerous studies have emerged in the last 20 years in order to verify the effects of different types of exercises in peripheral markers of BBB injury, looking at the way by which exercise could act as a "villain" - i.e. promoting damage at the cerebral level. In some cases, the execution of certain types of exercises (in specific situations), can exert an effect called "double-edged sword" when, at the same time, has beneficial and deleterious effects to their practice.

Evidences in this topic have been pointed out by Kaste and colleagues in 1982 (Kaste *et al.*, 1982), who verified brain damage in boxers even after retirement from their professional career. This effect had remarkable attention for several years, where a series of works suggested that exercises involving direct impact on the head can promote damage to the BBB, as evidenced by some studies with boxers and other sports involving impact (Otto *et al.*, 2000; Graham *et al.*, 2011; Neselius *et al.*, 2012). Simultaneously with this evidence, not only the impact was studied, but the relationship between cytokines and free radicals produced during exercise and their effects on BBB permeability were also investigated (Bailey *et al.*, 2011). The mechanisms by which acute exercise can promote BBB permeability are shown in figure 2.4.

However, increased permeability of BBB promoted by exercise is an acute effect, since this structure is restored in few hours - except in severe damage after exercise (Neselius *et al.*, 2012). In this sense, the evidence around the effects of long-term exercise on BBB structure is still scarce in humans.

The idea that the BBB integrity can be promoted by long-term (regular) physical exercise is appealing, since the same exercise protocol (cycling 40 min at 75% of aerobic

power) performed by athletes and non-athletes individuals showed that peripheral markers of BBB permeability were increased after exercise on those who were not engaged in exercise practice, suggesting that athletes had better BBB integrity (Uba Chupel *et al.*, 2014).

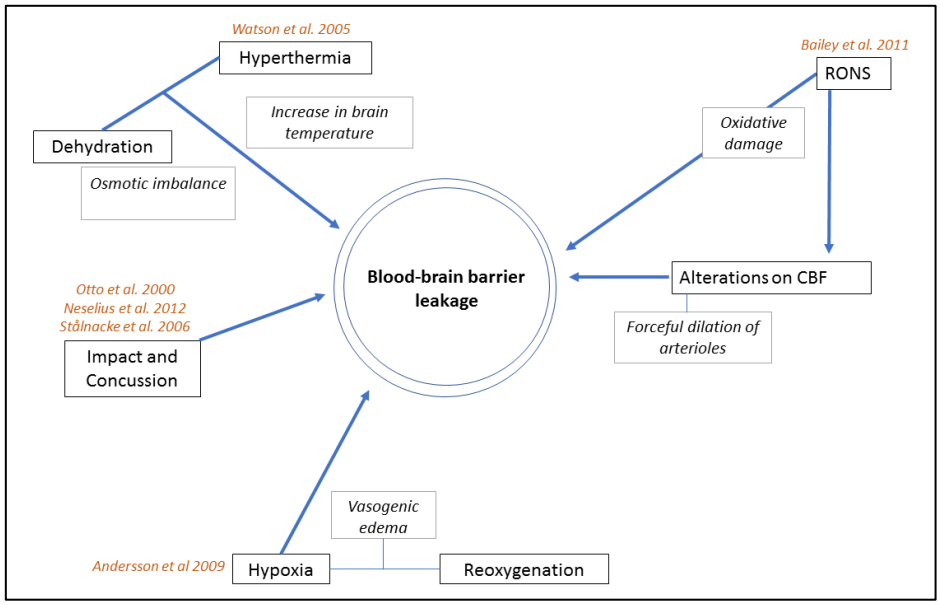

Figure 2.4. Mechanisms by which acute exercise can increase blood-brain barrier permeability.
The know physiological mechanisms related to acute exercise-induced BBB permeability are represented in the figure. Some of these mechanisms interact with each other (such as dehydration and hyperthermia), and both can contribute to the deterioration of the BBB structure. Reactive oxygen and nitrogen species (RONS) can act directly (by oxidative damage), and indirectly (by promote changes in cerebral blood flow – CBF), on BBB leakage.

The concept of strengthened the BBB by exercise is still theoretical and based on the suggestion above. In animal models, however, some evidence pointed to that the long-term exercise ameliorated the BBB stability (Wolff *et al.*, 2014, 2015; Souza *et al.*, 2016), but the mechanisms behind these improvements need to be explored in humans.

2.5.2. Combined Exercise Training (CET)

The positive influence of exercise training on the health of elderly subjects is well known, and there is a great number of evidences that report the improvement of the

immunological parameters (Beavers *et al.*, 2010), physical fitness (So *et al.*, 2013), as well in the lipid profile and body composition due to long-term intervention. Different approaches have been used as physical therapies to promote these effects, from aerobic exercises (e.g: walking), muscle strength/resistance training (either with free weights or elastic bands), flexibility exercises (stretching), and combined training (strength, aerobic, and flexibility).

The strength training has been proposed to attenuate the loss of muscle mass during normal aging (Tseng *et al.*, 1995), and increase muscle strength and muscle size, even in institutionalized frail population (Fiatarone, 1990; Morganti *et al.*, 1995). Indeed, quite similar physiological responses are produced with strength training in old and young individuals (Roth *et al.*, 2001). Recent studies have also shown the effectiveness of 28 weeks of elastic band strength training in decreasing inflammation in institutionalized older women, simultaneously with improvements in cognition and physical fitness (Chupel *et al.*, 2017).

Aerobic-based exercises are also effective in improving the immunity of older persons, by lowering levels of TNF-α and increasing levels of IL-10, thus promoting an anti-inflammatory environment (Santos *et al.*, 2012). Evidence also suggests benefits of this type of training for physical function and gait improvement (Arcolin *et al.*, 2016).

Despite the existing evidence regarding changes in the enhancement of the antimicrobial immunity on mucosa and the reduction of stress-related hormones due practice of flexibility training, stretching exercises seem to be ineffective to increase physical fitness of institutionalized older population (Furtado *et al.*, 2016; Marques *et al.*, 2017).

However, considering that the maintenance of functional physical capacity in the elderly depends on the efficiency of mechanisms such as muscle strength generation, stretching capacity and aerobic resistance, the application of a combined exercise training protocol (CET) can be more complete, less monotone and more effective in improving several body functions of institutionalized older people than just one isolated method of training.

CET, also known as multimodal exercise training, has been pointed out in the literature as an efficient and powerful method in promoting health for elderly individuals. In a very complete review study, Baker and colleagues (Baker, Atlantis and Fiatarone

Singh, 2007) concluded that CET is especially effective in preventing falls in older population. More recently, CET with slightly higher intensities has been shown to be effective in co-therapy to prevent atherosclerosis (Park and Park, 2017), to improve immunity and body composition (Lee, Kim and Oh, 2013; Theodorou *et al.*, 2016), lipid profile (dos Santos *et al.*, 2014), and better health outcomes related to the regulation of the autonomic nervous system (McKune *et al.*, 2017). A randomized clinical trial with Portuguese community-dwelling elderly people also showed that combined exercise training is effective in promoting better related daily living activities (Sousa *et al.*, 2014).

3.METHODS

The aims of the present study are to verify the effects exercise and supplementation with taurine on blood-brain barrier integrity in elderly women. Considering that the focus of this work is on the effects of both interventions in inflammation and oxidative stress, this current chapter was organized to show the study design, the analyzes and instruments used for all markers.

Firstly, the method used for intervention with exercise will be presented, specifying the modality and describing the main activities involved, and then the description of the process of supplementation with taurine. Secondly, the laboratory procedures adopted for the analyzes of the biomarkers, as well the procedures for data collection of biosocial, cognitive and physical fitness will be described.

This chapter closes with the statistical procedures used for acquisition of data.

3.1. SAMPLE SELECTION AND ETHICAL PROCEDURES

For the accomplishment of this study permission for the data collection of all the individuals of two centers for social and health care support (CSHS) that agree in participate was obtained. In order to motivate the participation and clarify the objectives of research, the study was presented in detail in the CSHS. All individuals were informed about the purpose, main objectives and potential conflict of interest involved. The potential risks and benefits of their participation were clearly explained as well the guarantee of confidentiality of the data.

After agreeing to participate in the study, a declaration of permission and consent was obtained for data collection and access to each subject's medical record. The approval by the medical staff was a condition to check the eligibility of each individual to participate in the study. Part of this investigation is inside and integrated in the research project entitled "PRO-HMECSI: Hormonal mediation of exercise on cognition, stress and immunity" (Teixeira *et al.*, 2016) and financed by FCT (Portuguese Foundation for Science and Technology).

This work respect the Portuguese resolution (Artº4st, Law nº12/2005, 1st series) on ethics in research with humans (Braga, 2013), and follows the guidelines for ethics experiments in exercise science research.

Confidentiality of data was ensured as all participants were given a coded number. All data were coded and stored on the author's password protected computer. The data will be destroyed after seven years in accordance with the ethics committee policy. Permission to conduct this study in the CSHS was given by Dr. António Alexandre (Director of the Santa Casa de Misericórdia de Cantanhede), Dr. José Bernardes (consultant doctor of health in Santa Casa de Misericórdia de Cantanhede).

All participants were asked to sign an "Informed Consent Form", agreeing in participate in the study. The procedures as well as the form of participation of those involved and the contribution of this type of study to the development of health and sport sciences were explained. Participants were told that they were free to withdraw from the study at any point of time with no disadvantage to themselves.

3.2. Study Design

This was a prospective, non-randomized controlled trial (treatment vs care as usual). The effects of interventions with exercise and supplementation with taurine (alone and in combination between them) were tested in comparison to the baseline levels and with a control group.

The sample size was estimated using adjusted ANOVA for repeated measures effects using the G*Power software (version 3.1.9.2). The number of measurements (=2) and groups (=4) were adjusted. Alpha (type I error rate) was set at 0.05, and power (type II error rate) at 0.85 with inclusion of forty participants as sufficient power.

3.2.1. Eligibility Criteria

Some inclusion and exclusion criteria were used to classify individuals as possible (fit or appropriate to the study design) or not (unfit) to be part of the study and subsequent analyzes.

After obtaining the signed consent, data was collected regarding biosocial, global health and general medical history with the medical staff of the nursing home. Based on the initial assessment, we excluded volunteers with history of recent head trauma, uncontrolled diabetes mellitus and hypertension, current chronic renal, liver or respiratory

disorders, neurologic disorders or those with severe cognitive impairment according to the cut-off Mini Mental State Examination criteria (MMSE) ≤ 9 points, recent myocardial infarction or stroke (within the previous 6 months). We also excluded those individuals who use hormone replacement therapy. The remaining subjects were allowed to continue using their usual prescribed medication, however, individuals with unstable medical conditions, highlighted by starting new medications within the data collection period, were also excluded.

To be eligible for the study participants needed to fulfil the following criteria: being a woman living in a nursing home support centre; age > 60 years; capacity to practice exercise without causing harm to themselves with approval of the medical department.

3.2.2. Subjects Allocation into interventions

Forty-eight older women (83.5±6.9 years old) participated in the study and were allocated into four groups:

- Combined Exercise Training Group (CET: n=13)

- Taurine Supplementation (TAU: n=12)

- Combined Exercise Training + Taurine Supplementation (CET+TAU: n=11)

- Control Group (CG: n=12)

Details of experiment design are presented in Figure 4.0.

The subjects included in groups CET and CET+TAU participated in a 14-week exercise program, while participants in groups TAU and CET+TAU were given taurine supplementation orally for the same period of time. The individuals in the CG were not involved in any structured physical activity program during this period.

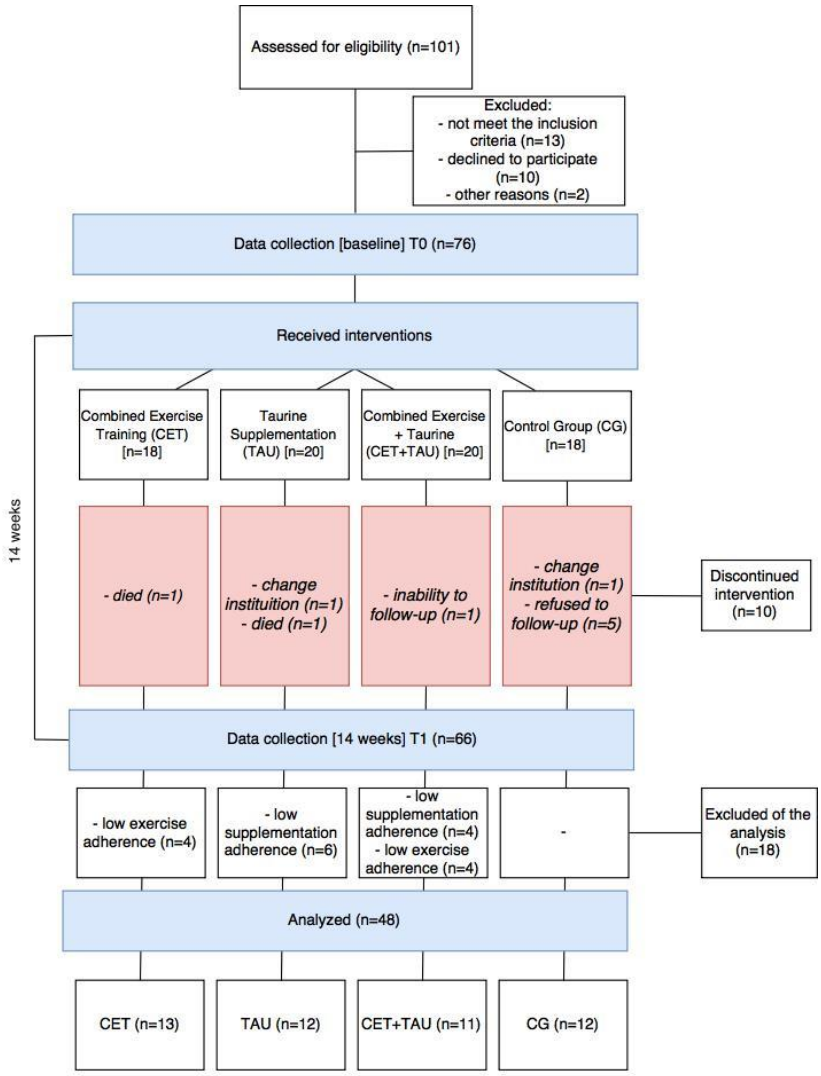

Figure 3.0. Flowchart of the Study Design

3.3. EXERCISE PROGRAM

3.3.1. Characterization of the Program

A combined exercise training program (CET) was applied for the purpose of this study. The classes took place 2 times per week during 14 weeks, totalizing 28 sessions. The duration of each class was 60 minutes involving warm-up, main part and cool-down. The description of activities are defined in the Table 4.0. The classes were held within the CSHC and care was taken for them not to occur on two consecutive days of the week. This program was divided into two microcycles (Microcyle 1: week 1-7; microcycle 2: week 8-14), in order to induce a progression of exercise intensity during the intervention.

The activities of the CET program were conducted by specialists in exercise prescription and intervention, and adjusted to the population studied following the main

guidelines for multi-modal exercise prescription for older adults, according to systematic reviews and recommendations for this topic (Baker, Atlantis and Fiatarone Singh, 2007; Nelson *et al.*, 2007). All classes were administrated by two trained professors who kept the consistency between sessions. Guidelines for exercise prescription to elderly, as recommended by the American College of Sports Science and Medicine were followed regarding the intensity for exercise programs in these populations, which was designed to be held between 65% to 75% of predicted maximum heart rate for age (Nelson *et al.*, 2007). In addition, the chair-based exercise guidelines were also used during the design of the CET program (Robinson *et al.*, 2014), and some activities were based on the study protocol for elderly population (Teixeira *et al*. 2016). The exercise intensity was monitored using a cardio frequency meter (Polar, 810, Denmark), which were randomly distributed between the participants during the exercise program. Additionally, evaluation through 10-point Borg scale was applied. The scale was explained as many times as the elders needed to comprehend it, and they were oriented to tell their own sense of perceived exertion during the lesson at the end of exercise session.

3.3.2. Description of the CET program

Participated in the CET program those individuals included in both CET and CET+TAU groups. CET is characterized as a group exercise class where were used aerobic exercises (AE) in combination with elastic-band strength training (ST). The application of the exercises intercalated AE and ST, being this latter as a chair-based exercise. This was very important for the accomplishment of the program since it allowed the participants to maintain a good consistency during each session without feeling (totally) fatigued. The ST incorporated progressive weight training and weight bearing exercises involving the major muscle groups, and was performed using a determined number of exercises that ranges from 4-8 activities, 2-3 sets and 15-20 repetitions. The cadence of execution was 2:2 and rest between sets range from 30-45 seconds. The AE part consisted on walking through the room class combining movements of upper body limbs, chair sit-and reach exercises, walking through obstacles, marching and upper body twist. The walking time increased during the program, but care was to avoid extenuating activities.

Table 3.0 Characterization of the Chair-Based Combined Exercise Training

Modality	Warm-up phase (6 min.)	Main part of the CET (48 min.)	(%)HR PE	Cool-down phase (6 min.)
Microcyle 1 (week 1-7)				
AE	General body mobilization and dynamic stretching chair-based exercises; familiarization with the elastic bands (moves the elastic upward; stretch the elastic until the beginning of the tension point)	Aerobic exercises included: chair-based exercises (simulated walking, upper body movements) 7-10 sets. They were held a series containing 4-8 chair-based aerobic exercises. After performing 2-3 sets, the participants were encouraged to combine the walk around the gym-room during 2-3 minutes. Walking time was increased gradually during the program. Example of exercises: 1) chair-based sit and reach, leg extension and overhead reach and standing rear leg extension (2-3 sets x 10 reps); 2) 2-minutes walking; 3) arm rising, hip marching, chair stand and upper body twist; 4) 2- minutes walking.	~50-60%	General body mobilization and static stretching chair-based exercises; breath exercises in sit position
ST		Muscle-Strengthening Activity: 8-10 exercises using the first level of elastic Thera-band. Were consisted in to pull-up the elastic-band for 10 reps x 2 sets, with the concentric phase for 1 second and eccentric phase for 2 seconds with 45 seconds-rest between sets and exercises. Examples of exercises: 1) Front Squat; 2) Unilateral hip flexion in the chair; 3) Bench over row; 4) Chest Press; 5) Standing reverse fly; 6) Spine twist extension arm; 7) Shoulder press/twist arm front position; 8) Frontal total raiser; 9) Biceps arm curl stand/chair; 10) Overhead triceps exertion.	3-4	
Microcycle 2 – (week 8-14)				
AE	General body mobilization, dynamic stretching chair-based and stand-up exercises; minutes of walking on the room; chair-based leg extensions and upper body movements	The progress of intensity of the AE part included more difficult and complex chair-based aerobic exe and challenges sequences. Additionally, were increased the walking time and placed obstacles duri walking route (cones, floor markers, arcs) to work handedness; walking with changes of directio	60-70%	1-2 minutes easy-walking, general body mobilization and static stretching stand exercises; breath exercises in sit position
ST		The progress of ST part was based using the same elastic band, but increasing the time of muscle contraction in some exercises or using more complex progressions (example: 2-3 sets x 10 reps of front Squat in the chair + frontal raiser)	5-6	

3.4. Supplement Intervention

The amino acid taurine was in powder form and administrated in drinking water. The supplement was supplied by LaborSpirit LTDA, (Lisbon), Portugal. The dosage used was 1,5g (Beyranvand *et al.*, 2011) of taurine diluted in 150 mL of water once a day during 14 weeks, which is reported to be safe and effective to humans (Shao and Hathcock, 2008). Supplementation was given every day in the morning, and subjects of both (TAU and CET+TAU) groups received the supplementation at the same time of the day. In the days when there were CET sessions for CET+TAU it was guaranteed that the supplementation was ingested at least 30 minutes before the session. In total, each subject received 98 doses of 1.5g of taurine in a period of 14 weeks.

Only the principal researcher and the staff of CSHS had access to the supplement. The caregivers were responsible to dilute the powder in water and give it to the subjects. The staff were oriented as to the correct administration of supplement and clarification of doubts concerning their use.

3.5. Exercise and Supplementation Adherence

A total of 28 CET sessions were offered during the program. A presence list was used and completed by the instructor to assess each participant's adherence to the exercise sessions. The level of adherence was calculated by the number of presences of each individual in the total number of sessions. In order to be characterized as an effective participant in the intervention group, the individual had to have a minimum of 70% attendance during the 14 weeks sessions. The instructors were oriented in order to motivate the participants when they were absent from two consecutive classes. The assistance of the CSHS staff was also used as a motivation strategy in order to avoid dropouts during the study. At the same time, the taurine ingestion was monitored daily by CSHS staff where a list was filled to control the subjects who ingested the amino acid. Nurses were instructed to clarify any doubts among the elderly, as well as to record the possible adverse effects of the amino acid intake. In case of the appearance of undesirable effects the staff was instructed to suspend the supplement of the elderly person.

3.6. Control Group

The CG were formed by the individuals who did not wish to participate in the exercise program but who volunteered to took part in all data collection. These individuals were not enrolled in any kind of structured physical activity during the 14 weeks of the study, at the same time, they were not receiving special nutritional support during this period, but receive care as usual in the CHSH. Care was taken to minimize the possible interactions between the individuals of CG and the CET classes.

3.7. Data Collection

All tests procedures followed the health and safety guidelines of data collection with humans. Due care and attention was paid to ensure that the rooms were clean, safe and suitable for the blood collection and application of the battery of physical and cognitive tests to the elderly. All blood collection was made by a registered and experienced nurse. All sharps and biohazard materials were disposed of immediately after use for later incineration in accordance with institutional risk assessments. The work surfaces and floor where were applied the physical tests were thoroughly cleaned previously. Care was taken to ensure that the floor was safe and did not present a risk of slippage or fall for the elderly.

All data collection was done by trained specialists. The application of cognitive questionnaires was done by an individual who did not take part in the exercise program to diminish the interference of familiarization between participants and researcher. The teachers who applied the exercise classes were not involved in the data collection, except in those moments when the elderly needed additional support. The following data was collect to fulfill the accomplishment of the study: biosocial and global health, blood collection, cognitive function, anthropometric measures, and physical fitness.

3.7.1. Biosocial

Basic information of age, genre, marital status, schooling, place of birth and physical activity enrollment were done by an interview and fulfillment of a biosocial questionnaire. This data was collected once at the beginning of the program (screening process).

3.7.2. Global Health

Data regarding clinical history of the participants were collected conjunctly with the medical staff of the CHSH. The presence and severity of the morbidity was registered according the Charlson Comorbidity Index (CCI) (Charlson *et al.*, 1987) in the screening process to participate in the study.

3.7.3. Anthropometric Measures

The anthropometric measures considered were the determination of body weight using a portable scale (Seca®, model 770, Germany) with precision of 0,1kg. Stature was measured using a portable stadiometer (Seca Bodymeter®, model 208, Germany) with precision of 0,1 centimeters.

3.7.4. Physical Fitness Tests

The functional fitness variables of each participant were measured using the Senior Fitness Test battery developed and revised by Rikli and Jones (Rikli and Jones, 2012). Briefly, the determination of the dynamic lower and upper body strength, forearm strength, aerobic endurance, flexibility and dynamic balance and agility were done before and after the program.

Lower and Upper Body Strength: the strength of elderly legs was evaluated with the "30 second's chair-and-stand test" (30s-CS) that measures the total number of stands and seated completed in 30's with arms folded across the chest. The evaluation of arm strength was done using the "30 seconds Arm-curl test" (30s-AC) that measures the total number of bicep curls that can be completed in 30's, holding a hand weight of 2,27kg for women and 3,63kg for men.

Aerobic Endurance: an alternate aerobic endurance test was used in substitution of the 6-minute walk test, in accordance to the protocol described by Rikli and Jones (2012), due to space limitations. In this case, endurance was evaluated by the "2-minute step test" (2ST) that measures the number of full steps (elevation of each knee to a point

midway between the kneecap and iliac crest) completed in 2 min. The score is the number of times the right knee reaches the required height.

Agility and dynamic balance: the application of "8 Foot-Up and Go Test" (8-FGT) is used to measure the agility and dynamic balance of the participant. The test consisted in the number of seconds required to get up from a seated position after order, and walk 2,44m (8 feet) to a marker on the floor, turn around, and return to the seated position.

Forearm strength: additionally, the hand-grip test (HGT) was used to evaluate the strength of forearm in stand position. A dynamometer (Lafayette, 78010, Indiana, USA) was used to measure both hands twice. Subjects performed the test with 30 seconds of rest between measurements for both hands. The best value of each hand was computed and the higher value was used.

3.7.5. Cognitive Profile

The assessment of cognitive profile consisted in an application of two questionnaires designed to detect cognitive impairment. Due to technical procedures and to avoid differences between measures, both questionnaires were applied by the same professional to the same elderly participant in baseline and after the program.

Mini Mental State Examination (MMSE): the tool developed by Folstein and co-workers (Folstein, Folstein and McHugh, 1975) is one of the most used test for the evaluation of cognitive function by assessing five areas of cognition: orientation, immediate recall, attention and calculation, delayed recall, and language. It is a 30-point scale instrument and was used to classify the individuals by cognitive profile according to the criteria described by Mungas (Mungas, 1991): [0-9] severe cognitive impairment; [10-18] moderate cognitive impairment; [19-24] mild cognitive impairment; [25-30] normal cognitive profile. The MSSE was used in both measurements and included in the study since it had been shown to be sensitive to the effects of exercise in an older population (Hogervorst and Clifford, 2012).

Montreal Cognitive Assessment (MoCA): The MoCA is a high sensitivity and specificity tool for detect mild cognitive impairment (Nasreddine *et al.*, 2005). It is a one-page 30-point test, that evaluates the short-term memory, visuospatial abilities, attention, concentration, working memory, language, orientation to time and place, and multiple

aspects of executive functions. Scores less or equal 24 points indicate cognitive impairment. The application of this test occurred using the validated Portuguese version (Freitas *et al.*, 2010).

3.7.6. Blood Collection

Blood collection was done by venipuncture by a registered nurse. The blood collection took place in two moments. First, baseline collection was done one week prior to the start of the exercise and supplementation program. The last sampling was done after 14 weeks of the program, and at least 48 hours after the last exercise session. A total of 15 mL of blood was collected from the ulnar ante-veins of all participants seated after fifteen minutes of rest. All collections took place between 10:00h and 11:30h in the morning in order to avoid differences due to circadian rhythm in some biological markers between moments. After the blood was drawn through a syringe it was allocated into 3 different tubes (BD Vacutainer®): one containing EDTA, one heparinized tube, and one tube with gel separator for serum. It was ensured that all subjects were hydrated at the time of collection. After processing, plasma and serum were allocated into eppendorfs and stored at -80°C until determination of the biomarkers related to the purpose of this study.

Complete Blood Count (CBC): on the same day of blood collection the a CBC was performed using an automated hematology analyzer Coulter AcT Diff (Beckman Coulter, USA). The system used allows different counts with specific impedances to count red blood cells (RBC), white blood cells (WBC) and platelets.

3.8. Biochemical parameters analyzed by ELISA

3.8.1. Biomarkers

Shortened form of “biological marker”, the biomarkers refer to a measurable indicator that can demonstrated a biological condition. In medicine or even in sport science research, these are often measured to compare normal biological processes with pathogenic processes, or to identify responses to a medical treatment or intervention. Indicative tools have been effectively used in the last decades to detect changes in vascular, skeletal and cardiac muscles, brain and immune functions.

To achieve the objectives of this research several biomarkers were selected and evaluated in blood (serum and plasma), and briefly described below.

3.8.2. Peripheral markers of blood-brain barrier and Neuronal Damage

Due to the difficulty in accessing the integrity of the BBB directly in humans, some peripheral markers are commonly used for verifying damage in this structure. These proteins and enzymes analyzed in serum, were discovered in the last decades and are able to measure the degree of brain structures damage (Marchi *et al.*, 2003). If a component present in large amount in the brain (which naturally does not cross the BBB), can be found in the bloodstream, indicates that a leakage (or rupture) of that structure occurred (Marchi *et al.*, 2004).

S100β: The glial protein S100 belongs to a large family of calcium-binding proteins found as homo or hetero-dimers of two different subunits (alpha and beta). Different combinations of the subunits make up the heterodimeric forms (Nash, Bellolio and Stead, 2008; Blinov and Terent'ev, 2013). The principle involved is that the presence of TJ considerably minimizes the flow of large substances between blood and brain. For example, detection of the passage of albumin from the bloodstream to the CSF is a widely-used method for assessing BBB permeability by either direct lumbar puncture or contrast-enhanced CT-MRI (Heye *et al.*, 2014). However, the analysis of the opposite side (serum) by detecting the levels of S100β is also possible, since this protein is found exclusively at high concentrations in the astrocytes of the brain (Blinov and Terent'ev, 2013) and their detection in blood has been reported to be a very useful marker of BBB injury (A. a Kanner *et al.*, 2003; Marchi *et al.*, 2004; Pham *et al.*, 2010). In fact, its concentrations found in CSF is 40 times higher than that found in serum (A. a Kanner *et al.*, 2003), which may explain their high correlation between serum levels and severity of stroke (Nash et al. 2008). Compared to other markers, S100β protein utilization has reliable accuracy, relatively non-invasive method to access BBB permeability (Blyth *et al.*, 2009), since this barrier is usually impermeable to protein S100β (Marchi *et al.*, 2004).

Several studies indicate the viability of S100β determination in blood to assess the permeability of BBB (A. a Kanner *et al.*, 2003; Marchi *et al.*, 2003, 2013; Blyth *et al.*, 2009; Starr *et al.*, 2009; Vajtr *et al.*, 2009; Pham *et al.*, 2010; Kaciński *et al.*, 2012). In

this study, serum levels of S100β were analyzed by ELISA (Biovendor Laboratory Medicine, Czech Republic). The intra-assay coefficient of variability was 7,3%.

Neuronal Specific Enolase (NSE): NSE is a brain derived enzyme extensively studied as a peripheral biomarker for neuronal injury (Herrmann *et al.*, 2000; Schaf *et al.*, 2005). NSE is a cytoplasmatic glycolytic pathway enzyme, the isoform γγ being primarily neuronal (Sternberg and Mitchell, 2014; Koch *et al.*, 2015). Since it's levels increase in CSF and/or blood in several brain pathologies, NSE is considered to be a marker of neuronal damage (Li *et al.*, 2015; Olsson *et al.*, 2016), mainly when accompanied with BBB leakage (Marchi *et al.*, 2004).

Serum levels of NSE were analyzed by ELISA (R&D Systems, UK). The intra-assay coefficient of variability was 2.4%.

3.8.3. Inflammatory Response

The IL-1 family of cytokines is associated with acute and chronic inflammation, playing a role on non-specific innate response to infection. The biological properties of IL-1 family are typically proinflammatory (van de Veerdonk and Netea, 2013). Included in the inflammatory family is the IL-1β, which is mainly produced by monocytes, macrophages, lymphocytes and NK cells as well. Also, part of the IL-1 family is the anti-inflammatory cytokine IL-1ra, a receptor which acts inhibiting and neutralizing the IL-1β function (Dinarello, 2011). Plasma levels of IL-1β and IL-1ra were analyzed by ELISA (Invitrogen, CA), and intra-assay coefficient of variability was 2,7% for IL-1β, and 3,2% for IL-1ra.

TNF-α: The tumor necrosis factor-alpha (TNF-α) is a cytokine with important pathogenic functions (Kalliolias and Ivashkiv, 2015). Is composed by 19 ligands and plays a key role in immunopathology and, in elderly, is highly related to mortality, cognitive impairment and neurodegenerative diseases (Perry *et al.*, 2001; Bodmer, Schneider and Tschopp, 2002; Meylan and Siegel, 2017). Due to this, TNF-α levels might be a helpful biomarker for immunosenescence (de Gonzalo-Calvo *et al.*, 2010). Concentrations of TNF-α were analyzed in plasma using ELISA (Invitrogen, CA). The intra-assay coefficient of variability was 4.9%.

IL-10: The IL-10 production is non-specific, since it can be produced by almost all cells of immune system, which include mainly T regulatory cells, and also Th17, monocytes, macrophages and B lymphocytes (Saraiva and O'Garra, 2010). This cytokine acts in several immune responses, efficiently inhibiting the inflammatory process and activation of matrix metalloproteinases (Anker and von Haehling, 2004; Gleeson *et al.*, 2011), and plays a key role in attenuate the aging-related immune suppression (Dimitrijević *et al.*, 2014). IL-10 levels were analyzed by ELISA (Invitrogen, CA), using plasma samples. The intra assay coefficient of variability was 5,3%.

Taking to account the cytokine balance between pro-and anti-inflammatory mediators, the IL-1β/IL-1ra and TNF-α/IL-10 ratios were also calculated, since they might be helpful to understand the changes in immune response mediated by an intervention (Elenkov, Chrousos and Wilder, 2000; Merhi-Soussi *et al.*, 2005; Girard *et al.*, 2008; Lira *et al.*, 2009).

IL-17: The IL-17 family is composed by 6 cytokines (IL-17A to IL-17F), IL-17A and IL-17F being the most important in inducing inflammation (Cazzola and Matera, 2012), and responsible for the cytokine IL-17 being closely linked to chronic inflammation (Pappu *et al.*, 2010). Plasma levels of polyclonal IL-17 were analyzed by ELISA (Invitrogen, CA). The intra-assay coefficient of variability was 2,3%.

3.8.4. MPO and MMP-9

Myeloperoxidase (MPO): MPO is the most toxic enzyme found in the azurophilic granules of neutrophils (Strzepa, Pritchard and Dittel, 2017). Besides neutrophils, other sources of MPO production are the macrophages and monocytes (Nagra *et al.*, 1997). The major role of MPO is to catalyze the formation of hypochlorous acid ($HOCl^-$), a powerful chlorinating oxidant. MPO is involved in pathophysiological mechanisms of several conditions, the reason why it is classified as an oxidative-related disease enzyme (Nicholls and Hazen, 2005; Mocatta *et al.*, 2007; Heslop, Frohlich and Hill, 2010; Anatoliotakis and Deftereos, 2013). It quantification gives a good parameter to the clinical and research practice, especially because their high blood levels have been linked to predict cardiovascular events and mortality (Rana *et al.*, 2011). Serum samples were used to analyze levels of MPO by ELISA (R&D Systems, UK). The intra-assay coefficient of variability was 4,8%.

Matrix-Metalloproteinase-9 (MMP-9): MMP-9 is an enzyme involved in several mechanisms related to the brain physiology and pathology, and has been related to contribute in BBB damage and brain dysfunction (Vafadari, Salamian and Kaczmarek, 2016). Plasma samples were used to analyze MMP-9 concentrations by ELISA (R&D Systems, UK). The intra-assay coefficient of variability was 3,0%.

3.9. STATISTICAL ANALYSIS

This section will be dedicated to the description of the statistical procedures used in this study.

Taking in account the existence of several variables in the study, the results were divided and presented in small sections, according to the dimension evaluated. Because of the nature of data - most of them biological and likely to be great dispersed among the sample studied, some preferred statistical tests (such as multivariate analysis of variance, MANOVA) could not be performed. Furthermore, the small sample size lead us to analyze those parameters using univariate analysis and, in some cases, non-parametric tests, to avoid error rising from violations of assumptions required to perform parametric tests. However, all the study objectives were answered based on the statistical procedures presented below.

Firstly, all data were recorded in a spreadsheet using the Microsoft Excel 2016 (Microsoft Corporation®). After check for missing data, some variables received codification as needed (for categorical variables). Afterwards, the spreadsheet was open into the Statistical Package for Social Science (SPSS - IBM Statistics, version 23) for the statistical analysis.

In this study, all descriptive statistics are presented as mean ± standard deviation for all variables using actual values.

To check whether data were normally distributed among the sample, Shapiro-Wilk tests were performed. For statistical analysis, data were log-converted to reduce bias arising from non-uniformity error in those parameters without normal dispersion. After conversion, normality was checked again to confirm the symmetric distribution. In persistence of non-uniformity, the statistical analysis for these variables was done using non-parametric tests.

To verify differences in baseline parameters between groups in normally distributed parameters, one-way ANOVA were performed followed by a Tukey's test *post hoc* to detect differences between groups.

The analysis regarding the effects of the different interventions in normally distributed parameters were compared between groups using repeated measures ANOVA. When assumptions were not violated, the within measures effect was time (2 levels: before and after intervention) and between measures effect was treatment (4 types: CET, TAU, CET+TAU and CG). Tukey's test was applied *post hoc* to detect differences between groups. Visual inspection of plots was done to help in interpretation of data. However, when assumptions were violated for some markers due large differences in SD and non-sphericity, the univariate analysis were done within groups using the Student T-tests for paired samples.

Comparisons between groups for those variables without uniformity were made using the Kruskal-Wallis test at baseline, and for the effect of intervention for each group the Wilcoxon's signed-rank test was used.

The percent of change after the interventions was calculated and presented for each variable. Calculation for each subject variation (Δ) were done according to the formula:

$$\Delta = \left(\frac{PostValue}{PreValue}\right) - 1$$

Correlations between parameters and between changes in variables were assessed according to Spearman's rank correlation coefficient, even in the absence of non-uniformity data.

Level of significance for all results was set at $p<0.05$.

3.9.1. Effect Size Calculation

The level of significance for all results was interpreted together with the effect size calculation. Thus, to report the magnitude of interventions within groups, the effect size was calculated according to the following formula:

$$r = \frac{Z}{\sqrt{N}}$$

Where *r* means the non-parametric effect size, *Z* is provided in SPSS as a result from Wilcoxon-signed rank test and *N* means the number of observations among the analysis (Ivarsson *et al.*, 2013).

To avoid different interpretations regarding effect size estimators among the variables and different groups, the results from non-parametric *r* were converted to standardized Cohen's *d* changes in means, according to the formula described by Fritz and co-workers (Fritz, Morris and Richler, 2012):

$$d = \frac{(2 * r)}{\sqrt{(1 - r^2)}}$$

Afterwards, the effect size was categorized accordingly to the references described by Hopkins and co-workers (Hopkins *et al.*, 2009), as trivial ($d < 0.2$), small ($d \geq 0.2$ to ≤ 0.6), moderate ($d \geq 0.6$ to ≤ 1.2), large ($d \geq 1.2$ to ≤ 2.0), very large ($d \geq 2.0$ to ≤ 4.0) and nearly perfect ($d > 4.0$). The interpretation of the magnitude of effect within groups was used to clarify the difference between interventions for changes in each variable studied.

As mentioned earlier, all statistical analysis was performed using SPSS, however, graphical representations were done using the GraphPad Prism (version 5.1).

4. RESULTS

4.1. Participants Characteristics

The baseline characteristics of participants are presented below in the table 4.0.

Table 4.0 Participants Characteristics

Groups	Anthropometric and Physiological characteristics of participants before experiment						
	Age (years)	Stature (cm)	Weight (Kg)	BMI (Kg/m^2)	S-BP (mmHg)	D-BP (mmHg)	CCI
CET (*n*=13)	83.5(7.3)	155.4(6.0)	65.2(11.3)	27.2(3.8)	140.9(19.8)	69.7(12.6)	6.6(1.5)
TAU (*n*=12)	85(4.5)	157.7(7.4)	71(11.3)	27.1(3.2)	139.9(18.8)	72.4(8.1)	6.8(0.9)
CET+TAU (*n*=11)	83.8(8.6)	150.5(2.8)	62.6(9.5)	28.1(4.5)	139.5(13.5)	64.3(13.2)	7(1.7)
CG (*n*=12)	82(7.5)	151.9(7.5)	67.3(13.5)	30.3(3.5)	133.6(26.6)	66.1(7.1)	8.4(2.7)

Data are presented in Mean(Standard Deviation); CET: combined exercise training; TAU: taurine; CET+TAU: combined exercise plus taurine; CG: control group; BMI: body mass index; S-BP: systolic blood pressure; D-BP: diastolic blood pressure; CCI: Charlson comorbidity index (score).

No differences regarding age, anthropometric variables and cognitive profile were found between the four groups at baseline.

The major incidence of comorbidities (according to the medical record) in total sample is the presence of hypertension and others cardiovascular complications (table 4.1).

Table 4.1. Incidence of main pathologies found in the sample

Disease	**(%) of total sample**
Hypertension	75,8
Cardiac Disease	58,6
Dyslipdemia	34,4
Anxiety	27,5
Respiratory Disease	27,3
Osteoporosis	26,0
Diabetes	24,1

Note: the column “Disease” represents those most representative pathologies who are treated using pharmacological therapy administrated in the nursing home, according to the medical record.

There is a presence of 4,03±1,5 diagnosed comorbidities (that use pharmaceutical therapy), by each person in the sample studied, which means that this population had multiple comorbidities and makes use of more than three medicaments/day.

4.2. Exercise and Supplementation Adherence

All older women who completed the study reported no adverse events, injury or complications related to the interventions. Nevertheless, a drop-out was detected during the 14 weeks. A total of 28 subjects - from a total of 76 who started the study were not re-evaluated at follow-up. There were 18 participants who finished the study, but who were excluded from the analysis due the low exercise or supplementation adherence. Details of sample drop-out are provided in Figure 4.0.

Regarding the adherence to the interventions, people who dropped out were more likely to be less educated, presented with more co-morbidity, and lower cognitive score (from 23 participants: only 34% had completed the primary school, and 30,3% had more than five comorbidities, and mean level of MMSE was 15,6 from those who dropped out), than those who finished the trial. Among the participants who were analyzed after the interventions, 37,5% of total sample had uncompleted the primary school, while 33,3% just completed the four first years of education. Only three participants had graduate education at university.

4.3. Correlations at baseline

Table 4.2 present the results for correlation coefficient at baseline between age, blood pressure, CCI and biological markers.

BMI was correlated with CCI at baseline (r=.420). Levels of S100β were correlated with IL-17 (r=.448) and NSE (r=.292). At the same time, NSE were also correlated with TNF-α and IL-10 (r=.354). As expected, several correlations between cytokines were found at baseline, such as the association between IL-1β with levels of IL-1ra, TNF-α and IL-17 (r=.307, r=.306 and r=.339, respectively). Meanwhile, levels of TNF-α and IL-10 was also correlated (r=.718).

Table 4.2. Correlations at baseline

	BMI	BP(SIS)	BP(DIA)	CCI	IL-1β	IL-1ra	TNF-α	IL-10	IL-17	S100β	NSE	MPO	MMP-9
Age	-0,174	***,373*** **	0,204	0,224	0,122	-0,203	-0,080	-0,135	-0,147	-0,167	-0,187	-0,063	0,007
BMI		-0,137	***-,427*** **	***,420*** **	0,025	0,075	-0,004	0,091	0,180	0,091	-0,231	0,014	-0,105
BP(S)			***,444*** **	0,168	0,026	-0,184	0,050	-0,092	***-,380*** **	-0,178	-0,171	0,156	0,226
BP(D)				-0,050	0,243	0,036	0,046	0,050	***-,327*** *	-0,213	0,056	0,003	***,332*** *
CCI					0,256	0,145	0,031	0,100	0,025	0,167	0,007	-0,049	-0,162
IL-1β						***,307*** *	***,306*** *	0,196	***,339*** *	0,220	-0,083	0,226	0,235
IL-1ra							***,378*** **	0,250	0,079	0,141	0,089	***,285*** *	0,127
TNF-α								***,781*** **	0,192	0,098	***,354*** *	-0,002	0,069
IL-10									0,193	0,098	***,354*** *	-0,136	-0,004
IL-17										***,448*** **	-0,066	0,020	0,108
S100β											***0,292*** *	0,141	0,193
NSE												-0,228	-0,059
MPO													***,570*** **

Table present values of Spearman correlation coefficient. * Significant at level of $p<0.05$; ** Significant at level of $p<0.01$; Values of significance <0.05 are highlighted in bold.

4.4. Physical Fitness

Results from physical fitness parameters before and after intervention are presented in Table 4.3. At baseline, there were no differences in all parameters between the four groups. The 8-FGT time decreased significantly only in CET+TAU group after the 14 weeks of intervention (p<.01, d=1.38). CET+TAU group also presented an increase in performance for the 2'min STEP-test after the intervention (p=.01, d=1.26) while in the CG a decrease in this values occurred (p=.03; d=0.94). No significant differences were observed in 30'sCS, 30'sAC and hand-grip test after 14 weeks in all groups.

Table 4.3. Physical Fitness Parameters before and after interventions

Variables	Groups	Measurements			
		Before	After 14 weeks	ES (d)	Δ%
8-FGT (seconds)	CET	12.06(4.06)	11.58(7.38)	0.32	-8%
	TAU	13.69(5.87)	15.21(6.60)	0.75	11%
	CET+TAU	11.80(3.80)	9.73(3.70)**	1.38	-18%
	CG	15.10(5.78)	16.33(5.84)	0.53	8%
30's CS (repetitions)	CET	8.77(2.74)	9.15(4.33)	0.06	4%
	TAU	8.33(2.96)	7.83(3.15)	0.62	-6%
	CET+TAU	10.00(3.82)	10.82(4.21)	0.34	8%
	CG	7.08(2.67)	7.17(2.65)	0.06	1%
30's AC (repetitions)	CET	12.54(2.22)	13.54(3.84)	0.45	8%
	TAU	10.58(3.82)	10.25(5.24)	0.00	-3%
	CET+TAU	12.55(3.07)	13.73(4.12)	0.45	9%
	CG	10.75(4.35)	10.00(4.59)	0.10	-7%
2'min STEP-test (repetitions)	CET	37.85(13.39)	40.38(19.03)	0.32	7%
	TAU	34.08(12.06)	30.17(13.68)	0.41	-11%
	CET+TAU	37.00(15.10)	50.36(22.03)*	1.26	36%
	CG	36.08(15.79)	26.00(12.64)*	0.94	-28%
Hand-grip test (Kg)	CET	16.92(4.97)	17.46(4.55)	0.18	3%
	TAU	15.00(6.23)	14.83(7.12)	0.04	-1%
	CET+TAU	17.55(5.97)	18.55(5.02)	0.41	6%
	CG	16.58(7,78)	14.25(4.30)	0.49	-14%

Data are presented in Mean(Standard Deviation); Between groups comparison using ANOVA one way. Comparison within groups using t-test for paired samples. * significant for p value <0.05 compared to baseline. ** significant for p value <0.01 compared to baseline.

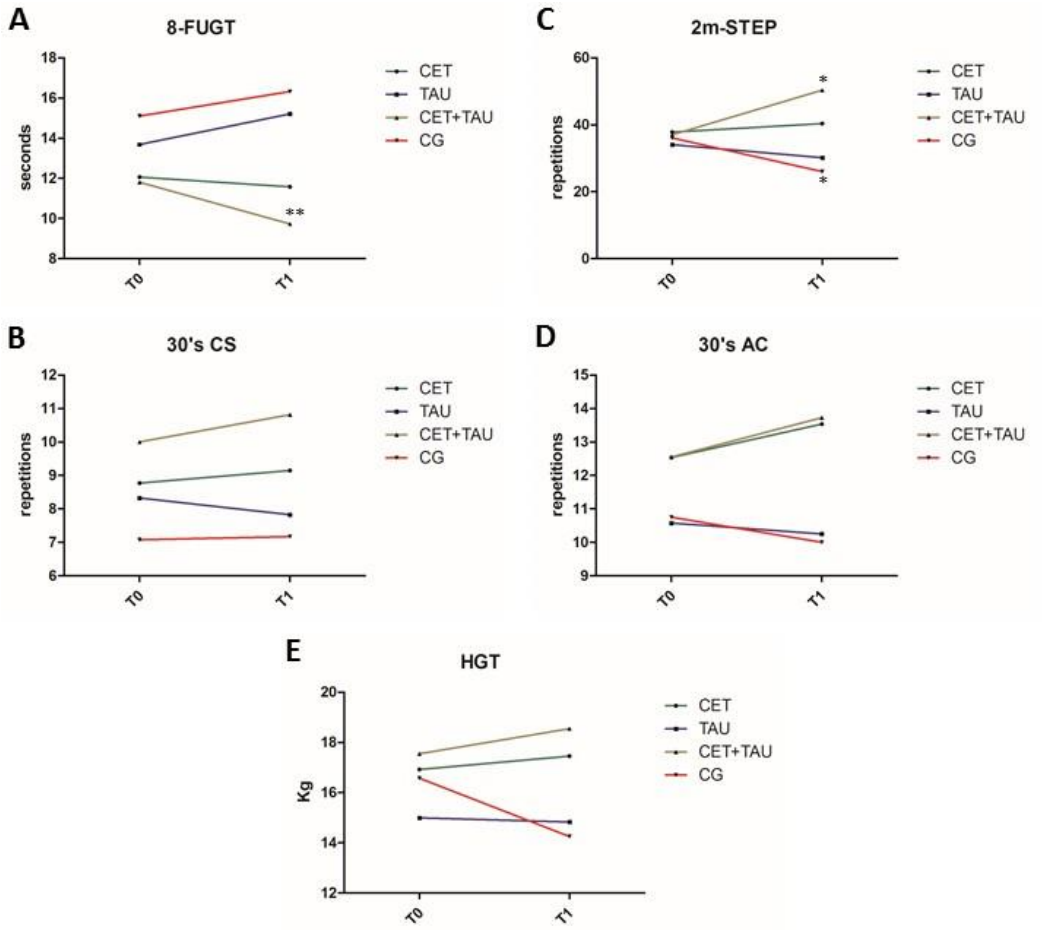

Figure 4.0. Values for Physical Fitness tests before and after interventions for **A**: 8-foot-up and go test, **B**: 30'seconds chair-stand test, **C**: 2 minutes' step test, **D**: 30'seconds arm-curl test, **E**: Hand-grip test. Colors represents different interventions (green line for CET, blue line for TAU, brown line for CET+TAU and red line for CG). T0: baseline; T1: after 14 weeks. Values of significance represented by * for $p<0.05$ and ** for $p<0.01$.

4.5. Complete Blood Count

The Table 4.4 present the results for changes in blood cell count.

Table 4.4. Complete Blood Count parameters before and after interventions

Variables	Groups	Measurements			
		Before	After 14 weeks	ES (*d*)	Δ%
Leukocytes (x 10/uL)	CET	8.54(2.42)	7.60(3.05)	0.52	-11%
	TAU	7.20(2.10)	6.56(1.30)	0.64	-9%
	CET+TAU	6.08(1.59)	6.44(0.85)	0.39	6%
	CG	8.85(2.69)	7.50(2.37)	0.49	-15%

Lymphocytes (x 10/uL)	CET	2.10(0.73)	1.94(0.59)	0.21	-7%
	TAU	2.00(0.58)	1.62(0.34)*	1.01	-19%
	CET+TAU	1.96(0.62)	1.95(0.38)	0.15	0%
	CG	2.27(0.78)	2.04(0.58)	0.38	-10%
Monocytes (x 10/uL)	CET	0.30(0.15)	0.33(0.12)	0.20	10%
	TAU	0.44(0.45)	0.43(0.24)	0.15	-2%
	CET+TAU	0.39(0.21)	0.31(0.09)	0.61	-19%
	CG	0.37(0.22)	0.49(0.18)	0.70	31%
Granulocytes (x 10/uL)	CET	6.16(2.48)	5.32(3.04)	0.74	-14%
	TAU	4.75(1.89)	4.54(1.21)	0.13	-5%
	CET+TAU	3.70(1.25)	4.12(0.98)	0.82	12%
	CG	6.20(2.61)	5.01(2.26)	0.53	-19%
Erytrocytes (x 10/uL)	CET	4.33(0.66)	4.47(0.51)	0.83	3%
	TAU	4.20(0.66)	4.04(0.35)	0.24	-4%
	CET+TAU	3.89(0.74)	4.32(0.23)	1.08	11%
	CG	4.23(0.54)	4.15(0.61)	0.24	-2%
Hemoglobin (g/dL)	CET	12.69(1.76)	12.30(1.30)	0.81	-3%
	TAU	12.73(1.85)	11.51(1.03)*	1.18	-10%
	CET+TAU	11.96(1.97)	12.42(0.42)	0.02	4%
	CG	12.25(0.94)	12.21(1.41)	0.19	0%
Hematocrit (%)	CET	38.28(4.91)	39.50(3.88)	0.90	3%
	TAU	38.00(5.43)	36.85(2.99)	0.26	-3%
	CET+TAU	35.61(5.89)	39.74(1.44)	1.29	12%
	CG	38.64(2.80)	37.90(3.59)	0.06	-2%
MCV (fL)	CET	88.69(4.47)	88.46(4.58)	0.12	0%
	TAU	90.74(2.89)	91.33(2.67)	0.46	1%
	CET+TAU	91.98(4.20)	92.03(2.76)	0.31	0%
	CG	92.23(10.53)	92.34(11.62)	0.02	0%
MCH (pg)	CET	29.36(1.72)	27.57(1.42)**	1.60	-6%
	TAU	30.41(1.18)	28.52(1.23)**	1.60	-6%
	CET+TAU	30.90(1.33)	28.80(0.80)**	1.61	-7%
	CG	29.27(4.13)	29.59(3.49)	0.43	1%
MCHC (g/dL)	CET	33.11(0.85)	31.16(0.56)**	1.60	-6%
	TAU	33.55(0.59)	31.23(0.78)**	1.60	-7%
	CET+TAU	33.60(0.49)	31.30(0.27)**	1.61	-7%
	CG	31.67(1.25)	32.10(1.11)	0.29	1%
Platelet (x 10/uL)	CET	253.00(86.70)	245.61(72.25)	0.21	-3%
	TAU	191.08(51.98)	217.33(52.04)	0.87	14%
	CET+TAU	188.36(56.25)	184.54(37.29)	0.04	-2%
	CG	234.33(76.37)	235.91(52.18)	0.36	1%
MPV (fL)	CET	8.38(0.77)	8.39(0.86)	0.04	0%
	TAU	8.27(0.64)	8.22(0.73)	0.15	-1%
	CET+TAU	8.60(1.42)	8.81(0.92)	0.22	3%
	CG	8.75(1.00)	8.82(1.44)	0.04	1%

Data are presented in Mean(Standard Deviation); Within comparisons using T-test for paired samples. * significant for p value <0.05 compared to baseline; ** significant for p value <0.01 compared to baseline.

Significant changes in WBC after interventions were observed in lymphocytes for TAU group (-19%, moderate effect, p=0.02). Despite non-significant, subtle decrease was also

observed for total leukocytes and CET and TAU groups (-11%, small effect, p=0.202 and -9%, moderate effect, p=0.160). A trend to increase in monocytes were observed after 14 weeks in CG (31%, moderate effect, p=.054).

Despite non-significant, erythrocytes presented a trend to increase after 14 weeks in CET and CET+TAU groups (moderate effect, p=0.07 and large effect, p=0.06, respectively). No significant changes were observed for hemoglobin levels after interventions, except for a decrease in TAU (large effect, p=0.01). Significant decrease was observed for MCH in CET, TAU and CET+TAU groups (large effect, p<0.01 for all). Simultaneously, MCHC were significant decreased after interventions in CET, TAU and CET+TAU groups (large effect, p<0.01 for all), and no changes were observed for CG.

No significant changes were observed for platelet count and MPV after all interventions and controls (p>0.05).

4.6. Cognition

Repeated measures for MMSE showed a significant interaction for time x treatment (F=7,49, p<.01). Linear regression analyses showed that group membership was an independent predictor of MMSE change, with change in monocyte counts as an independent predictor. None of the other variables (IL-1β, IL-1ra, TNF-α, IL-10 and IL-17) contributed to the equation.

Table 4.5. Cognitive parameters before and after interventions

Variables	Groups	Measurements			
		Before	After 14 weeks	ES (*d*)	Δ%
MMSE (score)	CET	20.2(5.8)	21.7(5.0)	0.64	7
	TAU	18.6(5.8)	18.2(5.8)	0.43	-2
	CET+TAU	21.3(4.5)	23.8(3.6)*	1.06	11
	CG	19.4(6.3)	17.3(4.9)*	0.98	-11
MoCA (score)	CET	15.6(6.4)	15.69(5.7)	0.10	0
	TAU	12.3(5.7)	11.42(6.2)	0.28	-7
	CET+TAU	15.7(7.3)	16.82(6.8)	0.50	7
	CG	14.5(6.1)	13.08(5.9)*	0.93	-10

Data are presented in Mean(Standard Deviation); Within comparisons using T-test for paired samples; * significant for p value <0.05 compared to baseline.

Univariate analysis showed that after 14 weeks of interventions, an increase in MMSE scores occurred in the CET+TAU group (p=.02, 11%, d=1.06). These results are presented in Table 4.5. No significant changes in MMSE were observed after CET and TAU or for CET, TAU and CET+TAU on MoCA (p>.05), while scores of cognitive profiles decreased for the CG for both cognitive tests (MMSE: p=.03, d=0.98; MoCA: p=.03, d=0.93).

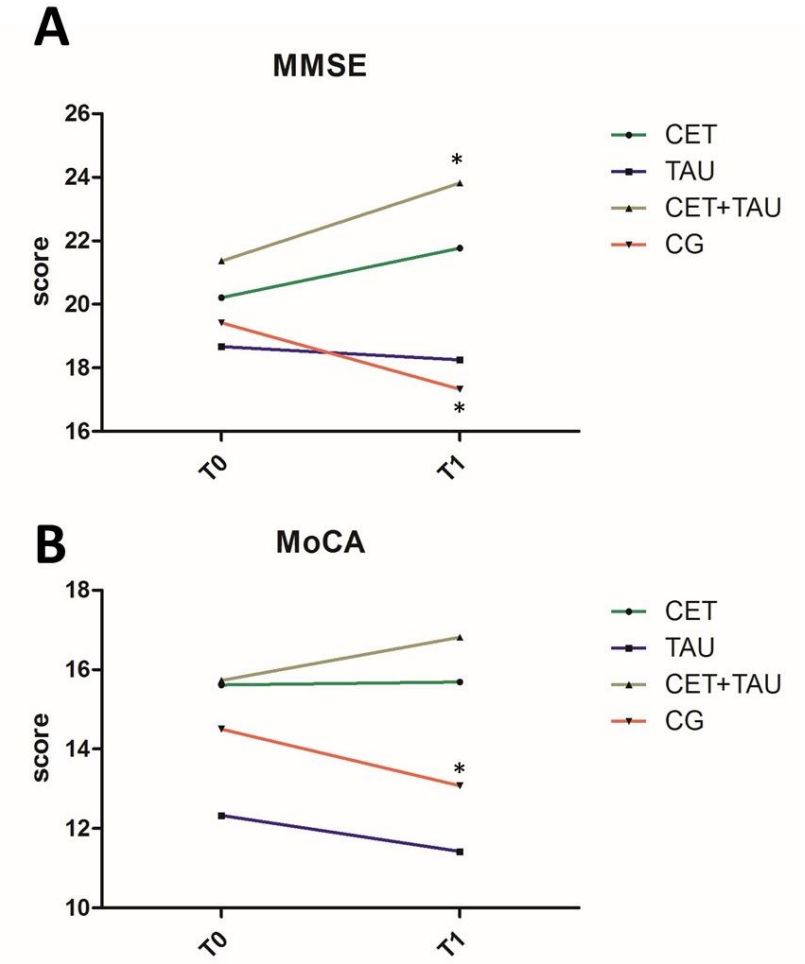

Figure 4.1. Global Cognition before and after interventions.

A) Mini Mental State Examination; **B)** Montreal Cognitive Assessment. Colors represents different interventions (green line for CET, blue line for TAU, brown line for CET+TAU and red line for CG). T0: baseline; T1: after 14 weeks. Values of significance represented by * for p<0.05.

4.7. Cytokines

At baseline, one-way ANOVA showed that TNF-α, IL-10, and hence TNF-α/IL-10 ratio were different between groups. Afterwards, Tukey's *post hoc* showed that these differences were present between TAU and CET+TAU for TNF-α (p=0.027), TAU and CG for IL-10 (p=0.015). CG was also different for the TNF-α/IL-10 ratio between CET (p=0.028) and CET+TAU (p=0.035).

Table 4.6. Cytokine concentrations before and after intervention

Variables	Groups	Measurements		ES (*d*)	Δ%
		Before	After 14 weeks		
IL-1β (pg/mL)[b]	CET	4.5(1.2)	4.0(0.3)	0.60	-11
	TAU	4.0(0.2)	3.8(0.5)	0.65	-3
	CET+TAU	4.3(0.4)	4.3(0.5)	0.19	0
	CG	4.6(0.9)	4.2(0.6)	0.29	-9
IL-1ra (pg/mL)[a]	CET	26.3(13.6)	35.1(13.7)	0.62	33
	TAU	29.1(19.3)	28.0(10.0)	0.36	-4
	CET+TAU	25.6(16.0)	24.9(8.1)	0.04	-3
	CG	26.8(12.9)	28.4(10.2)	0.26	6
IL-1β/IL-1ra ratio[a]	CET	0.2(0.1)	0.1(0.0)*	0.88	-39
	TAU	0.3(0.1)	0.1(0.0)*	1.00	-51
	CET+TAU	0.2(0.1)	0.1(0.0)	0.23	-16
	CG	0.2(0.1)	0.2(0.2)	0.26	0
TNF-α (pg/mL)[a]	CET	12.8(7.5)	9.7(3.9)*	0.99	-25
	TAU	8.6(6.4)	7.7(5.2)	0.57	-11
	CET+TAU	16.8(8.1)	18.3(6.9)	0.27	9
	CG	12.8(5.6)	9.6(3.7)*	0.68	-25
IL-10 (pg/mL)[a]	CET	3.0(1.9)	3.3(1.9)	0.07	7
	TAU	2.2(1.1)[#]	2.0(1.1)	0.32	-9
	CET+TAU	3.5(1.1)	3.5(0.7)	0.11	1
	CG	4.4(1.6)[#]	2.2(1.5)**	1.30	-35
TNF/IL-10 ratio[a]	CET	4.6(1.6)[#]	3.6(1.7)*	0.85	-22
	TAU	3.6(1.3)	4.0(1.6)	0.43	9
	CET+TAU	4.6(1.7)[#]	5.1(1.3)	0.51	9
	CG	3.1(1.5)[#]	3.7(1.5)*	1.14	22
IL-17 (pg/mL)[b]	CET	10.3(6.4)	9.1(4.6)	0.26	-11
	TAU	17.8(9.6)	14.9(6.5)	0.50	-16
	CET+TAU	17.4(10.7)	16.3(12.2)	0.11	-6
	CG	18.4(12.4)	19.0(13.5)	0.19	3

Data are presented in Mean(Standard Deviation); [a] compared using T-Test for paired samples; [b]compared using Wilcoxon signed ranked test; [#]different from control group at baseline; * significant for p value <0.05 compared to baseline; ** significant for p value <0.01 compared to baseline.

Repeated measures ANOVA showed no significant treatment*group interactions for IL-1β and IL-1ra (p>0.05). Univariate analysis were carried out and showed that IL-1β and IL-1ra did not presented significant changes over time within the four groups (p<0.05). A slight decrease was observed in CET and TAU groups for IL-1β levels (-11%, d= 0.6 and -3%, d=0.65, respectively), while a subtle and non-significant increase in IL-1ra concentration was observed in CET (d=0.62, p=.06). However, taken together, these little changes induced a significant effect using the IL-1β/IL-1ra ratio in both the CET and TAU groups (p=.04, -39% and p=.01, -51%, respectively).

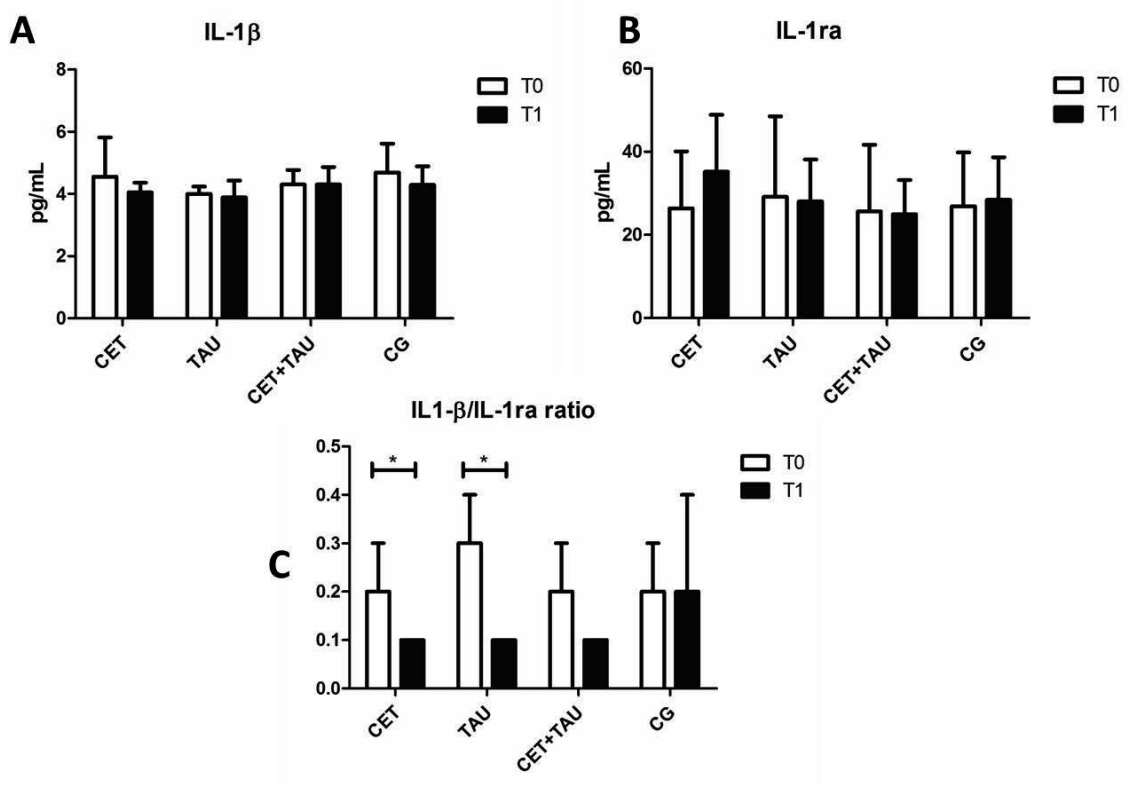

Figure 4.2. Graphical representation for IL-1β, IL-1ra and IL-1β/IL-1ra ratio

Plasma concentrations for **A**: IL-1β, **B**: IL-1ra, **C**: IL-1β/IL-1ra ratio. Values are expressed in means (white columns for baseline and black columns after 14 weeks), with standard deviations bars. T0: baseline; T1: after 14 weeks. Values of significance represented by * for p<0.05.

There was a no significant treatment or group interactions for TNF-α levels among the interventions (p=0.09). Afterwards, univariate analysis showed that a significant decrease in TNF-α levels was observed in CET (p=.02, d=0.99) and CG (p=.01, d=0.68), whereas no significant changes were seen in the other groups. Repeated measures ANOVA showed a

significant treatment*time interaction for IL-10 levels ($F(df\ 1, 44)=12.189$, $p=.001$), where a decrease of 35% in CG was observed. Additionally, a paired t-test was applied and showed that levels of IL-10 remain unchanged after interventions in the CET, TAU and CET+TAU groups, but for controls a large decrease was observed ($p=.008$, $d=1.3$). Taken together, these changes showed a significant treatment*group interaction for changes in TNF-α/IL-10 ratio ($p=0.01$), where afterwards univariate analysis showed a significant decrease in CET group ($p=.04$, $d=0.85$), while an increase in this ratio was observed for CG after 14 weeks ($p=.01$, $d=1.14$). The TNF-α/IL-10 ratio remain unchanged for TAU and CET+TAU groups, as can see observed in Table 4.6.

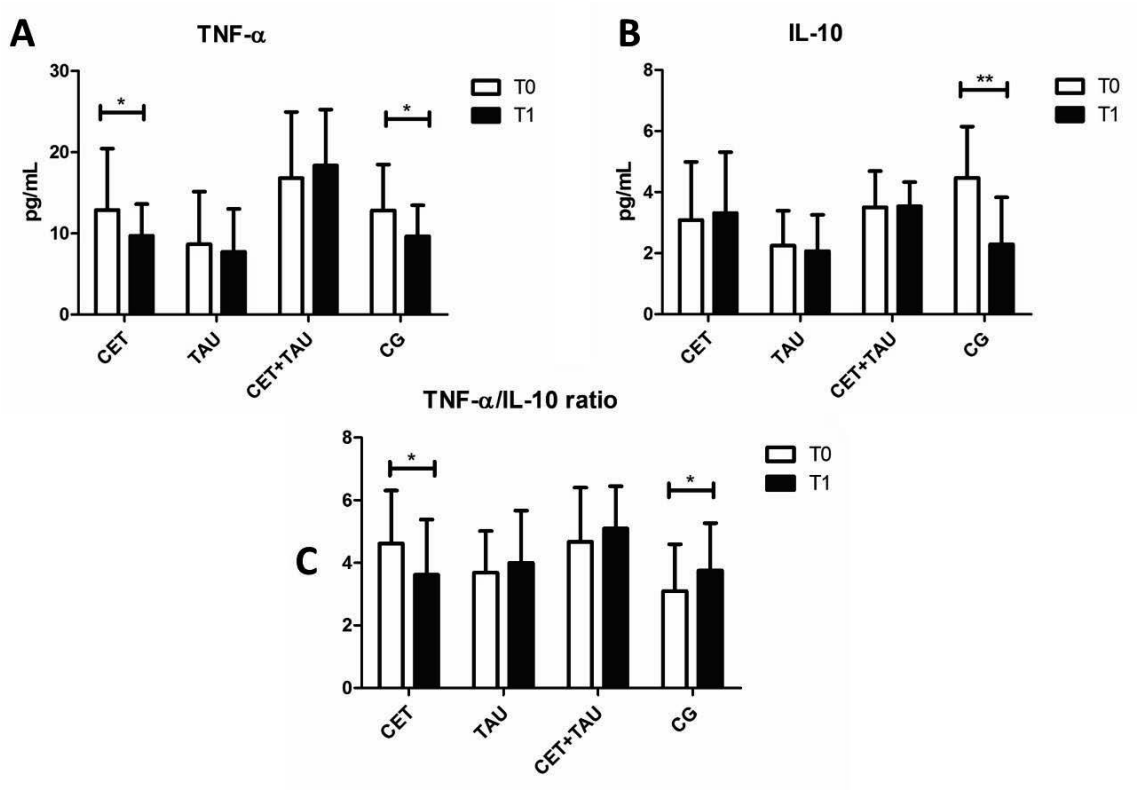

Figure 4.3. Graphical representation for TNF-α, IL-10 and TNF-α/IL-10 ratio.

Plasma concentrations for **A**: TNF-α, **B**: IL-10, and **C**: TNF-α/IL-10 ratio. Values are expressed in means (white columns for baseline and black columns after 14 weeks), with standard deviations bars. T0: baseline; T1: after 14 weeks. Values of significance represented by * $p<0.05$, and ** $p<0.01$.

No significant changes were observed in IL-17 levels for all groups between baseline and after 14 weeks (Figure 6.4).

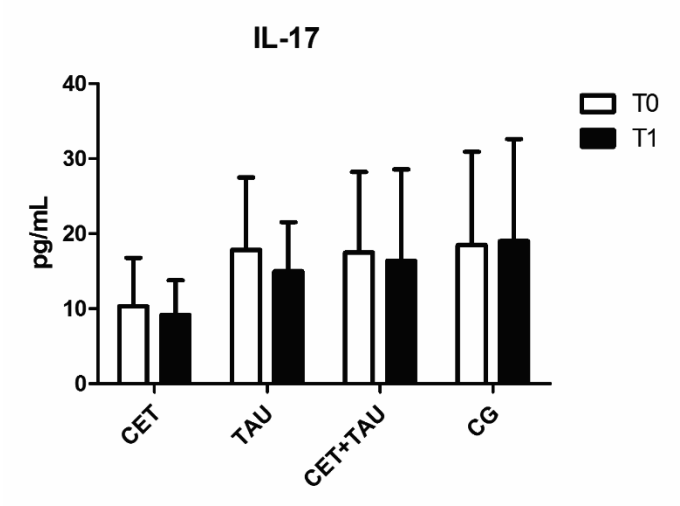

Figure 4.4. Graphical representation for IL-17 concentration.

Plasma concentrations are expressed in means (white columns for baseline and black columns after 14 weeks), with standard deviations bars; T0: baseline; T1: after 14 weeks.

4.8. MPO and MMP-9

Repeated measures ANOVA presented significant treatment*group interactions for MPO levels (p=0.03). Subsequently, univariate analysis (paired t-test) showed that MPO levels decrease in TAU (p=0.02; d=1.19), and no significant changes were observed in other groups, despite a slight decrease in CET+TAU (-13%) and a subtle elevation in CET (17%, d=0.62).

Table 4.7. MPO and MMP-9 before and after interventions

Variables	Groups	Measurements			
		Before	After 14 weeks	ES (*d*)	Δ%
Myeloperoxidase (ng/mL)	CET	223.58(211.38)	262.46(153.43)	0.62	17
	TAU	281.80(151.74)	216.72(168.93)*	1.19	-23
	CET+TAU	244.85(78.09)	214.13(44.86)	0.43	-13
	CG	198.32(104.75)	224.86(101.89)	0.23	13
MMP-9 (ng/mL)	CET	218.22(120.80)	208.72(115.69)	0.04	-4
	TAU	242.72(90.44)	162.22(81.98)*	0.83	-33
	CET+TAU	194.27(68.86)	167.19(38.56)	0.64	-14
	CG	181.36(102.98)	128.59(73.30)	0.45	-29

Data are presented in Mean(Standard Deviation); Comparisons using T-test for paired samples; *significant for p value <0.05 compared to baseline.

No significant treatment*group interactions were showed for the results in MMP-9 (p=0.322) between groups. However, as described in Table 4.7, there was a decrease in MMP-9 in TAU group after 14 weeks (p=0.04, d=0.83), and these levels remain unchanged in other groups.

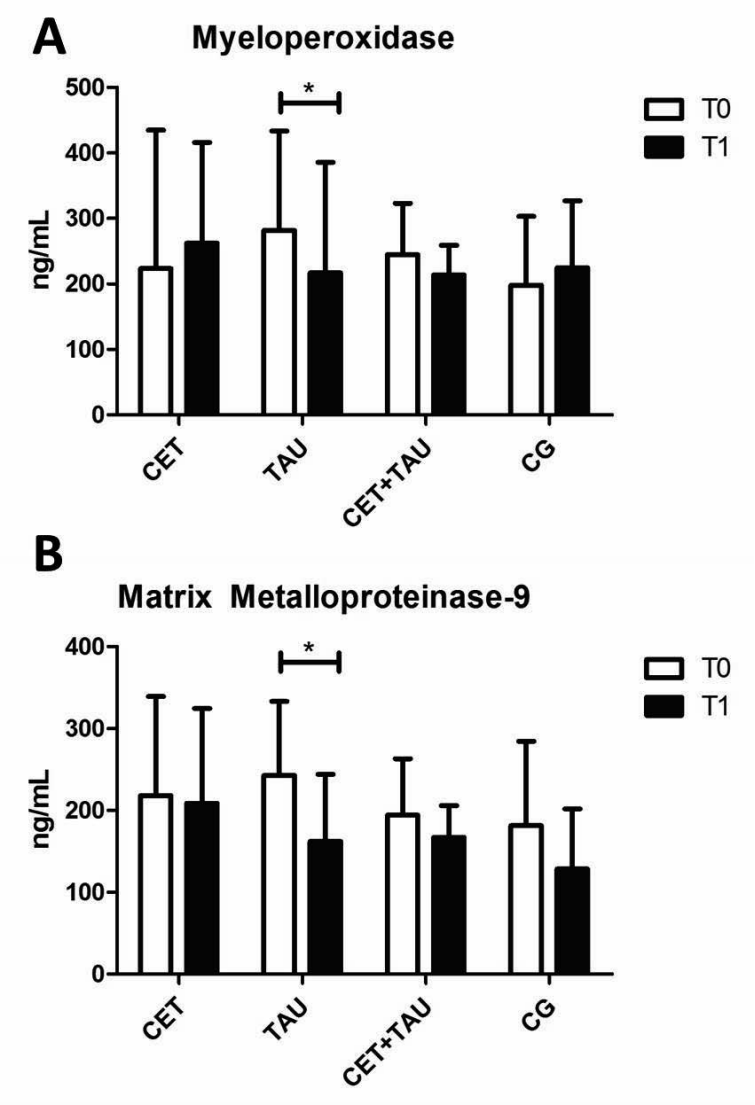

Figure 4.5. Graphical representation for MPO and MMP-9 concentrations before and after interventions.

Concentrations for **A**: Myeloperoxidase and **B**: Matrix Metalloproteinase-9. Values are expressed in means (white columns for baseline and black columns after 14 weeks), with standard deviations bars. T0: baseline; T1: after 14 weeks. Values of significance represented by * for p<0.05.

4.8. Peripheral marker of BBB permeability and neuronal damage

S100β and NSE: We performed repeated measures ANOVA, but assumptions were violated (i.e., large differences in SD) and none of the interactions (time x treatment) reached significance (*p*=0.308). However, adjusted plots indicated that all active treatment groups declined and only controls showed an increase in S100β. Multivariate stepwise backward regression analyses including the interleukins percent changes and baseline co-morbidity showed that only group membership significantly determined the changes in S100β, while there was a trend for changes in IL-1β to be independently associated with changes in S100β (*p*=0.056). All other variables (changes in IL-1ra, TNF-α and IL-10) were removed in these stepwise backward analyses and did not contribute to the model. These results are presented below in Table 4.8.

Table 4.8. Multiple Linear Regression Analysis of Cytokine-induced Blood-Brain Barrier permeability changes

	ΔS100β			
	R^2	β coefficient	*p* value	*p* ANOVA
ΔIL-1β		.278	.056	
ΔIL-17	0.163	.205	.162	.048
CCI baseline		.259	.076	

CCI: Charlson Comorbidity Index; Variables removed in the stepwise backward analyses: ΔIL-1ra, ΔIL-10 and ΔTNF-a.

Subsequently, univariate analyses were carried out using paired t-tests which also indicated that no significant changes were observed in serum S100β between 14 weeks of intervention in all groups. There was a trend for a decrease in serum S100β in CET (*p*=.06; *d*=0.68) but no changes were observed in TAU and CET+TAU. Meanwhile, a slight (but non-significant) increase in serum S100β in CG was observed after 14 weeks (26%, *p*=.44).

Table 4.9. Peripheral Markers of Blood-Brain Barrier permeability before and after interventions

Variables	Groups	Measurements			
		Before	After 14 weeks	ES (*d*)	Δ%
S100β (pg/mL)[a]	CET	5.2(4.4)	2.4(1.5)	0.68	-53
	TAU	9.7(5.3)	6.7(4.8)	0.79	-30
	CET+TAU	8.4(7.1)	7.3(4.6)	0.59	-13
	CG	7.4(5.9)	9.4(7.8)	0.26	26
NSE (ng/mL)[b]	CET	4.4(2.1)	4.7(0.9)	0.31	7
	TAU	3.0(1.5)	3.5(1.4)*	0.96	17
	CET+TAU	3.5(1.7)	3.0(1.0)	0.51	-16
	CG	5.3(4.3)	8.2(8.1)	0.32	54

Data are presented in Mean(Standard Deviation); [a] compared using T-Test for paired samples; [b] compared using Wilcoxon signed ranked test; *significant for *p* value <0.05 compared to baseline.

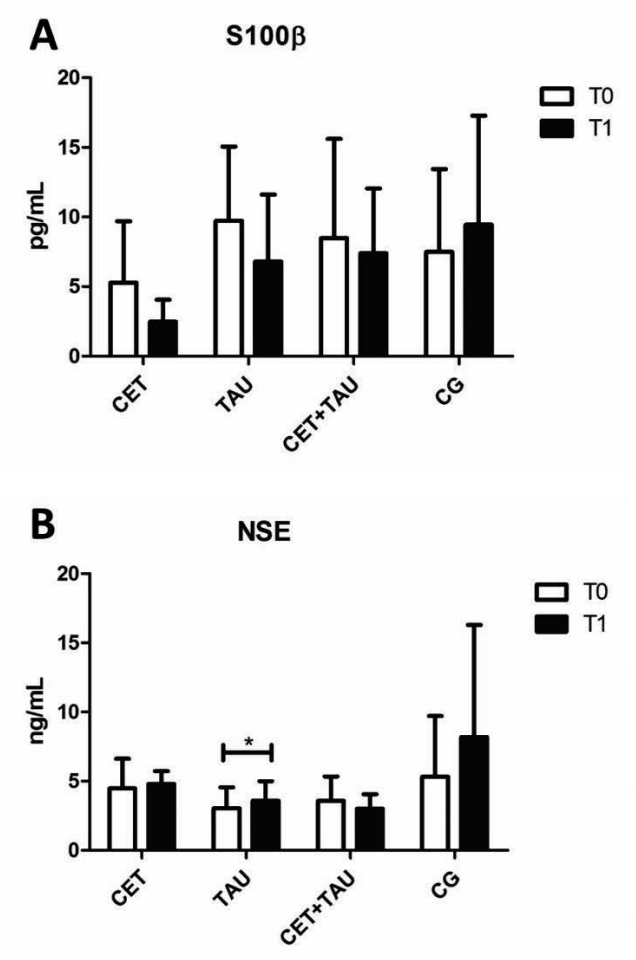

Figure 4.6. Graphical representation for S100β and NSE concentrations.
Serum concentrations of **A**: S100β, peripheral marker of blood-brain barrier permeability, and **B**: NSE, marker for neuronal damage. Values are expressed in means (white columns for baseline and black

columns after 14 weeks), with standard deviations bars. T0: baseline; T1: after 14 weeks; Values of significance represented by * for $p<0.05$

Repeated-measures ANOVA revealed that there was only a time effect for NSE changes (p=.04), but no significant treatment × time interactions (p>.05). Univariate comparisons showed no significant changes in CET, CET+TAU, and CG in comparison to baseline; however, a moderate increase in NSE was observed in the TAU group after the 14-week intervention (p = .03, d =0.96).

4.8. Correlation between changes

Table 4.10 presents Spearman's rank correlations between changes for biological variables evaluated.

Changes in monocytes were negatively correlated with changes on the MMSE and MoCA (r=-.339, p=.018 and r=-.377, p<.01, respectively). NSE changes were highly correlated with changes in IL-10 (r=.358), IL-17 (r=.315) and S100β levels (r=.359, p<.05 for all). Despite being non-significant, changes in S100β suggested a positively correlation with changes in IL-1β levels (p=.07, r=.257).

Table 4.10. Correlations Between Changes

	ΔIL-1β	ΔIL-1ra	ΔTNF-α	ΔIL-10	ΔIL-17	ΔS100β	ΔNSE	ΔMMSE	ΔMoCA
ΔMonocytes	-,236	***,360****	-,174	-,142	-,071	,080	-,114	***-,339****	***-,377*****
ΔIL-1β		-,028	,143	,127	***,329****	,257	,022	,161	,057
ΔIL-1ra			***,308****	***,289****	,110	-,128	,121	,123	,138
ΔTNF-α				***,532*****	,193	,095	,283	,027	,076
ΔIL-10					,222	,126	***,358****	,259	,099
ΔIL-17						,225	***,315****	-,127	-,067
ΔS100β							***,359****	-,118	-,205
ΔNSE								,011	-,134
ΔMMSE									***,649*****

Table presents values of Spearman correlation coefficient of variation (Δ) * Significant at level of p<0.05; ** Significant at level of p<0.01; Values of significance <0.05 are highlighted in bold.

IL-1ra changes were correlated with both TNF-α and IL-10 changes (r=.308 and r=.289, respectively, $p<.05$ for both). Meanwhile, although the correlation was not significant, changes in IL-10 and MMSE presented a trend ($p=.07$, r=.259).

5. DISCUSSION

5.1. Sample Characteristics

Before the analysis of the different interventions on each variable, we will dedicate a brief discussion to the characteristics of the sample. Firstly, it is important to observe that the participants who were involved in this study have higher average ages than other studies involving effects of exercise in similar populations (Bautmans *et al.*, 2005; Campbell *et al.*, 2009; dos Santos *et al.*, 2014; Bittar *et al.*, 2015). It is important to keep in mind the age of the sample for a contextualized analysis of the results, since the response to exercise at this age is different from that obtained with younger individuals. In fact, compared to other studies of the same environment (institutionalized) and the same population (Portuguese), the sample of this study has slightly poorer results for physical fitness at baseline (Lobo, Carvalho and Santos, 2010). It is noteworthy also to note that body mass and mean BMI are higher than some studies with older people in Europe (Battaglia *et al.*, 2016) and even more specifically in Portugal (Lobo, Carvalho and Santos, 2010).

The sample of this study was composed only of institutionalized elderly, where the level of daily physical activity is already expected to be lower than the community-dwelling people (Król-Zielińska *et al.*, 2011). This is reflected in the physical fitness of the individuals who, in fact, was different from other studies involving Portuguese community-dwelling elderly (Branco *et al.*, 2015). As expected, the institutionalized population is already known to be more debilitated. This is reflected in overall health status of CCI values, where almost all of the sample has three or more morbidities that interfere with their health status. The sample of this study is characterized as polymedicated according to the classification for Portuguese elderly individuals (Santos and Almeida, 2010), as seen in the information described in the Table 6.1. regarding the data of the CCI, and Table 6.1. regarding diseases incidence. In fact, the blood pressure values of most of the sample designate it as hypertensive, considering the cut-off values established for the Portuguese population (Macedo *et al.*, 2005). In addition, when comparison between Portuguese values for cell count to detect anemia (Fonseca *et al.*, 2016), about 27% of the study sample are within the values determined as moderate and severe anemia.

Although it was not the objective of the present study to verify the effects of exercise and supplementation on the variables mentioned above, is vital to previously

consider the characterization of the sample for any subsequent analysis of the results obtained in the interventions.

Regarding adherence to the different interventions, although the exercise and supplementation program was supervised during the 14 weeks, both interventions had difficulties in maintaining adherence to the sessions, as it is often seen in other studies involving elderly people, and the rate of drop-out was significant during the study. To match the interference of adherence among individuals allocated to different groups, the following criteria were applied for exclusion of the analyzes for those with less than 70% of: frequency in the exercise sessions (for the CET and CET + TAU groups); and days of intake of the supplement (for the TAU and CET+TAU groups). Because they did not participate in any type of supervised intervention, the control group (CG) was not subject to such exclusion criterion. Since the calculation of adherence within the CET + TAU group involved the participation of the elderly in both programs, this was the group that presented the highest drop-out rate. It is difficult to establish which were the main factors responsible for dropping out of the program, but we speculated that demotivation and low physical condition of the subjects were the main reasons for abandoning the program, even with the existence of external motivation by the staff of the nursing home and by the research team.

Although no adverse effects of supplementation with taurine were reported, only 60% of the sample that started the intervention with supplementation reached the minimum number of 68 doses over the 14 weeks (details of sample dropping-out are presented in Figure 4.1).

Regarding the environment of classes and evaluations, especially for the groups that involved exercise (CET and CET + TAU), all the procedures were standardized, occurred in the same place, and were given by the same teacher and auxiliaries. This care was taken to minimize differences in criteria, external motivation, intensity of exercise, among other factors recognized as capable of influencing the exercise sessions.

5.2. Considerations on the study design

This study was a non-randomized, prospective, naturalistic, controlled experimental design of independent samples with 14 weeks of intervention.

As expected for a non-randomized study, the mean values of some variables were not homogeneous between groups at baseline. However, the presence of a control group (for comparison), as well as the effect size calculations for each variable between the different interventions, helped to answer the study questions, minimizing the limitations due a heterogeneous sample.

Research Questions Addressed

1) Does combined exercise training improve BBB integrity in institutionalized elderly?

2) Does combined exercise training improve the anti-inflammatory profile or decrease the oxidative enzymes of the elderly?

3) Does 14 weeks of combined exercise training improve cognition in elderly, and this improvement could be correlated with changes in immune profile?

4) Can supplementation with taurine (alone) enhance the variables mentioned above in the same population?

5) Does the combination of exercise and supplementation with taurine have an additive effect to the isolated intervention on the several study markers evaluated?

6) Are there any association between the changes of peripheral markers of BBB permeability and oxidative and inflammatory markers over 14 weeks?

7) Are functional fitness variables altered after a CET program, taurine supplementation, or combination of both?

5.3. Physical Fitness Parameters

As expected for a combined exercise training, the maintenance and, in some cases, improvement in physical fitness performance occurred after 14 weeks of intervention.

Improvement in physical fitness has been demonstrated in previous studies with aerobic exercise (Branco *et al.*, 2015), strength training (Hunter, McCarthy and Bamman, 2004; Gerage *et al.*, 2013), and flexibility (Noradechanunt, Worsley and Groeller, 2017). Combined (or multimodal) training has also been shown to be effective to increase several physical fitness capacities in elderly (Foley and Hasson, 2016). However, these enhancements are not extended to all exercise programs, since factors such as duration of intervention, baseline physical condition of the sample and intensity of effort can be determinant issues in the significance and/or magnitude of the results. Previous studies with yoga/flexibility training did not demonstrated significant effects on the performance of physical fitness tests in the elderly (Furtado *et al.*, 2016; Marques *et al.*, 2017).

The results of the present study showed that practice of combined exercise training decreased the 8-FUGT test time, and increased the number of repetitions of the 2min-STEP-test. Both results were observed in the group who associated exercise and supplementation with taurine (CET+TAU). Although many physical fitness variables were maintained in CET, the magnitude of the effects observed was not the same in comparison to the combined intervention with supplementation.

Evidences suggests that supplementation with taurine may increase the ability of muscle producing force (da Silva *et al.*, 2014), and ameliorate the metabolic/energy control during strenuous activities (Lee, Paik and Park, 2003; Ahmadian, Dabidi Roshan and Ashourpore, 2017). However, considering that these studies enroll young/middle-aged individuals, it is difficult to extend these results to an elderly population.

Evidence in animal models also shown that Taurine supplementation increased the skeletal muscle force production and helped to ensuing the recovery period (Goodman *et al.*, 2009; Terrill *et al.*, 2016). The contractile and fatigability properties of muscle in absence of taurine due guanidinoethane sulfonate (inhibitor of taurine transporter) was studied in mouse, and resulted in 40% decline of muscle taurine content compared to untreated controls, which also significantly decrease the peak twitch force production (Hamilton *et al.*, 2006).

Different from animal model, however, the major effects of taurine supplementation in exercising humans are limited to interactions occurring outside of the skeletal muscle cell (Spriet and Whitfield, 2015), specially due to the lack of evidence regarding the rate of taurine content entering the muscle. Some good reviews in this topic are already published and bring recent and relevant information (Schaffer *et al.*, 2010; De Luca, Pierno and Camerino, 2015b; Spriet and Whitfield, 2015).

In fact, the mechanism by which taurine can influence muscle force production are knew, however, the evidences for the increased strength after supplementation in elderly are still scarce. It is plausible that the main mechanism by which CET+TAU group presented better results in some parameters of physical fitness is more related to the exercise and, to a less degree, to taurine supplementation *per se*. It must be considered that the physical parameters where significant changes after intervention in CET+TAU occurred are more related to agility and aerobic fitness rather than pure peak-torque muscle contraction. However, evidence for the taurine improving aerobic capacity have been reported in animals (Manabe *et al.*, 2003) and young/middle-aged humans (Beyranvand *et al.*, 2011; da Silva *et al.*, 2014). A small increase (d=0.41) on isometric strength measured by the HGT was also observed in CET+TAU, possibly explained by an addictive effect of taurine supplementation on the exercising elderly.

5.4. Hematological Markers

Although the purpose of this study was not to specifically verify changes mediated by exercise and supplementation in complete blood cell counts (CBC), a brief discussion of these results will be made. Despite the limited changes, their importance is significant for the interpretation of some of the results obtained.

Excluding the effect of acute infection, our leukogram showed that 14 weeks of supplementation with taurine decrease lymphocyte counts in older women. Contrary to our initial hypothesis, CET did not have a significant influence on reduction of the total leukocyte in these individuals. However, once again, attention is needed regarding the period of intervention and type of exercise involved.

Evidence suggests that exercising individuals throughout life have lower leukocyte levels than sedentary people (De Gonzalo-Calvo *et al.*, 2012). Controlled

studies developed in our laboratory also showed that intervention with 28 weeks of strength training with elastic bands decrease total leukocyte and lymphocyte in institutionalized elderly women (Chupel *et al.*, 2017). However, while not entirely conclusive, these effects reinforce the evidence that leukocyte levels and physical activity are closely related to overall health in the elderly. The existing evidence in this matter points to that participation in high levels of physical activity is associated with phenotypic and functional changes in the adaptive immune response, more precisely in lymphocytes subtypes, which attenuates the loss of effectiveness to generate potent immune responses (Moro-García *et al.*, 2014; Minuzzi *et al.*, 2017). A previous study in our lab showed that there is an inverse relationship between aerobic capacity and number of lymphocytes (Minuzzi *et al.*, 2017), and recognizing the existing decline in aerobic capacity (represented by the VO_{2max} levels) during aging (Ades and Toth, 2005), we propose that the maintenance/reduction of those cells with the exercise intervention can slowdown the ageing of the immune system. This mechanism might explain why exercising elderly maintain immune health even in advanced ages. Despite the difficulty in extending these effects to our results, perhaps a longer intervention period (>14 weeks) might promote a significant decrease of these levels in those individuals involved in CET and CET+TAU.

The mechanism by which taurine, alone, decreased lymphocytes after 14 weeks in elderly are still unknown. Comparisons between taurine transporter knockout and wild-type mice showed that RBC and platelets are lower and the packed cell volume smaller in taurine deficient than in taut+/+ mice. However, white blood cell count is significantly higher when taurine deficiency is present compared to non-deficient taurine transporter mice (Lang *et al.*, 2003), suggesting that taurine deficiency may lead to an imbalance in blood cells (Vijitjaroen *et al.*, 2015). Previous studies with supplementation showed that taurine displayed increased RBC, hematocrit, and hemoglobin, but decreased neutrophils (-45%) and platelets (Vijitjaroen *et al.*, 2015). Compared to that, taking in account differences in experimental model, our results had similar decrease in WBC components in elderly supplemented with taurine, but no changes in RBC or platelet count.

Regarding changes observed in RBC, significant decreases in MCH and MCHC in CET, TAU and CET+TAU groups were found. The significance of this changes may not have clinical implications, since changes in MCV and hemoglobin were not different between moments and groups (except for a decrease of hemoglobin in TAU group). Increased MCHC are seen in conditions such as hyperchromia, which occurs when the

hemoglobin is more concentrated inside the red cells. This events are more likely to be observed in patients with autoimmune hemolytic anemia (Park *et al.*, 2014).

Nevertheless, erythrocytes presented a trend to increase in CET+TAU and CET groups (much more pronounced in CET+TAU with large magnitude of effect), indicating the plausibility for exercise to maintain/increase this parameter. Hu and Lin (Hu and Lin, 2012) suggests that exercise training can increase hemoglobin and erythrocyte count due increased needed of oxygen in response to activity. It is proposed that the exercise ameliorates the hematopoietic environment even in elderly (Simmonds, Meiselman and Baskurt, 2013). A decreased erythrocyte's count was observed in sedentary older women (Ko *et al.*, 2014), showing that even in absence for a significant increase in hemoglobin levels after an exercise program, the increased physical activity might maintain stable erythrocyte count. In our study, only the exercising groups (CET and CET+TAU) presented this trend.

5.5. Cognition

Regarding cognition, the results showed a significant increase in the MMSE values for CET+TAU, while there were no significant changes for the other groups. The magnitude of effect and tendencies showed that participants who exercised (exercise alone and exercise with taurine) presented greater magnitude of effect on cognitive change (CET p=0.109 and CET+TAU p=0.01, moderate effect size for both). In contrast, control group decreased values of MMSE after 14 weeks. A similar trend was found in MoCA results, where the only significant effect was a decrease for the control group after 14 weeks, and no major changes were observed in the other groups.

Taken together, these results show that exercise was probably the factor responsible for the individuals' cognitive increase, with an additive effect of taurine supplementation for the CET+TAU group.

The effects of exercise on global cognition have been previously investigated, and there are several evidences for improvement in overall cognition after an exercise program (Kwak *et al.*, 2008; Hogervorst and Clifford, 2012). However, different types and time of interventions, as well the baseline cognitive level of the participants, may consist bias of analysis on the true effects that physical exercise generally exerts on the

cognitive parameters of the elderly (for more information, consult a good based-scientific review from Etnier and co-workers (Etnier *et al.*, 2006).

The mechanisms by which exercise improves cognition range from the influence on the immune system (Sartori *et al.*, 2012; Stranahan, Martin and Maudsley, 2012), to the improvement in the cardiovascular system as well (Intlekofer and Cotman, 2013; Kirk-Sanchez and McGough, 2014). As it will be discussed later, the groups that presented improvement in cognition presented, simultaneously, a better immune balance. However, cognitive outcomes may be due, in part, to the effects mediated by taurine supplementation.

In animal models, taurine has been shown to act to protect or even improving cognition (Malcangio *et al.*, 1989; Rivas-Arancibia *et al.*, 2000; Vohra and Hui, 2000), and maintenance of locomotor functions in fluoride-induced biochemical deficits in rats (Adedara *et al.*, 2017). Analogues of taurine such as homotaurine, have been proposed for therapeutic applications due to its antiamyloid activity (Caltagirone *et al.*, 2012). This effect might be, at least in theory, relevant in the treatment of severe cognitive impairment conditions like Alzheimer Disease. Due to the similarity with GABA, taurine is known as an inhibitory neurotransmitter and neuromodulator (Ripps and Shen, 2012). Taurine can bind to GABA receptors and act as an agonist, and exert neuronal hyperpolarization and inhibition (Bhattarai *et al.*, 2015), and hence decreasing the neuronal excitability. This involvement may explain the significance of taurine in cognitive function, since GABA influence cognition (Gabriella and Giovanna, 2010). The principal role of GABA is to reduce the neuronal excitability through CNS of mammals and, in humans, is also directly responsible for regulation of muscle tone (Watanabe *et al.*, 2002). The inhibition mediated through GABA receptors help in regulation of normal neuronal activity for appropriate network dynamics that support the maintenance of cognition (McQuail, Frazier and Bizon, 2015). The importance of supplementation with taurine in elderly is explained due the age-dependent reduction in their levels. Even in healthy elderly there are a 49% decrease in plasma taurine concentration in comparison with middle-aged individuals (Jeevanandam *et al.*, 1990), which may justify the supplementation in elderly population (Caine and Geracioti, 2016). Although physiological levels of taurine achieved by supplementation could generate several neuroendocrine responses in healthy brain, further research is needed in pathological conditions.

Although plasma levels of taurine were not quantified in our sample, it's speculated that the supplementation given (1,5g/day), during 14 weeks was sufficient to increase taurine content and potentially exert cognitive improvements. Perhaps, the mechanism by which this improvement occurred beyond the hypothesis of the GABAnergic pathway, is by an immunomodulatory action. As mentioned earlier, the CET+TAU group presented simultaneously to the enhanced cognition, a decrease in monocytes count. In fact, inspite the lack of statistical significance, the only groups who showed a tendency to decrease monocytes were the supplemented groups (for TAU -2%, a trivial effect d=0.15; and CET+TAU -19%, a moderate effect d=0.65). Taking into account these effects, we proposed that the correction of age-related taurine decline by supplementation in the elderly could be useful for cognitive performance, even in advanced ages.

These results further indicate that taurine and exercise had a combined/additive effect on cognition, since supplementation (*per se*), despite maintaining cognition during 14 weeks, did not induce significant increases on this variable.

Despite the lack of significant effects on elderly's cognition who only exercised (CET), the effect of this intervention in elderly's cognition cannot be ignored, since there are several studies showing the maintenance, and even the increase in cognition after an exercise program (Etnier *et al.*, 2006). In addition, it is possible that the overall baseline characteristics of the sample, considering their existing differences in some health parameters, might mediate the magnitude of the cognitive responses induced by the interventions. In fact, symptoms such as pain, exhaustion, feeling of sickness and discomfort – which frequently accompany the incidence of several comorbidities, may reduce the effect on cognition after an exercise intervention in an older sample. However, considering that the CET group presented a smaller CCI score in comparison to the CET+TAU, we can suggest that a combination of exercise and taurine supplementation was more effective to improve elderly's cognition than exercise alone during 14 weeks. It is possible that the neuroprotective effect of Taurine, and also the influence in neurotransmission due to its similarities with GABA, might potentiated the exercise effect on cognition in those participants who ingested the supplementation.

5.6. MPO and MMP-9

Oxidative stress is directly and indirectly related to the genesis of several neurodegenerative diseases, and most of these pathologies are closely related to BBB dysfunction. As part of the objectives of the present study, the responses to different interventions on MPO and MMP-9 levels of elderly women were analyzed. This aimed to verify the modulation of this enzymes concentrations by exercise and supplementation with taurine, as well as to verify if there were associations between these enzymes and markers of inflammation and BBB permeability.

As described previously, MPO levels decreased after supplementation with taurine (p=0.02; d=1.19), and slightly after combination of exercise and taurine (p>0.05, d=0.43).

Taken together, these results show that taurine supplementation can reduce levels of MPO in elderly women, which might have a public health importance. However, contrary to our hypothesis, the exercise intervention alone did not reduce the MPO levels, which indicates that the subtle reduction in this enzyme observed in CET+TAU group is more related to the taurine rather than to the exercise intervention.

It is well stablished that in excessive exercise the contracting myocytes produce RONS, which can overwhelm the antioxidant defence and lead to cell damage. However, moderate exercise and long-term enrollment in physical activity can reduce the oxidative stress damage due to increased stimulation of several antioxidant mechanisms (Aldred, 2007; Fisher-Wellman and Bloomer, 2009; Powers, Nelson and Hudson, 2011). It is possible that a longer exercise intervention period would be necessary to bring about the antioxidative adaptations needed. MPO is a marker of oxidative stress, and previously proposed as a useful indicator of risk and diagnostic tool for acute coronary syndromes (Loria *et al.*, 2008). While the increase of MPO concentration is not likely to be definite to cardiac illnesses, the significant reduction of MPO levels following the supplementation might suggests that taurine is devoid of inducing cardiovascular risk and, at the same time, can promote antioxidant benefits in this specific age group.

Taurine can lead to a reduction of 27% of MPO activity (Mühling *et al.*, 2002; Shimizu *et al.*, 2009), however, evidence for a reduction in MPO concentration due to supplementation is still scarce. In animal models, taurine decreases MPO levels in a dose-dependent manner (Nakajima *et al.*, 2010). It is possible that this effect is due to

production of Taurine Chloramine (TauCl), which reduces the HOCl toxicity and afterwards decrease the expression of oxidative enzymes and other pro-inflammatory cytokines (Marcinkiewicz and Kontny, 2014). It is suggested that the generation of these taurine derivatives with the induction of hemoxigenase-1 (HO-1), are synergistic actions able to induce an anti-inflammatory effect. However, studies using HO-1 knockout mice showed that TauCl inhibited the production of TNF-α, IL-6 and IL-12, clearly indicating that this taurine derivate might mediate the anti-inflammatory properties independently from HO-1 (Marcinkiewicz *et al.*, 2009).

The dose of taurine used in this study (1,5g/day) is the same proposed to be safe (Shao and Hathcock, 2008) and effective to produce beneficial effects (Fennessy *et al.*, 2003; Beyranvand *et al.*, 2011). This dose was demonstrated to increase taurine levels in blood and has a beneficial effect on macrovascular endothelial function and it is equivalent to the amount of taurine found in 100g of fresh fish (Fennessy *et al.*, 2003).

It is difficult to understand the reason by which reductions in MPO levels did not occurred in the CET group, however, some explanations can be suggested. Previous evidence in community-dwelling elderly people showed a reduction in MPO levels after 12 weeks of low-frequency, explosive resistance training (Beltran Valls *et al.*, 2014). Reduction of MPO was also shown after 12 week endurance training in people with cardiovascular risk (Richter *et al.*, 2005). However, the average ages of both samples were significantly lower than those in our study, and the type of exercise used might modulate differences in MPO responses over time. The reduction in MPO levels observed in TAU might have an important role in the treatment of Parkinson Disease, for example. A recent study points out that the chlorination of dopamine by MPO-derivant toxin $HOCl^-$ causes death of dopaminergic neurons in the substantia nigra (Jeitner *et al.*, 2016), which theoretically can be suppressed by taurine supplementation. However, further studies are needed in this matter.

Reduction in MPO levels plays an important role in coronary heart dysfunction (Hou *et al.*, 2013) and neurodegenerative diseases (Jeitner *et al.*, 2016). In both examples, other enzymes, such as MMP-9, appear to be involved in worsening of the clinical condition. Our results showed a reduction in MMP-9 levels in TAU group (p=0.04, d=0.83). However, despite subtle variations, concentrations of MMP-9 remained unchanged in the other groups.

MMP-9 plays important roles in immune function in pathogenesis and disease progression, being upregulated in several pathophysiological conditions and exacerbating disease progression (Yabluchanskiy *et al.*, 2013). Moreover, senescence may increase *per se* the total enzyme and activity of MMP-9 (Nadarajah *et al.*, 2011), which in turn creates an imbalance in the immune system that intensifies inflammation. In these cases, MMP-9 lead to increased BBB permeability contributing to neuronal disease progression (Dhanda and Sandhir, 2017).

Taurine is effective in the inhibition of MMPs expression induced by adiponectin (Kim *et al.*, 2010), but this is more related to suppression of MMP-1 and MMP-13. However, the evidence regarding the effect of taurine in reduction MMP-9 is limited (Vaz *et al.*, 2015). Regulation of MMP-9 can be modulated by several mechanisms such as the TNF-α and IL-1β signaling pathway (Brown *et al.*, 2007; Yabluchanskiy *et al.*, 2013), cytokines that can be both inhibited by TauCl (Marcinkiewicz and Kontny, 2014).

The evidence regarding MMP-9 reduction due to antioxidant supplementation are well investigated in animal and human models. Supplementation with luteonin for example, reduces MMP-9 levels significantly (Pandurangan *et al.*, 2014). Furthermore, supplementation with omega-3 downregulates, the MMP-9 activation, playing an anti-inflammatory role in animal (Kavazos *et al.*, 2015) and human models (Shinto *et al.*, 2009; Derosa *et al.*, 2012). In human pathology, antioxidant supplementation such as coenzyme Q10 in multiple sclerosis (Sanoobar *et al.*, 2015) and conjugated linoleic acid in patients with cancer (Mohammadzadeh *et al.*, 2013), significantly reduced MMP-9 levels.

We suggest that the significant reduction of the IL-1β/IL-1ra ratio seen in the TAU group may induce the decreased observed in MMP-9 levels for this group, since IL-1ra has been suggested to play a role in inhibiting the expression of MMP-9 *in vitro* (Nee *et al.*, 2004). Nevertheless, this process may occur together with other physiological mechanisms involving the antioxidant and anti-inflammatory actions of taurine, since the reduction of the IL-1β/IL-1ra ratio observed in the CET group did not produce the same decrease in MMP-9.

The evidence for the reduced production of MMP-9 due to taurine seems to involve the production of TauCl and suppression of kinases, such as protein kinase C (Prpic *et al.*, 1987), pertussis toxin sensitive guanine nucleotide kinase and protein

tyrosine kinase (Weinstein, Gold and DeFranco, 1991). All these kinases are involved in overexpression of MMP-9 and taurine might play a role in attenuating them (Park, Quinn and Schuller-Levis, 2002). Despite the fact that the levels of TauCl were not evaluated in our groups, it seems plausible that the dose of supplementation used, was enough to promote increased taurine content in blood, hence inducing production of TauCl at higher levels compared to the untreated groups.

5.7. Cytokines

There are some evidences showing that exercise practice, even when started at advanced ages, is able to reduce markers of systemic inflammation in older persons. Starkweather (Starkweather, 2007) observed that 30 minutes of walking, repeated five times per week during 10 weeks decrease levels of pro-inflammatory markers in older men and women. Cross-sectional studies show that individuals who reported low levels of physical activity had significantly higher levels of TNF-α and IL-6, both markers of inflammation (Colbert *et al.*, 2004). However, some data are still controversial, since exercise can either induce reductions as described above, or even no changes in pro-inflammatory cytokines concentrations (White, Castellano and Mc Coy, 2006). Most evidence in literature points to resistance or aerobic exercise-induce changes in inflammatory profile, and data regarding combined exercise training are still scarce.

As our results showed, none of the interventions promoted significant changes in IL-1β levels between pre-and post-14 weeks. Examination of effect size showed that the groups who obtained the highest values for magnitude of differences between pre and post comparison were TAU (d=0.65), followed by CET (d=0.6), despite the non-significance value obtained from the paired t-test.

It has previously been shown that taurine has the ability to decrease and/or prevent the production of IL-1β in animal models (Ozsarlak-Sozer *et al.*, 2016; Caetano *et al.*, 2017). A multi-nutrient component containing taurine decrease pro-inflammatory cytokines and improved performance in healthy men and women (Dunn-Lewis *et al.*, 2011). One mechanism by which taurine can inhibit the IL-1β production is through the increase in TauCl and TauBr, both homoamines with anti-inflammatory properties (Marcinkiewicz *et al.*, 1995; Park *et al.*, 1997; Barua, Liu and Quinn, 2001). Although

this study does not evaluate the production of TauCl and TauBr as a result of supplementation with taurine, and despite the plausibility of this mechanism on maintenance of the inflammatory balance, this magnitude of effect was not observed on the group who combined exercise with supplementation. One of the hypothesis of this study was that the combination of exercise and taurine could have an additive effect on this inflammatory cytokine. The information regarding the effect of exercise in modulating the IL-1β levels in elderly women is scarce, since the majority of the studies present results with animal models. In this sense, the reasons by which the effect of supplementation and exercise together did not produce an additive response in the human model need to be better investigated.

In addition, a comparison to other studies on the modulatory effects of exercise in pro-and anti-inflammatory cytokines might explain the tendency of our results. First, CET group presented a trend to decrease levels of IL-1β, simultaneously with a clear (although not significant) increase in IL-1ra levels with a moderate effect size (-11%, and +33%, respectively). IL-1ra is the antagonist of IL-1β, and its increased production can attenuate the effect of the pro-inflammatory cytokine IL-1β in humans (Sauer *et al.*, 1998; Arend, 2002; Iida and Komiyama, 2009). Taken together, these little changes caused a significant change in the IL-1β/IL-1ra ratio in both CET and TAU groups.

Previous evidence showed that elevation in IL-1ra expression – and hence IL-1β inhibition, reduced CNS inflammation in neurodegenerative conditions such as multiple sclerosis (Burger *et al.*, 2009). Moreover, levels of IL-1ra are elevated in those patients with better outcome in comparison to those with severe encephalitis and, among patients with herpes simplex virus, the increased IL-1β/IL-1ra ratio, is associated with increase in BBB permeability (Michael *et al.*, 2016).

Regarding the immunomodulatory effects of exercise in older population, the exercise intensity achieved in the present study was slight less than the informed intensity used in others who reported significant reduction in inflammatory cytokines after an exercise program (Santos *et al.*, 2012; Nascimento *et al.*, 2014), reason that might explain the lack of significance in reduced concentration of IL-1β after 14 weeks for CET and CET+TAU groups. Another factor may be the age difference between the participants in the present study and the previous publications cited above (~20 years). Forti and co-workers (Forti *et al.*, 2016) showed an increase in IL-1ra levels only in men who practiced

12 weeks of resistance training at high intensity, which is in accordance with the effect occurred in the CET group. The moderate effect (+33%) observed in this group might imply a benefit of exercise in combating low-grade inflammation and suppressing the increase in IL-1β levels. Since there was an absence of weight loss in the CET group after intervention, it's plausible to speculate that the slight reduction in IL-1β was due to exercise-induced better anti-inflammatory profile in recurrence of muscle work during the 14 weeks. However, the nonappearance of this effect in CET+TAU is a matter to future investigation. Considering the slight baseline differences in comorbidity between TAU and CET+TAU groups, this factor may explain the different response to treatment in modulation of IL-1β.

Different from other studies, that report no changes after exercise intervention in TNF-α levels (Prestes *et al.*, 2009; Ogawa *et al.*, 2010; Marques *et al.*, 2013), 14 weeks of combined exercise training significantly reduced its concentration with a large magnitude of effect in the CET group. However, no significant changes were observed in CET+TAU or TAU groups.

Previous cross-sectional study showed that there were no differences between the combination of exercise and anti-oxidant supplementation and exercise alone on long-term modulating levels of TNF-α (Colbert *et al.*, 2004). One of the mechanisms by which antioxidant supplementation can attenuate TNF-α formation is due to inhibition of NF-kB activation (Barua, Liu and Quinn, 2001). In the present study, none of the groups who were supplemented with taurine promoted changes in TNF-α levels, despite a subtle and non-significant decrease in TAU group (-11%, d=0.57). Although the precise mechanisms by which taurine derivate inhibit pro-inflammatory cytokine expression remains unclear, it is speculated that formation of TauCl may be a physiologic controlling pathway whereby a pathogenic action can be less harmless and TNF-α is no longer required. TauCl might act as a neutrophil-derived signaling molecule which is responsible for the downregulation of inflammatory mediators (such as TNF-α) production by macrophages (Redmond *et al.*, 1998). TauCl has been shown to act at the macrophage level, since in the mouse macrophage cell-line RAW 264.7, taurine does not influence the formation of NO nor TNF-α, however, it attenuates phagocyte-derived NO in a dose-dependent manner through transcriptional and translational processes, modulating TNF-α production by these cells (Park *et al.*, 1993). Perhaps, these mechanisms may support

the maintenance of TNF-α levels in TAU and CET+TAU groups, attenuating the expected increase of their formation during aging.

TNF-α decreased after 14 weeks in the CG, but the mechanism by which the occurrence of this reduction in elderly people who did not take part in the intervention program (nor exercise neither supplementation) is still unknown. An impaired immune function in aged individuals could be responsible for this decrease. In fact, as described below, this reduction was accompanied by a significant decrease in IL-10 levels in the same group, and lead to an increase in TNF-α/IL-10 ratio.

IL-10 is a key anti-inflammatory cytokine that inhibits TNF-α production (Saraiva and O'Garra, 2010). IL-10 plays an important role in inhibition of monocyte/macrophage activation, and hence suppressing the expression of TNF-α and several other pro-inflammatory mediators (Mosser and Zhang, 2008). The molecular pathway to inhibit TNF-α due to IL-10 expression involves the suppression of TNF-α gene transcription in human PBMC due to the activation of transcription factor NF-B (Wang *et al.*, 1994; Schottelius *et al.*, 1999). Different from previous findings, a genetic approach of Denys and co-workers (Denys *et al.*, 2002) showed that IL-10 seems to use at least two independent pathways for inhibiting TNF-α expression, a transcriptional and a post-transcriptional, by targeting either the 5' promoter or the 3'untranslated region (UTR). The mechanisms by which IL-10 exerts anti-inflammatory properties are somewhat contradictory and need to be better investigated in exercising humans. Some proposed mechanisms, however, seem to be diverse and dependent of the nature of the exercise stimulus (type / duration / intensity), the population studied (young / athlete / elderly), and the cell system investigated.

Long-term exercise intervention, for example, increase IL-10 formation probably due the induction of acute inflammatory response by bouts of exercises sessions, at repeated times, leading to an immune adaptation and increase in basal anti-inflammatory profile (Pedersen and Bruunsgaard, 2003; Petersen and Pedersen, 2005; Gleeson *et al.*, 2011). In fact, a specific immunoregulatory influence of exercise practice, is the increasing IL-10 and attenuating TNF-α formation (Moldoveanu, Shephard and Shek, 2001; Chupel *et al.*, 2017). In the present study, IL-10 levels decreased only in the CG, probably indicating that aging and physical inactivity were more definite in diminish the anti-inflammatory properties of the immune systems rather than in increasing pro-inflammatory cytokines *per se*. In this case, the increased physical activity promoted

during the 14 weeks of the exercise program might be constructed as a key way to create an anti-inflammatory environment in those individuals who practice exercise, since a maintenance of IL-10 levels was observed in these persons (CET changed +7% and CET+TAU changed +1%). The same condition was observed in previous findings, where elderly persons who performed exercise training maintained or even increased levels of IL-10, in comparison to the controls where a decrease was observed after 6 weeks (Bautmans *et al.*, 2005). Evidence for significant increases in IL-10 levels after exercise intervention have also been reported (Ribeiro *et al.*, 2012; Santos *et al.*, 2012; Simmonds *et al.*, 2016).

There is a growing number of studies on the effect of exercise on IL-10 levels, however, most of them enrolled patients with pathologies and chronic diseases such as diabetes (Kadoglou *et al.*, 2010; Simmonds *et al.*, 2016), coronary artery disease (Goldhammer *et al.*, 2005), and chronic obstructive pulmonary disease (Ramos *et al.*, 2014). Probably, these individuals often present much higher levels of pro-inflammatory mediators and less concentration of IL-10 and other anti-inflammatory cytokines. Such status may allow greater exercise-induced improvements in these biomarkers, compared to healthy individuals. Although the objective of the present study was not to evaluate cytokine response in elderly participants according to their pre-conditioning pathologies, it is important to known that the sample of the present study was institutionalized and had several comorbidities. However, the non-significant changes in IL-10 in CET and CET+TAU, as well as in those individuals who only were supplemented (TAU group) lead us to suggest, that the interventions used in this study were more effective in preserving IL-10 concentrations (which not occur in controls) rather than in increasing it.

Regarding supplementation, recent findings showed that the combination of fish oil intake and strength training increased IL-10 levels in older adults (Rodacki *et al.*, 2015). There are evidences for other antioxidant supplements used and their effects on IL-10 levels. For example, omega-3 supplementation attenuates the decline in IL-10 levels of patients with Chagas disease in comparison to controls (Silva *et al.*, 2017) however, effects of taurine supplementation had not been investigated in the immune system of exercising elderly.

In animal models, IL-10 was upregulated after taurine supplementation (Lu *et al.*, 2017). Our results showed that the groups who were supplemented with taurine had a

maintenance of IL-10 levels after intervention (-9% for TAU and +1% for CET+TAU, respectively).

However, considering that the formation of TNF-α and IL-10 are related, the analysis of each cytokine response alone does not explain the mechanism by which exercise and/or supplementation acted in modulating their changes observed after 14 weeks. That is why an analysis of the TNF-α/IL10 ratio was made.

When changes in TNF-α and IL-10 production are taken together, a significant decrease in TNF-α/IL-10 ratio in CET group was observed (p=.04, d=0.85), while an increase in this ratio occurred for the CG after 14 weeks (p=.01, d=1.14). TNF-α/IL-10 ratio remained unchanged for TAU and CET+TAU groups. Taken together, these results may explain the immunoregulatory effect of exercise that, even at advanced ages, ameliorates the anti-inflammatory balance (since the same occurred with the IL-1β/IL-1ra ratio). Similarly to the present study, the TNF-α/IL-10 ratio also decreased in elderly individuals engaged in aerobic training during 6 months (Santos *et al.*, 2012).

Further investigations are needed to clarify the mechanism by which exercise training and/or supplementation can ameliorate the anti-inflammatory profile, especially in elderly persons free of pathological conditions, but it is plausible that IL-6 may modulate this effect via regular exercise, since repeated exercise sessions induce increased expression of IL-6 which in turn is followed by an increase in IL-1ra and IL-10, both anti-inflammatory cytokines (Petersen and Pedersen, 2006).

No significant changes were observed in IL-17 levels after 14 weeks of interventions in all groups, despite a slight reduction in CET and CET+TAU.

In animal models, Alizadeh and co-workers (Alizadeh *et al.*, 2015) showed a significant increase in IL-17 levels after 8 weeks of different exercises (aerobic and anaerobic), and the same occurred in the group who additionally was supplemented with eicosapentaenoic acid (EPA). In humans, however, evidence for IL-17 changes due to an exercise intervention are still scarce. Furthermore, the disease state of the subjects may difficult the comparison between our results. A randomized controlled trial with children and adolescents with asthma submitted to exercise showed no reduction of IL-17 levels after 6-weeks of intervention (Andrade *et al.*, 2014).

IL-17 plays an important role in the disruption of BBB, especially due to its role in increasing the production of RONS (Huppert *et al.*, 2010). In multiple sclerosis patients (a situation where increased BBB leakage exists), the combined exercise training decreased the plasma and PBMC levels of IL-17, suggesting an anti-inflammatory and antioxidant effect of this type of training (Golzari *et al.*, 2010). It is difficult to explain why our results with exercising and supplemented elderly did not show significant reductions in IL-17 levels after intervention. Despite decreased the standard deviation in CET and TAU after interventions, with small effect size, the non-significance of the results obtained was probably mediated by the great dispersion of data regarding IL-17 levels between subjects in the groups. A shift towards to decline IL-17 in CET and TAU groups in comparison to baseline levels occurred with the groups that also demonstrated the major reductions in BBB permeability markers after intervention. However, the large intra-variability made it difficult to interpreted this data in a grouping sample.

5.8. Peripheral markers of Blood-Brain Barrier integrity

The main finding of this study is that the combined exercise training, the supplementation with taurine and the combination of both, done during 14 weeks, maintained the levels of the peripheral marker of BBB permeability (S100β) in institutionalized elderly, when compared to the untreated group. This pattern was not observed in the control group where the levels of S100β increased.

The S100β protein is recognized as a peripheral marker of BBB permeability (A. A. Kanner *et al.*, 2003; Marchi *et al.*, 2003, 2012). This protein is over expressed in neurodegenerative conditions such as Alzheimer and Parkinson Disease, as well as in traumatic brain injury, situations when an increase in BBB permeability appears (Steiner *et al.*, 2006; Mori, Asano and Town, 2010; Yardan *et al.*, 2011; Sathe *et al.*, 2012).

However, clinical significance of S100β levels in different fluids (such as serum or CSF), has different interpretations. First, the CSF is much more appropriate for monitoring discrete changes in S100β in CNS. On the other hand, serum concentrations of S100β may reflect processes in CNS with less accentuated dynamics. Second, changes in concentration of S100β in serum could be delayed and their changes can be less pronounced than in CSF (Yuan, 2014; Tsai and Huang, 2017). Thus, significant changes of S100β levels in serum could indicate a great extent of BBB leakiness.

Regarding the results of the present study, it is important to keep in mind that as expected in a non-randomized controlled study, a slight different average value of S100β between groups at baseline was verified, and this deserves some attention regarding the the reasons for these differences between subjects.

An analysis controlled by comorbidity status (dividing the sample in low and high comorbidity incidence), showed differences in S100β values between the two groups – low CCI (score ≤ 7) and high CCI (score ≥ 8). This cut-off value was established by being the median of CCI in the total sample. At baseline, a greater incidence of high comorbidities was verified in the TAU and CET+TAU groups, exactly the groups who presented higher mean values of S100β in comparison to the rest of the sample. Although the objective of the present study was not to verify the relationship between CCI and BBB-related markers, it is important to recognize that the initial stages of Alzheimer, Parkinson, and even previous stroke, which contribute to increase the CCI score, are related to increased levels of S100β (Rothermundt *et al.*, 2003; Michetti *et al.*, 2012) and hence, can explain the heterogeneity of this variable in our sample.

We first, performed a repeated measures ANOVA, but some assumptions were violated (probably due the large differences in SD) and none of the interactions (time x treatment) reached significance. However, adjusted plots of these analyses indicated that all active treatment groups declined and only controls showed an increase in S100β. A multivariate regression analysis was performed after including the interleukins change and baseline co-morbidity. The results showed that only group membership determined change in S100β significantly, while there was also a trend for change in IL-1β and baseline CCI to be independently associated with change in S100β.

Our results showed a slight trend for reduction in S100β for exercising and supplemented groups, but a subtle increase for controls in this parameter (+26%).

The pathway by which exercise can decrease the permeability of the BBB in humans is still subject to debate, and until today the few evidence regarding this topic is correlative and not causal.

In animal model, Guo and co-workers (Guo *et al.*, 2008) pointed out that the exercise (run) could ameliorate the BBB structure by ameliorating the integrity of basal lamina, in association with a decreased expression of MMP-9. Exercise could also protect

the striatal BBB, even in an animal model of diabetes (de Senna *et al.*, 2015). It clearly seems that exercise can cause a protective effect in the BBB structure.

The results of the present study corroborate other animal findings, since exercise produced an immunomodulatory effect, by reducing the pro-inflammatory cytokines and increasing the anti-inflammatory profile. Production of IFN-γ and TNF-α directly affect the BBB permeability (Larochelle, Alvarez and Prat, 2011). In fact, recent evidence showed that physical exercise inhibited the production of IFN-γ, IL-17 and IL-1β, and showed a significant upregulation of regulatory T cells levels, suppressing IL-6 and TNF-α production associated with the inhibition of adhesion molecules and re-establishment of tight junction proteins expression, thereby restraining the BBB permeability (Souza *et al.*, 2016). Another study carried out in animal models showed that physical training exerts a prophylactic effect enhancing IL-10, inhibiting MPO activity and production of TNF-α and IL-1β, changes that are associated with attenuation of BBB breakdown (Mota *et al.*, 2012).

Exercise can modulate the redox status in microvessels comprising the BBB, which suggest a role for exercise in preserving barrier integrity by modulatory activity of redox-sensitive small GTPase (Wolff *et al.*, 2014). Since claudin-5 is one of the proteins present in tight junctions of BBB, their decreased expression is related to increased BBB permeability (Jia *et al.*, 2014). Recent evidence demonstrated that rho kinase (ROCK) can induce phosphorylation of claudin-5, leading to TJ disruption and monocyte migration through the BBB (Persidsky *et al.*, 2006; Yamamoto *et al.*, 2008). Since ROCK is activated by rhoA GTPases (Julian and Olson, 2014), and exercised mice (runners) had less activation of rhoA than sedentary animals, this mechanism can also support the idea of exercise practice in maintaining BBB integrity. In fact, previous demonstration of claudin-5 expression maintained in microvessels, was shown in exercised mice, whereas in sedentary mice microvessels, this protein was less expressed, suggesting that exercise may impact the maintenance of TJ integrity through the rhoA/ROCK signaling pathway (Wolff *et al.*, 2015).

Regarding effects of supplementation with taurine on BBB permeability, our results showed a slight decrease in S100β after 14 weeks of supplementation in both, TAU and CET+TAU groups. The mechanism by which taurine acted on BBB integrity is probably due to its anti-inflammatory and antioxidant effect. Previous evidence showed that lipoic acid (an organosulfur compound derived from octanoic acid) inhibits monocyte

migration across the BBB and stabilizes the BBB integrity (Schreibelt *et al.*, 2006). Lipoic acid is a ROS scavenger that also induces endogenous antioxidants such as glutathione (Rochette *et al.*, 2013). Since MPO derived production of hypochlorous acid ($HOCl^-$) is a very powerful oxidative species that was previously related to BBB breakdown (Üllen *et al.*, 2013), and supplementation with taurine can abolish the formation of $HOCl^-$ (Marcinkiewicz and Kontny, 2014), it's plausible to think that 14 weeks of taurine ingestion could suppress the MPO-oxidative pathway and contributed to maintain the BBB integrity, beyond the potential to increase anti-inflammatory cytokines.

Considering these evidences, it seems clearly that one of the most important mechanisms by which both, exercise and taurine, can ameliorate the BBB integrity is due to an immunomodulatory pathway. Indeed, the correlation between changes in IL-1β and S100β levels were slightly associated (r=.257), and the same trend was observed between changes in S100β and IL-17 (r=.225) in total sample, showing that variations on BBB integrity may be related to modulation of inflammatory cytokines. This can be extended to the control group where an increase in TNF-α/IL-10 ratio was observed after 14 weeks, which could contribute to the subtle elevation observed in S100β.

Since all interventions (exercise and supplementation) act on an immunomodulatory pathway, this mechanism may prevent an increase in BBB permeability over time. However, the different magnitude of effects between interventions could probably be due the baseline comorbidity. Since CET presented the lowest CCI score between the four groups, especially in comparison to the CET+TAU, it seems that this phenomenon influenced the participants' intensity during exercise classes, which then influenced the training response and the magnitude of effect for grouping changes. This hypothesis is also confirmed in our results by the statistical significance mediated by baseline CCI in a multiple regression analysis of changes in S100β over time.

Another molecule used as a peripheral marker of BBB permeability is neuronal specific enolase (NSE). More than an indicator of BBB leakage, NSE is thought to be a specific marker for neuronal damage as well (Hans *et al.*, 1993; Sankar, Shin and Wasterlain, 1997; Rech *et al.*, 2006), but results need to be better exploited and interpreted with caution when the assessment occurs in blood (Chaves *et al.*, 2010). Since NSE does not appear increased in blood in physiologically healthy conditions, an over expression of this marker in serum or plasma is related to damage in neuron cells accompanied by BBB leakage, and it has been detected in pathological conditions, such as TBI (Stålnacke

et al., 2005), stroke (Gelderblom *et al.*, 2013; Haupt *et al.*, 2015; Lu *et al.*, 2015), and cognitive decline in older people (Jones *et al.*, 2013). In brain, however, NSE exerts a role in neuronal regeneration for a long time (Kirino *et al.*, 1983) and more recently, has been shown to act on differentiation and maturation (Isgrò, Bottoni and Scatena, 2015). NSE constitutes between 0,4% and 2,2% of the total soluble protein found in brain, and in some regions, it accounts for 3-4% of total soluble protein (Marangos and Schmechel, 1987), making it a useful marker for neuronal cells (Isgró *et al*., 2015). Zaheer and co-workers (Zaheer *et al.*, 2013) found a positive correlation between peripheral blood NSE levels and aneurysm extent evaluated by computed tomography scan, a negative correlation between the Glasgow scale and NSE levels, and a positive strong correlation between this biomarker and early neurological outcome assessed by modified Rankin scale (blood concentration of NSE is significantly higher when the worse outcome is present). In fact, circulating levels of NSE and S100β are correlated with radiological measures of the infarct volume within the first week after the stroke event (Ahmad, Wardlaw and Whiteley, 2012).

In the present study, the levels of S100β and NSE were correlated at baseline (r=292, *p*=.04), and the same pattern of correlation was found between changes in both markers (r=.359, *p*=.01). Taken together, these correlations may indicate the viability to use it as a marker for neuronal damage, which could be accompanied by BBB leakage (Marchi *et al*., 2004; Isgró *et al*., 2015). Nevertheless, contrary to our hypothesis, the changes mediated by exercise or supplementation with taurine on modulation of NSE levels did not reflect this tendency.

The baseline levels of NSE were similar between groups, however, TAU increased its levels significantly after 14 weeks of supplementation (Table 6.9.). Even so, its level remained lower than in CET and CG groups. This level of significance was not observed in the other groups, where CET, CET+TAU and CG promoted only slights changes after 14 weeks. A comparison between NSE concentration among the four groups after intervention showed differences between CET+TAU and CG (where percent change for these groups after intervention were -16% and +54%, respectively).

NSE in serum has been proposed to be increased in cases of BBB permeability (Tanabe *et al.*, 2001; Marchi *et al.*, 2003; Lima *et al.*, 2004) or structural damage to neuronal cells (Streitbürger *et al.*, 2012). However, the precise mechanism by which intervention with taurine and exercise can act on NSE levels are still unknow.

Taurine is one of the most abundant free amino acids in the brain and is essential to the normal growth and development of the nervous system (Saransaari and Oja, 2000), being related to neurogenesis, differentiation (Gebara *et al.*, 2015), and neuroprotection (El Idrissi, Shen and L'Amoreaux, 2013). Since NSE in brain is also involved in maturation of neuronal cells (Isgrò, Bottoni and Scatena, 2015), an interaction between taurine content in brain and NSE levels can be hypothesized. However, until this date, there were no studies involving taurine supplementation and NSE levels in humans.

An *in vitro* study increased expression of NSE in neurons was shown after culture with taurine (Chen *et al.*, 1998). Taurine also protected neuron survival, improved neuronal proliferation and increase neurotrophic factors in animal model by increasing expression of NSE in fetal rat brains (Liu *et al.*, 2013).

It would be plausible to think that the above mechanism could explain the increase of NSE in the group that supplemented with taurine. However, regarding the methodology of the present study - where the analysis of NSE occurred only in the blood and not in the CSF, it is difficult to know the precise mechanism by which taurine promoted the increase of NSE serum levels. We would expected that an increase in NSE would occurred simultaneously with an increase in S100β. This is further supported by the fact that there was a direct correlation between S100β and NSE levels at both, baseline and changes over 14 weeks. However, since the TAU group showed a trend of decrease in S100β, it was surprising to note that the same group was the only one to show an increase in NSE.

However, in the group that supplemented with taurine in association with exercise (CET+TAU), a slight decrease in NSE levels was observed after 14 weeks (-16%). This results seems to be more plausible, since S100β concentration also decreased in this group, suggesting a reduction in BBB permeability.

6. CONCLUSION

To date, this was the first study that looked at the effects of a long-term physical exercise and supplementation intervention on markers of BBB integrity in the elderly. Despite some limitations, this work addresses important contributions to the field of sports science and medicine.

The major conclusions of this study were:

- The practice of 14 weeks of combined exercise training promoted the maintenance of the blood-brain barrier structure in elderly women;
- The supplementation with taurine also acted beneficially to maintain the integrity of the blood-brain barrier, however, there was no additive effect from association of exercise and supplementation on this structure;
- The combined exercise ameliorated the inflammatory balance in the elderly, maintaining the concentration of anti-inflammatory cytokines and attenuating the formation of inflammatory mediators;
- The supplementation with Taurine lead to a decrease in oxidative enzymes related to increased blood-brain barrier permeability (such as myeloperoxidase and matrix metalloproteinase-9), but statistically significant results were only observed in the group who only took the supplementation;
- It seems that the comorbidity status is determinant to the magnitude of effects mediated by the different interventions, mainly on the concentration of cytokines, oxidative enzymes and markers of blood-brain barrier permeability;
- There is an effect of exercise training on increased global cognition, but the supplementation (alone) did not demonstrated significant effect in improving this parameter;
- Some components of physical fitness were significant enhanced only on those groups who made the exercise training.

Considering the results obtained from this study it is possible to suggest that the exercise (alone) is the best intervention to maintaining the levels of markers of the BBB integrity and neuronal damage in elderly. In the same manner, this type of intervention is also efficient in improving the anti-inflammatory profile.

In turn, taurine supplementation, when administrated alone, also seem to be a feasible option for the immune inflammatory balance and was more effective in

decreasing the concentration of oxidative enzymes, especially those closely linked to the BBB leakage evaluation (MPO and MMP-9).

The combination of both interventions (exercise + taurine), was the most efficient method to develop/maintenance the physical fitness in the elderly. In addition, MMSE and MoCA scores were only significantly increased in this group, this being the best option to increase the cognitive profile in the elderly.

6.1. Limitations

Despite the strengths of the study's conclusions, and as occur in several studies with humans, some limitations are worthy of note:

Firstly, the non-randomization of the sample was probably the main factor to induce heterogeneity in some variables at baseline. In accordance to the magnitude of effect observed for some parameters after 14 weeks, it seems that the different baseline comorbidity index between groups might represent a limiting factor to create powerful comparisons between interventions. Secondly, the small sample size for each group at the final analysis (due the rate of drop-out during the study) might construct a negative factor to perform some statistics (such as multivariate analysis and regression models), specially because the presence of less than ten individuals for some analysis (in CET+TAU group) leads to misleading interpretation and could increase the error rate. To avoid this problem, several results were drawn through applying univariate analysis. Also, cytokines concentrations are very variable in advanced ages, and given the accuracy of our estimates, a larger sample size may produce different results.

Other limitation is the use of peripheral markers of BBB damage, such as S100β and NSE. Despite the validation of those serum markers as indicators for BBB permeability in humans, is possible that studies using CT scan or CSF-related markers would have yielded different results.

6.2. What this study adds and future directions for BBB research and exercise

As mentioned earlier and, despite some limitations, the present study adds important insights to the field of exercise science and medicine.

First, the possibility to use safe and inexpensive non-pharmacological therapies such as exercise and supplementation with taurine to induce better health outcomes in the elderly is worth of attention, since it can represent a new approach to co-treatment of several age-related pathologies.

The focusing of exercise on blood-brain barrier integrity is still new and until the date most research has been done looking at acute effects. However, as the present study suggests, the importance of long-term exercise might represent a powerful tool to ameliorate the blood-brain barrier condition and the immune system. To our knowledge, this was the first study to verify the effects of long-term exercise in markers of blood-brain barrier structure in the elderly.

Further research is needed to provide evidence of the exercise effects in a wide range of ages (>20 to 80 years old) and the possibility to maintain the structure of BBB throughout life. Some results of the present study involving exercise and supplementation have public health relevance, since their effects seems to be associated with a better outcome of neurodegenerative diseases and, in addition, can provide better health-related quality of life of the elderly population.

In addition, taurine supplementation appeared to be more effective in some markers (such as IL-1β, myeloperoxidase and matrix metalloproteinase-9), when given alone, rather than in combination with exercise. This may also represent a powerful mechanism as an auxiliary in treatment of diseases that compromise the ability of old person to perform exercise. Other amino acids, vitamins, and several potential nutritional components deserve attention and should be better investigated further. However, our results show the importance in focusing in components like taurine, which can be important in targeting dramatic health condition, and could represent a safe and inexpensive application for adjuvant treatment of some diseases related to oxidative stress and brain endothelial injury. Since increased levels of pro-inflammatory cytokines cytokines and reactive oxygen and nitrogen species could mediate the blood-brain barrier permeability, pharmacological and non-pharmacological therapies against these particular agents could also be investigated as strategy for treatment of cognitive impairment and neurodegenerative conditions.

The effects of exercise in Alzheimer and Parkinson's Disease also needs to be investigated in humans, since the blood-brain barrier in these conditions is often disrupted

and the potential use of non-pharmacological therapy might represent an important co-adjuvant in treatment of those neurodegenerative conditions.

The role of exercise in depression needs further research in the elderly, however, an attempt to introduce the analysis of blood-brain barrier permeability is also important, since this structure controls the influx of amino acids responsible for the generation of neurotransmitters associated with this disease pathology. Research regarding the effect of exercise in brain angiogenesis and barrier formation also need to be investigated.

7. REFERENCES

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ANNEX

ANNEX 1

QUESTIONARIO BIOSSOCIAL

1	**Nome completo:**_____
2	**Qual a sua idade?** _____
3	**Sexo** 1. Masculino 2. Feminino
4	**Estado civil:** 1.Solteiro 2. Casado/união de fato 3.Viúvo 4.Separado/divorciado
5	**Escolaridade:** 1.Nunca frequentou a escola 2.Não completou Primário 3.Primário 4.Preparatório 5.Secundário 6.Ensino profissional 7.Universitário
6	**Naturalidade (Concelho):** _____
7	**Residência (Concelho):** _____
8	**Onde vive atualmente?** 1.Casa própria 2.Lar 3.Casa dos filhos 4.Casa dos parentes
9	**Pratica exercício físico/ginástica de manutenção/ginásio/prática corporal** 1. Sim 2.Não

Índice de comorbilidade de Charlson
(Mourão, 2008; Charlson et al., 1987)

ICC

Instruções para preenchimento: Marcar com uma cruz caso seja acometido por uma ou mais destas doenças ou condições clínicas listadas em baixo:

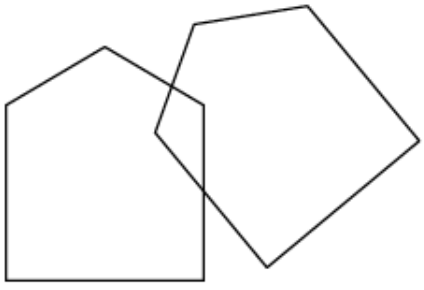
	1	Enfarte do Miocárdio
	2	Insuficiência Cardíaca
	3	Doença Arterial Periférica
	4	Doença Cerebrovascular (AVC)
	5	Demência
	6	Doença Respiratória Crónica
	7	Doença do Tecido Conjuntivo
	8	Úlcera Gastroduodenal
	9	Hepatopatia Crónica Leve
	10	Diabetes
	11	Hemiplegia
	12	Insuficiência Renal Crónica Moderada/Severa
	13	Diabetes com Lesão em Órgãos Alvo
	14	Tumor ou Neoplasia Sólida
	15	Leucemia
	16	Linfoma
	17	Hepatopatia Cronica Moderada/Severa
	18	Tumor ou Neoplasia
	19	Sida definida
	20	_____

ANNEX 2

	Mini Exame do Estado Mental (Guerreiro et al., 1994; Morgado et al. 2009)	**MMSE**
I	**Orientação** (Um ponto por cada resposta certa)	
1	Em que ano estamos?_____	
2	Em que mês estamos?_____	
3	Em que dia do mês estamos?_____	
4	Em que dia da semana estamos?_____	
5	Em que estação do ano estamos?_____	
6	Em que país estamos?_____	
7	Em que distrito vive?_____	
8	Em que terra vive?_____	
9	Em que casa estamos? _____	
10	Em que andar estamos? _____	
	Pontos:_____	
II	**Retenção** (contar um ponto por cada palavra corretamente repetida)	
11	"Vou dizer três palavras; queria que as repetisse, mas só depois que eu as dizer todas, procure sabê-las de cor":	
	(**PÊRA – GATO – BOLA)**	
	Pontos:_____	
III	**Atenção e cálculo** (um ponto por cada resposta correta. Se der uma errada mas depois continuar a subtrair, consideram-se as seguintes como corretas. Pára ao fim de 5 respostas)	
12	"Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado voltar a tirar 3 e repete assim até eu dizer para parar" 30__27___24___21___18___15____	
	Pontos:_____	
IV	**Evocação** (um ponto por cada resposta correta)	
13	"Veja se consegue dizer as 3 palavras que pedi há pouco para decorar" (Pêra – Gato – Bola)	
	Pontos:_____	

Part 2

V	**Linguagem** (um ponto por cada resposta correta)
14	"Como se chama isto?" Mostrar os objetos: **Relógio e lápis** **Pontos:**_____
15	"Repita a frase que eu vou dizer: "O RATO ROEU A ROLHA" **Pontos:**_____
16	"Quando eu lhe der esta folha, pegue nela com a mão direita, dobre-a ao meio e coloque-a sobre a mesa", (ou "sobre a cama", se for o caso); dar a folha, segurando com as duas mãos. **a) Pega com a mão direita; b) Dobra ao meio; c) Coloca onde deve** **Pontos**_____
17	"Leia o que está neste cartão e faça o que lá diz". Mostrar um cartão com a frase bem legível, **"FECHE OS OLHOS**"; sendo analfabeto lê-se a frase. *Fechou os olhos* **Pontos**_____
18	"Escreva uma frase inteira aqui". Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação. **Frase:**_____ **Pontos**_____
VI	**Habilidade construtiva** (um ponto pela cópia correta do desenho)
19	Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar tremor ou rotação.

Desenho	**Cópia**
	

Pontos_____

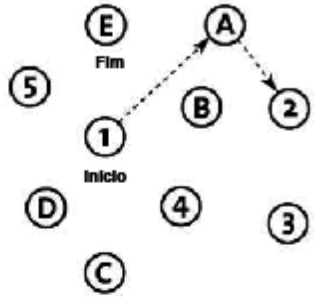
Part 3

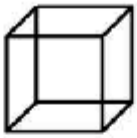
MONTREAL COGNITIVE ASSESSMENT (MOCA)

VERSÃO PORTUGUESA – 7.1 VERSÃO ORIGINAL

Nome: _____ Idade: _____
Género: _____ Data de Nascimento: _____
Escolaridade: ____ Data de Avaliação: _____

VISUO-ESPACIAL / EXECUTIVA





Copiar o cubo

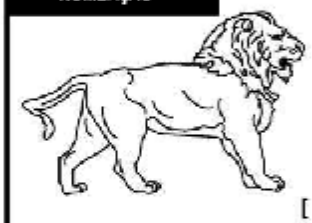
[ ] [ ]

Desenhar um Relógio (onze e dez) (3 pontos)

[ ] Contorno [ ] Números [ ] Ponteiros

Pontos: __/5

NOMEAÇÃO



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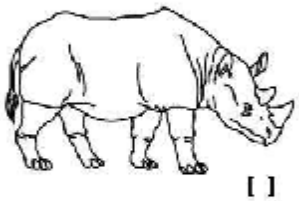

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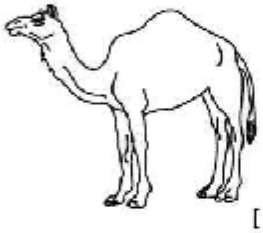

[ ]

__/3

MEMÓRIA — Leia a lista de palavras. O sujeito deve repeti-la. Realize dois ensaios. Solicite a evocação da lista 5 minutos mais tarde.

	Boca	Linho	Igreja	Cravo	Azul
1º ensaio					
2º ensaio					

Sem Pontuação

ATENÇÃO

Leia a sequência de números. (1 número/segundo) O sujeito deve repetir a sequência. [ ] 2 1 8 5 4
O sujeito deve repetir a sequência na ordem inversa. [ ] 7 4 2 __/2

Leia a série de letras (1 letra/segundo). O sujeito deve bater com a mão cada vez que for dita a letra A. Não se atribuem pontos se ≥ 2 erros.
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Subtrair de 7 em 7 começando em 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 ou 5 subtracções correctas: 3 pontos; 2 ou 3 correctas: 2 pontos; 1 correcta: 1 ponto; 0 correctas: 0 pontos __/3

LINGUAGEM

Repetir: Eu só sei que hoje devemos ajudar o João. [ ] O gato esconde-se sempre que os olhos entram na sala. [ ] __/2

Fluência verbal: Dizer o maior número possível de palavras que comecem pela letra "P" (1 minuto). [ ] _____ (N ≥ 11 Palavras) __/1

ABSTRACÇÃO

Semelhança p.ex. entre banana e laranja = fruta [ ] comboio - bicicleta [ ] relógio - régua __/2

EVOCAÇÃO DIFERIDA

	Deve recordar as palavras SEM PISTAS	Boca [ ]	Linho [ ]	Igreja [ ]	Cravo [ ]	Azul [ ]	Pontuação apenas para evocação SEM PISTAS
Opcional	Pista de categoria						
	Pista de escolha múltipla						

__/5

ORIENTAÇÃO

[ ] Dia do mês [ ] Mês [ ] Ano [ ] Dia da semana [ ] Lugar [ ] Localidade __/6

©Z.Nasreddine MD

Examinador: _____

TOTAL __/30

Versão Portuguesa: Freitas, S., Simões, M. R., Santana, I., Martins, C. & Nasreddine, Z. (2013). *Montreal Cognitive Assessment (MoCA): Versão 1.* Coimbra: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

Exercise and taurine supplementation: from antioxidant to ergogenic effects

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Abstract:

Taurine (2-aminoethanesulfonic acid) is one of the most abundant amino acids in the human body. Animal and human studies have shown that supplementation with taurine has several beneficial actions, such as anti-inflammatory, antioxidant and neuroprotective effects, as well the health-related benefits on endothelial, cardiac and skeletal muscle function. In sport performance, taurine has been widely studied in several commercial beverages, since is assumed to act together with other substances (i.e., caffeine, glutamine, BCAA) in improving performance. While there is an abundance of good quality data supporting the ergogenic and health-related benefits of taurine supplementation in a variety of different applications in animal model, a lack of conclusive results remains in human, probably due to different dependent factors such as dose, age, pre-conditioning disease status and diet. This systematic review will focus firstly on screening the evidences of supplementation with taurine in association with exercise in humans, in performance and health-related biomarkers. Secondly, will be focused on different effects of taurine supplementation in animal and human models, discussing it application to promote health and as strategy in treatment several pathological conditions.

Key Words: taurine; exercise; inflammation; disease;

1. INTRODUCTION

There are emerging attempts to study the role of non-pharmacological therapy for treatment of systemic inflammation and oxidative stress in humans. In this case, the exercise is pointed as a potential mechanism to ameliorate healthy conditions in presence of clinical pathology, and their association with supplementation have been formed a basis against immunosuppression-related diseases (Pedersen and Hoffman-Goetz, 2000; Kohut and Senchina, 2004; Bjelakovic *et al.*, 2012; Conti *et al.*, 2016). At the same time, the use of supplements has been widely studied in the field of sports, since many well controlled clinical trials have reported about the benefit of supplementation with vitamins (Veasey *et al.*, 2015), amino acids (Figueroa *et al.*, 2016) and proteins (Ferguson-Stegall *et al.*, 2010; Hansen *et al.*, 2015) in improvement of several physiological mechanisms linked to exercise performance. Evidence from animal model emerged in the last decades showing the effects of supplementation of vitamins (Aumailley *et al.*, 2016; Minshull *et*

al., 2016) and amino acids (Cruzat *et al.*, 2014; Zhao *et al.*, 2016) associated with exercise, on markers of inflammation, muscle damage and oxidative stress. However, the data remain controversial (Kim, Park and Lim, 2016). One type of amino acid that has received increased attention in recent years is taurine, since it has been linked to an anti-inflammatory, antioxidant and hypothetical ergogenic effects (Lee, Paik and Park, 2003; Marcinkiewicz and Kontny, 2014). In animal and human models, taurine has been proposed to upregulate the anti-inflammatory balance in cardiac disease (Lu *et al.*, 2017), to decrease adiposity (Caetano *et al.*, 2017), and to protect the body against the diabetes cardiovascular complications (Zhang, Bi, *et al.*, 2004; Ito, Schaffer and Azuma, 2012; Imae, Asano and Murakami, 2014; Sun *et al.*, 2016). Despite the benefits described above by their usefulness in treatment of different types of diseases, the possible effects of taurine in exercising humans remains unanswered, once only a few controlled trials with taurine supplementation in this population have been reported. Until the date, in exercising humans, taurine have been proposed to attenuate the arterial stiffness due eccentric muscle contractions (Ra *et al.*, 2016b), to prevent oxidative stress (Zhang, Izumi, *et al.*, 2004) and to reduce the delayed onset muscle soreness (Ra *et al.*, 2013).

In this sense, the aims of this study are to review the function of taurine on organism in health and pathological conditions, describing it uses as supplementation associated with exercise, and discuss their results regarding the effects in performance and in health of humans thought a systematic review of literature.

2.METHODS

We searched PUBMED, LILACS and Scielo, for articles from their inception until September 2017. After, we restricted the search to humans, and only clinical trials were included, and the sampling allocation was not being necessarily randomized. Details of studies selection are provided in Figure 1. The searches were not restricted by the language, but eligible studies needed to provide enough information (at least in the abstract) about sample, methods used, dosage of taurine and main results, using one of the preferred languages: English, Portuguese, French or Spanish. The following terms or key-words were used in combination with "*taurine*": "*exercise*", "*performance*", "*strength*", "*endurance*", "*fatigue*", "*inflammation*", "*oxidative stress*", "*disease*", "*pathology*". In addition, we reviewed the reference list from the emerged publications searching for additional relevant studies to the topic. A great number of studies emerged and several of them were used to write this review. However, to make the review table, some inclusion and exclusion criteria were applied. Articles were selected according to the following criteria:

- original articles (review papers, letters and meeting reports were excluded);
- studies in humans (despite contributed to the scientific discussion, animal studies were not included in the table);
- intervention group received taurine (protocols with combination of taurine with other substances were not included), and control group received placebo or no treatment;
- the intake of supplementation needed to be more than one single dose and more than one day of treatment (not acute effect);
- were included only those studies involving an exercise protocol;

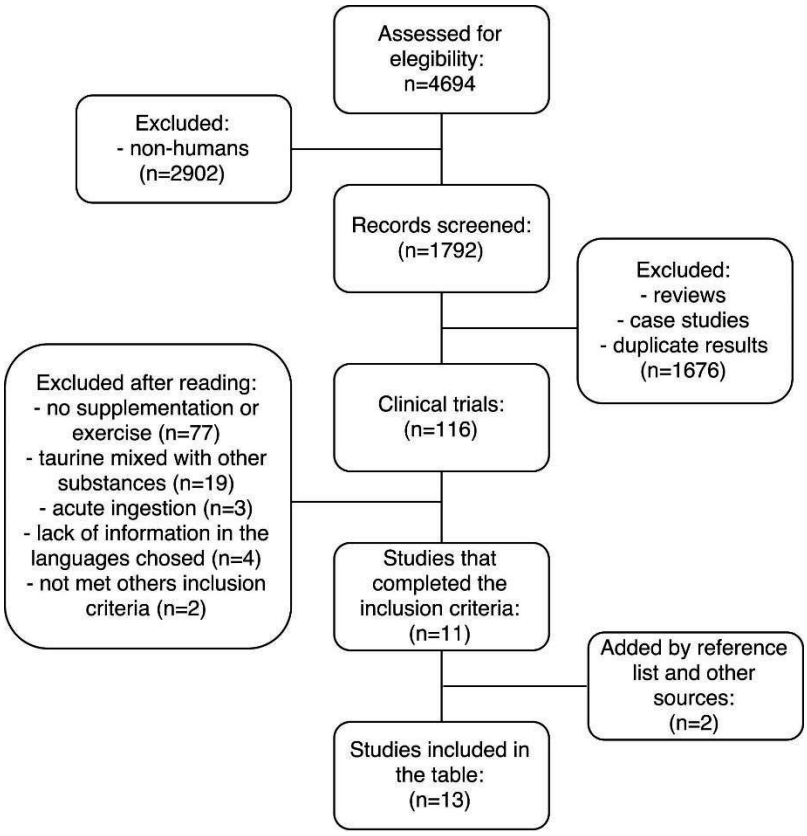

Figure 1. Flowchart of the multi-phase process of the study selection

2.1. Study quality

The Physiotherapy Evidence Database (PEDro scale) was used to check the quality of the included studies (Table 1). Each study received a score between 1 and 11 based on the fulfilment of several requirements regarding information about: eligibility, randomization, concealed allocation, homogeneity at baseline, blinding, minimum attendance of repeated measures, intention to treat, between-group comparison and measures of variability. According to the authors (Maher *et al.*, 2003), que scoring quality of study ranges from: 9-10 are "excellent," 6-8 are considered "good," 4-5 are considered "fair," and <4 are considered "of poor quality". All 13 studies included in the review table (Table 2) were considered between "fair" and "excellent".

Table 1. Study quality of screened results

	PEDro Scale (items)											
Authors (year)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total**
Zhang et al. (2004)	0	0	0	1	0	0	0	1	1	1	0	4
Zembron-Lacny et al. (2007)	0	1	0	1	0	0	0	0	1	1	0	4
Galloway et al. (2008)	0	0	1	1	1	0	0	1	1	1	0	6
Zembron-Lacny et al. (2009)	0	1	0	1	0	0	0	0	1	1	0	4
Beyranvand et al. (2011)	1	1	1	1	1	0	0	1	1	1	0	8
Ra et al. (2013)	0	1	1	1	1	0	1	1	1	1	0	8
Da Silva et al. (2014)	1	1	1	1	1	1	1	0	1	1	0	9
Ra et al. (2015)	0	1	1	1	1	1	0	0	1	1	0	7
Ra et al. (2016)	0	1	1	1	1	0	1	1	1	1	0	8
Ahmadian et al. (2017)	1	1	1	1	1	0	0	1	1	1	0	8
Ahmandian et al. (2017)b	1	1	1	1	1	0	0	1	1	1	0	8
De Carvalho et al. (2017)	0	1	1	1	1	1	0	1	1	1	1	9
McLeay et al. (2017)	0	1	1	1	1	0	0	0	1	1	0	6

3. RESULTS

The main characteristics of the selected studies are summarized in Table 2.

The length of the interventions ranged from 3 to 14 days. Only one study used 8 weeks of supplementation (Carvalho *et al.*, 2017). Most of them have young individuals in sample (Zhang, Izumi, *et al.*, 2004; S. D. R. Galloway *et al.*, 2008; Ra *et al.*, 2013, 2015, 2016a; da Silva *et al.*, 2014), and were performed with athletes or trained subjects (Zembron-Lacny, Ostapiuk and Szyszka, 2009; Carvalho *et al.*, 2017). Regarding studies outcomes, most of the selected trials evaluated oxidative stress and antioxidant status (Zhang, Izumi, *et al.*, 2004; Zembron-Lacny, Szyszka and Szygula, 2007; Zembron-Lacny, Ostapiuk and Szyszka, 2009; Ra *et al.*, 2013, 2016a; da Silva *et al.*, 2014; Carvalho *et al.*, 2017), and exercise performance (Zhang, Izumi, *et al.*, 2004; Beyranvand *et al.*, 2011; Ahmadian, Dabidi Roshan and Ashourpore, 2017a; McLeay, Stannard and Barnes, 2017). The effects of taurine supplementation on inflammatory indices after exercise were also evaluated (da Silva *et al.*, 2014; Ahmadian, Dabidi Roshan and Ashourpore, 2017b), as well their effects after exercise-induced muscle damage (Zembron-Lacny, Ostapiuk and Szyszka, 2009; Ra *et al.*, 2013, 2015; McLeay, Stannard and Barnes, 2017).

4.0. DISCUSSION

TAURINE – HISTORY, STRUCTURE AND FUNCTION

Taurine (2-aminoethanesulfonic acid) is a β-amino acid, with a sulphonic acid group replacing the characteristic carboxylic group of amino-acids, which is considered as a semi-essential (Stapleton *et al.*, 1997). Taurine is the most abundant free amino acid in humans and plays an important role in several essential biological processes (Marcinkiewicz and Kontny, 2014). Taurine was discovered by Leopold Gmelin and Friedrich Tiedemann which isolated the compound from the bile of the ox, which in latin is *Bos taurus*giving name of the amino acid (Demarçay, 1838; Huxtable, 1992).

The ability of biosynthesis of taurine in human is limited in newborns, and decreases with aging and in some pathological conditions. The main source of taurine in human is the diet (Redmond *et al.*, 1998) and the estimated intake is 40-400mg per day (Wójcik *et al.*, 2010). The highest amounts of taurine in food can be found in shellfish, especially scallops, mussels and clams. High amounts can also be found in the dark meat of turkey and chicken, and turkey bologna (Wójcik *et al.*, 2010).

Taurine keeps an intracellular concentration of 5-20umol/g wet weight (Chesney, 1985), and enters in cells across its transporter TauT, which belongs to a similar class of sodium-chloride dependent transporters to creatine, named as SLC6a6; this transporter is mostly expressed by mammalian tissue (Uchida *et al.*, 1992). In pathological conditions, it is observed that taurine content in cell is depleted and this event is observed as 48 hours when the cellular transporter is either suppressed by a competitive inhibitor (Jong *et al.*, 2010) or completely depleted (Ito *et al.*, 2010). The explanations for this depletion is that synthesis of taurine in tissues (such as heart and skeletal muscle) is limited, and cells appear to be dependent of the taurine uptake from the extracellular space. Once the average of the concentration in serum seems to be up to 100-fold less than cells (20-100uM), the active transport of taurine (through TauT) uptake works against a concentration gradient (Ito *et al.*, 2010).

In animal model of species that cannot naturally synthesize taurine, this amino acid is classified as an essential amino acid (eg: felines). In these animals, the deficit in taurine intake results in physiological changes that lead to myocardial failure, ocular and skeletal muscle impairment (Son, Kim and H Kwon, 2007; Wójcik *et al.*, 2010; De Luca, Pierno and Camerino, 2015). Although this level of deficiency is unlikely to occur in humans, these manifestations caused by lack of dietary taurine intake demonstrate that this amino acid plays an important role in controlling various bodily functions. Despite its classification as a semi-essential amino acid in humans, the functional deficiency of taurine in the body can be induced by increasing the intake of beta alanine or guanidininoethanesulfanate (GES), since both compete at the level of the same cellular transporter in due structural similarity (Lake, 1993; Pansani *et al.*, 2012).

Taurine is not involved in protein synthesis, and even being the most abundant free amino acid present in the heart, retina, skeletal muscle, brain and white blood cells (Schuller-Levis and Park, 2003), the effects of this amino acid are not yet completely understood. Several beneficial effects have been described in well controlled clinical studies about the role of Taurine in improve health, including: prevention of obesity and increase energy expenditure (Tsuboyama-Kasaoka *et al.*, 2006); maintenance of normal glucose metabolism (Ito *et al.*, 2015); treating cardiovascular diseases including hypertension, hypercholesterolemia and atherosclerosis (Murakami, 2014) by acting positively on cardiovascular system as modulation of Ca^{++} and antagonism action on Angiotensin II (Xu *et al.*, 2008). Other benefits are recognized as diminish the adipocyte diameter (Tsuboyama-Kasaoka *et al.*, 2006) and modulation of insulin (De La Puerta *et al.*, 2010).

4.1 TAURINE IN INFLAMMATION AND OXIDATIVE STRESS

Inflammation plays an important role in several diseases, including the appearance of hypertension, type 2 diabetes, atherosclerosis, cardiovascular disease and others. In addition, conditions that directly affect the central nervous system (CNS) function such as Alzheimer's and Parkinson's Disease are also related to chronic inflammation, since the increase of inflammatory cytokines contribute to the development of the pathology

(Gorelick, 2010). The accumulation of reactive oxygen (RO) and nitrogen species (RONS) and the initiation of oxidative stress are involved in cellular damage which leads to tissue dysfunction (El Assar, Angulo and Rodríguez-Mañas, 2013). There is a relationship between RONS accumulation and release of inflammatory mediators. In cancer, for example, the recruitment of leukocytes to the damaged tissue and an increase in oxygen consumption lead to the simultaneously spread and accumulation of RONS at the site of injury, which aggravates the tissue damage (Reuter *et al.*, 2010).

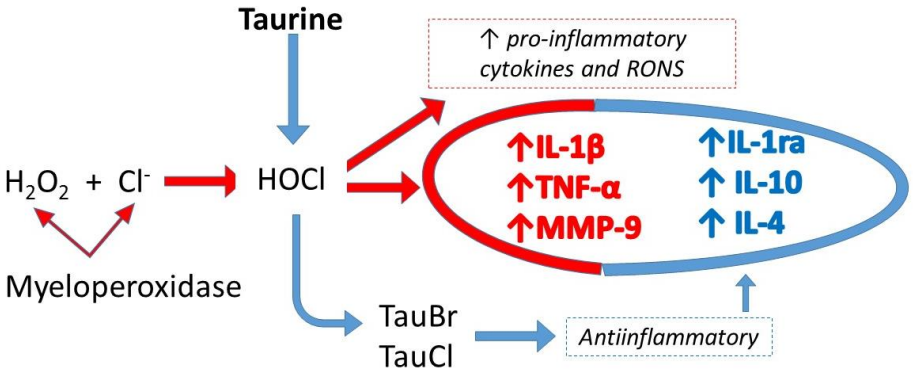

Figure 3. **Mechanisms by which taurine act as an anti-inflammatory and antioxidant agent.**

The formation of hypoclorous acid by mediation of MPO halide system can be suppressed by taurine reaction with HOCl and formation of taurine bronamine and taurine cloramine, which not react like HCIO but also have anti-inflammatory properties, inducing formation of IL-10, IL-1ra and IL-4. The formation of IL-10, for example, suppress the formation of TNF-α that can be induced by HOCl. The over formation of pro-inflammatory cytokines due to increased MPO activity affect negatively several bodily functions (mechanism indicated by red arrows representing the harmful effect of uncontrolled inflammation and/or oxidative stress). However, the formation of TauBr and TauCl due to supplementation with taurine (and their consequences indicated by blue arrows) can oppose the increased inflammation and act positively in human organism.

Cytokines such as TNF-α, IL-1β and IL-6 belong to a wide range of inflammatory markers that not only increase the risk of chronic diseases and contribute to pathogenesis, but also hamper the effectiveness of clinical treatment. For several cases by which oxidative stress and inflammation are involved in those pathogenesis, the amino acid taurine due to its antioxidant activity, has been shown to play an important role as a cytoprotectant and on attenuation of apoptosis (Marcinkiewicz and Kontny, 2014). Despite the apparent unrelated disorders in the etiology of the diseases mentioned, the prerogative that oxidative stress is closely linked to mitochondrial dysfunction is consensual (Crompton and Andreeva, 1993; Das and Sil, 2012; Perfeito, Cunha-Oliveira and Rego, 2013), and taurine can stabilize the electron transport chain and inhibit ROS generation (Schaffer, Azuma and Mozaffari, 2009; Ju, Junichi and Stephen, 2012), thus improving mitochondrial function. The Figure 3 illustrate biological mechanisms by which taurine can act in inflammatory balance.

The scenario described above indicates that antioxidant and anti-inflammatory therapies play a key role in preserving a balance between RONS or inflammatory mediator's

formation and antioxidant/anti-inflammatory content (Bjelakovic *et al.*, 2012; Poljsak, Šuput and Milisav, 2013; Conti *et al.*, 2016). Even in the field of exercise performance, accumulation of RONS and propagation of oxidative stress, as well the increased inflammation at the site of the skeletal muscle are also conditions which decrease the exercise capacity (Powers and Jackson, 2010). This assumption has led many researchers to verify the effect of different nutritional interventions to improve performance. From an immunologic point of view, taurine is recognized to play a role in innate immunity, since are presented in high levels in phagocytes (Schuller-Levis and Park, 2004).

It is suggested that taurine deficiency can affect immune function of cells, (Marcinkiewicz and Kontny, 2014). In human, taurine is found at particularly high concentrations in tissues that are exposed to elevated levels of oxidants. This may suggest its role in the antioxidant system (Jeon *et al.*, 2009)·(Oliveira *et al.*, 2010). The taurine haloamines (TauCl and TauBr) as potentially useful to anti-inflammatory and antimicrobial properties are good candidates for clinical use, especially for local treatment of infectious and inflammatory diseases (Gottardi and Nagl, 2010; Marcinkiewicz and Kontny, 2014). However, the evidence involving low levels of taurine with the deficit on immune system in humans still need to be investigated.

Some enzymes involved in oxidative and inflammatory processes act as correspondents for the promotion/increase of vascular diseases. The myeloperoxidase (MPO) is one of those, an enzyme responsible for myeloid-specific generation of hypochlorous acid and other reactive oxygen species (Pattison, Davies and Hawkins, 2012). The MPO admittedly plays an important role in promoting and/or spread of atherosclerosis and other vascular diseases (Nicholls and Hazen, 2005; Anatoliotakis and Deftereos, 2013). A byproduct of the oxidizing activity of MPO is hypochlorous acid (HOCl), characterized for potent reactive species. The overproduction of HOCl are linked to development of RONS, and hence oxidative stress, chronic inflammation and related diseases (Stephen J. Nicholls and Hazen, 2005; Ray and Katyal, 2016). In this case, an important strategy as nutritional supplementation with taurine may contribute to the local formation of Taurine Chloramine (TauCl) or Taurine Bromamine (TauBr) from reaction with the hypochlorous acid and hypobromous acid (HOBr) (Marcinkiewicz and Kontny, 2014), which in addition to oxidative potential mismatches still have antioxidant properties (Chapman *et al.*, 2009). Both TauCl and TauBr are linked to anti-inflammatory actions, since acts in inhibition of pro-inflammatory cytokines such as TNF-a, IL-1β and IL-6 (Marcinkiewicz *et al.*, 1995; Barua, Liu and Quinn, 2001; Kim *et al.*, 2011). The action of taurine in inhibition RONS production may be evidenced by enhanced expression of antioxidant enzymes such as Cu/Zn superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), which demonstrate their antioxidant-like effects (Zhou *et al.*, 2011; Marcinkiewicz and Kontny, 2014; Vanitha *et al.*, 2015).

The increased expression of hemeoxygenase-1 (HO-1) induced by products of taurine reactions decreases the cyclooxygenase-2 and iNOS formation (Ryter *et al.*, 2002), and the maintenance of their levels play and important role protecting various cells from oxidative stress and inflammation (Wagener *et al.*, 2003).

Recognizing that inflammatory and oxidative stress events are involved in the pathogenesis of obesity, diabetes, hypertension, coronary disease and others (Rani *et al.*, 2016), and considering that taurine may play an antioxidant and anti-inflammatory role in these situations, below there are some evidences pointing to the role of this amino acid in the treatment of these immune suppressed-related diseases.

4.2 TAURINE AND METABOLIC SYNDROME

Studies involving supplementation with taurine and its effects on the metabolic syndrome, hypertension, atherosclerosis and heart disease in humans are still limited. However, evidence show that taurine intake can be useful in prevention and treatment of metabolic syndrome such as hypertension, obesity, dyslipidemia and diabetes.

The maintenance of taurine levels was showed as important to maintain healthy conditions, since healthy population has higher levels of taurine compared to those who are obese (Rosa *et al.*, 2014) or had diabetes (Franconi *et al.*, 1995). A reduction of inflammation and lipid peroxidation was observed after supplementation in obese(Rosa *et al.*, 2014), showing that many risk factors linked to metabolic syndrome are reduced by therestoration of blood levels of taurine. Recently, in monosodium glutamate (MSG) -induced obese rats, a decreased obesity and normalization of TNF-α and IL-4 levels was showed after 13 weeks of taurine supplementation. Because its action in upregulating MTP mRNA and ameliorating hepatic lipid efflux, taurine had a potential role to prevent obesity and hepatic triglycerides accumulation (Bonfleur *et al.*, 2015; Caetano *et al.*, 2015). At the same time, taurine intake can contribute to loss of fatty acid, due to its functions as enhancement of oxygen consumption rates and up-regulation of genes involved in fatty oxidation like the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1a) (Tsuboyama-Kasaoka *et al.*, 2006).

The acute ingestion of taurine before prolonged cycling increased total fat oxidation suggesting that taurine may have a direct effect through the activation of the adenylate cyclase probably by increasing cAMP (Rutherford et al 2010).

Taurine supplementation in overweight individuals led to a reduction in body weight and decrease in triglyceride levels and atherogenic index as well (trycgiceryde/HDL-c) (Ahmadian *et al.*, 2017), emphasizing the idea that taurine plays an important role in the lipid metabolism and, consequently, in prevention of cardiovascular diseases overweight-related. These effects are probably linked to the regulatory action that taurine exerts on the LDL-cholesterol receptor, as well due to antioxidant capacity (Zhang, Bi, *et al.*, 2004).

The oral administration of taurine to hypertensive individuals had already demonstrated positive effects in alleviating symptoms related to disease (Kohashi and Katori, 1983). The reduction of systolic, diastolic and mean blood pressure was associated with increased activity of the kallikrein-kinin and prostaglandin renal system. Those related beneficial effects occur probably because that taurine supplementation upregulated the expression of hydrogen sulfide-synthesizing enzymes, reducing the agonist-induced vascular reactivity in both, human and mouse arteries (Sun *et al.*, 2016).

In young Type 1 Diabetics subjects, taurine reversed the augmentation index, marker of arterial stiffness, and reestablished conduit vessel dysfunction, reflected in improvements in flow-mediated dilation (Moloney and Casey, 2010). Oral taurine has been shown to ameliorate the lipid-induced functional beta cell decompensation and insulin resistance in non-diabetic obese subjects (Xiao, Giacca and Lewis, 2008). Administration of streptozotocin or alloxan is typically made for treatment of Type 1 diabetes, however, it was previously demonstrated that both destroy pancreatic β cells. Moreover, taurine is effective to improve alloxan-induced declines in the number and the size of pancreatic islets (Gavrovskaya *et al.*, 2008).

The elevated levels of platelet aggregation present in diabetic subjects also are reduced to the same levels encountered in controls after supplementation (Franconi *et al.*, 1995), but the mechanism of the taurine-induced decrease in platelet aggregation is still unknown.

Considering these evidences of short-and medium-term trials, and even their effects on non-diabetic individuals, it is currently proposed that taurine supplementation has the potential to help the treatment of diabetic patients, which raises the hypothesis that larger periods of the taurine intake may attenuate and/or prevent the disease progression.

4.3 TAURINE AND CARDIOVASCULAR EFFECTS

The increased risk of obesity, hypertension and elevated cholesterol levels are associated with deficiency in taurine (Sagara *et al.*, 2015). An attempt to increase taurine levels to a normal stage was to improve clinical outcomes in subjects with heart muscle energy deficiency (Averin, 2015). In fact, the potential of taurine in heart energy production was demonstrated in exercising humans, since the ingestion of 500mg of taurine three times a day (1,5g/day) increases the exercise time and distance in patients who suffer from heart failure (Beyranvand *et al.*, 2011). According to the authors, taurine can contribute significantly in improve cardiovascular system function in patients with heart failure, by playing a regulatory role in modulate intracellular Ca^{2+} levels. Previous evidence showed the significant effect of taurine supplementation in systolic ventricular left function of patients with congestive heart failure, benefit that was not observed in subjects who receive other nutritional support (coenzyme Q10) (Azuma, Sawamura and Awata, 1992). In the same manner, recent evidence shown improvement in hemodynamic parameters such as decrease in Q-T segment andincrease in P-R interval values following exercise on supplemented patients with heart failure (Ahmadian, Dabidi Roshan and Ashourpore, 2017b).

4.4 TAURINE AND BRAIN

The structural similarity between taurine and γ-aminobutyric acid, as well as the distribution of these amino acids and its precursors and enzymes present abundantly in various regions of the brain, give reasons to taurine be classified as a neurotransmitter. Moreover, the application of taurine directly to CNS neurons exerts an inhibitory effect on its firing rate (Curtis and Watkins, 1965), which further contributes in the view that it is in fact a neurotransmitter.

Taurine supplementation improves the cerebral blood flow and may alleviate edema and the elevation in intracranial pressure after traumatic brain injury (TBI) (Wang *et al.*, 2016). Some effects in structural brain and neurological functions were also showed after supplementation with taurine, supporting its potential administration for clinical implications. A dose dependent effect of taurine supplementation was demonstrated in lowered brain edema and blood-brain barrier permeability, and decreased activity of superoxide dismutase and malondialdehyde as well in rats with head injury (Sun *et al.*, 2014; Jamshidzadeh *et al.*, 2017), and may protect brain from neuron damage caused by reactive nitrogen species (Ma *et al.*, 2010).

Regarding the cognitive decline related to aging, there are several studies demonstrating significant reduced numbers of GABA receptors and subpopulations of GABAergic neurons in older individuals (Huang *et al.*, 2016). Consequently, the age-related decline

in cognitive functions could be attributable, partly, to decreases in GABA inhibitory neurotransmission. Taurine can act as an $GABA_A$ receptor agonist (El Idrissi and Trenkner, 2004; El Idrissi, Shen and L'Amoreaux, 2013). Levels of GABA neurotransmitters are highly expressed in mice chronically fed with taurine (El Idrissi *et al.*, 2005). Recently, was showed that taurine supplementation ameliorates the age-dependent deterioration in spatial memory acquisition and retention in older mice and promotes several biochemical changes in brain in opposite to those who were naturally induced by aging. Taurine animals elevating the levels of both excitatory and inhibitory GABA neurotransmitters, increasing their performance in cognitive test compared to untreated controls (El Idrissi, Shen and L'Amoreaux, 2013). These modifications suggest that taurine can improve learning and memory through maintenance of GABAergic neurons functions.

4.5 TAURINE AND EXERCISE

In the last decades, there are emerged some studies aiming to verify the effects of the supplementation with taurine associated with physical exercise, and the effects of the pre-supplementation under the performance of athletes as well. The physiological mechanisms by which supplementation with taurine can improve performance and/or act beneficially in improving health when associated with physical exercise still need to be better investigated.Somereview studies and meta-analysis were published in the last decade concerning the effects of supplementation and exercise performance (Blancquaert, Everaert and Derave, 2015; McMahon, Leveritt and Pavey, 2017), but data in humans remain inconclusive. Regarding the effect of taurine supplementation and exercise, the major of the studies involved animal model that limits or makes it difficult to extend all the results to humans, togetherwith the lack of systematic studies in population. There are various hypothetical mechanisms by which taurine can beneficiate physical performance, since the ability to increase the anti-inflammatory and antioxidant capacity (Kato *et al.*, 2015) until the increase of a pool of important amino acids in the skeletal muscle (S. Galloway *et al.*, 2008).

Table 2. Exercise and Taurine supplementation in humans

	Study (year)	Objective: To verify the effect of taurine supplementation on:	Subjects	Exercise and Suppl. Protocols	Measurements	Markers	Main results with supplementation	Author's conclusions
01	Zhang et al. (2004)	Exercise-induced OS and exercise performance	11 young M (with and without taurine)	Cycle ergometer test (workload increase 20W/min until exhaustion) - Suppl: 6g of taurine/day, during 7 days	Before and after suppl. (Pre, Post and 6 hours after exercise)	- TBARS - DNA migration	↔TBARS* DNA migration ↓DNA migration 24h after exercise# ↑$VO2_{max}$ ↑Time to exhaustion	Taurine attenuates the DNA damage in induced by exhaustive exercise, due scavenging of free radicals, and induce antioxidant and other detoxifying properties
02	Zembron-Lacny et al. (2007)	Pro-antioxidant equilibrium compared to controls after high intensity exercise bout	30 healthy Men G1: taurine (n=15) G2: placebo (n=15)	5-7 series of strength training (~50%1RM with progressively increase) (suppl. 3g/day, during 3 days)	Pre, post, and 24h after exercise	- Protein thiols - SOD - GPx - Catalase - TBARS	↑ Protein Thiols (post-exercise)* ↔ TBARS ↑ SOD (24h)*# ↑ GPx (post-exercise and after 24h)*# ↑ CAT (post-exercise)*	Peroxidation intensity did not change after taurine supplementation compared to other cysteine derivates
03	Galloway et al. (2008)	On muscle amino acid content and substrate metabolism	8 young M	Cycling for 2h (~60% VO2max peak) after 7 days of suppl. (5g/day)	Before and after exercise protocol	- amino acids muscle content - Muscle metabolic responses	↔ Muscle metabolic responses at 120 min exercise# ↑ Valine, isoleucine, leucine, cystine, glutamate, alanine, and arginine*#	Taurine appears to have an impact on muscle amino acid response to exercise
04	Zembron-Lacny et al. (2009)	Plasma antioxidant status and oxidative damage	55 trained men: (Taurine n=15; Control n=15)	5-7 series of resistance exercise circuit, with 5 repetitions each, starting with 50% of RM with an increase of 10kg after each serie. Suppl. 3g/day during 3 days	Pre, post and 24h after exercise	- CK - TAS - Total thiols - UA - TBARS - PC	↔CK post,↑24h* ↔ TAS* ↑TTpost* ↔UA*# ↔TBARS# ↔PC#	Taurine did not influence plasma pro-antioxidant status after a single bout of resistance exercise
05	Beyranvand et al. (2011)	Exercise capacity of patients with heart failure	26 M and 3 F G1: taurine (n=15) G2: placebo (n=14)	ETT, Bruce Protocol or Modified Bruce Protocol before and after suppl. - Suppl. during 2 weeks (500mg 3x.day)	- Before and after suppl (2 weeks).	- Exercise time and distance - METS	↑ Exercise time, distance and METS*	Taurine increase exercise capacity in patients with heart failure
06	Ra et al. (2013)	DOMS and muscle damage	18 young M (taurine: n=9)	6x5 repetitions of elbow at 90% of MCV.	Pre, immediately after and 1, 2, 3,	- DOMS - CK	↑CK (days 3 and 4)*	Taurine contribute to attenuate DOMS and

			(placebo: n=9)	- 2g of taurine 3times/day during 2 weeks prior exercise and 3 days after.	and 4 days post exercise	- LDH - 8-OHdG	↑8-OHdG (day 2)*, but less than placebo group#	might play a protective role in DNA oxidation
07	Da Silva et al. (2014)	Inflammation and OS during recovery period after eccentric contraction	21 young M G1: taurine (n=11) G2: placebo (n=10)	3 sets of EE after 14 days of suppl (50mg.kg.day)	Before test: days 1 and 14. After test: days 14, 16, 18 and 21	- Xylenol Orange - PC - Thiol content - SOD - CAT - GPx - TNF-a - IL-1b - IL-10 - CK - MIF - Muscle Soreness	↑ Xylenol, PC in G1 and G2 * (G1 was lower at days 16, 18 and 21 #) ↓ TT in G1 and G2* (G1 was higher at days 16, 18 and 21#) ↑ TNF-a, IL-1b in G1 and G2 (days 16 and 18)* ↑ IL-10, SOD (days 16, 18 and 21)* ↑ CAT in G1 and G2 (day 16)* ↑ GPx (days 18 and 21)* ↑ CK in G1 and G2* (G1 was lower at days 16 and 18#)	Taurine improved performance, muscle damage, and oxidative stress during the recovery after EE
08	Ra et al. (2015)	DOMS and muscle damage after high-intensity EE	29 young men (Placebo n=15; Taurine n=14)	- 2x20 rep. of maximal EE (arm curl) - 2g taurine, 3 times/day, during 2 weeks before exercise	Pre, and 1, 2, 3 4 days after exercise protocol	- DOMS - Myoglobin - CK	↓ DOMS# ↔ Myoglobin# ↔ CK#	Taurine suppl. significantly reduces the severity of DOMS
09	Ra et al. (2016)	Attenuation the delayed increase in arterial stiffness after eccentric exercise	29 young healthy M (G1: taurine group; G2: placebo group)	- 2sets of 20 maximal effort EE - Suppl: 2g*3 times/day during 14 days before, and following 3 days after exercise	Pre, 1, 2, 3 and 4 days after exercise	- MDA - cfPWV	↔ MDA* ↔ cfPWV*	Taurine attenuated the delayed increase in arterial stiffness after EE induced by OS
10	Ahmadian et al. (2017)a	Functional capacity, myocardial oxygen consumption and electrical activity	16 patients with heart failure (Placebo n=8; Taurine n=8)	- Modified Bruce protocol performed twice (before and after suppl. or placebo); - Suppl: 500mg taurine, 3 times/day during two weeks	Pre and Post exercise (with and without taurine supplementation)	- Q-T segment - P-R segment - T wave - Q-T segment - Exercise distance/time - METS - Troponin 1 - CK	↑ P-R segment*# ↓ Q-T segment*# ↓ T-wave# ↑ Exercise distance/time*	Taurine enhanced the physical function and reduced the cardiovascular function parameters following exercise
11	Ahmandian et al. (2017)b	Anti-atherogenic and anti-inflammatory properties	16 patients with heart failure (Taurine n=8; Placebo n=8)	- Modified Bruce protocol performed twice (before and after suppl. or placebo); - Suppl: 500mg taurine, 3 times/day during two weeks	Pre and Post exercise (with and without taurine supplementation)	- AC - TC/HDL-c - LDL-c/HDL-c - CRP - Platelet	↓TC/HDL-c*# ↓LDL-c/HDL-c*# ↓AC*# ↓CRP# ↔Platelet	Taurine decrease atherogenic and inflammatory indices in heart failure patients

12	De Carvalho et al. (2017)	Oxidative stress, protein metabolism and aerobic parameters	10M triathletes, double blind, crossover	Maximal incremental running test (treadmill running); Suppl. 3g/day during 8 weeks	Pre and post exercise protocol, before and after 8 weeks of suppl.	Blood: - MDA, GSH and a-tocopherol; Urine: - nitrogen, nitrogen balance, creatinine and urea	↓MDA* ↔GSH*# ↔a-tocopherol*# ↓Nitrogen*# ↑ Nitrogen balance*# ↔ Urea ↔ Creatinine	Despite not improve aerobic parameters, taurine was effective in decrease lipoperoxidation
13	McLeay et al. (2017)	Serum CK and performance recovery following EE	10M, recreationally-fit, single-blinded, crossover	60 eccentric contractions (biceps brachii muscle) at maximal effort. Suppl. 0.1g/Kg of body weight of taurine or placebo during 3 days	Pre, 24h, 48h and 72h after exercise	Blood: - CK Performance: - Maximal isometric and concentric contractions - Peak eccentric force	↔CK#* ↑Peak eccentric force#	Taurine following EE may improve eccentric performance recovery, suggesting it antioxidant and cytoprotective roles within skeletal muscle

M: male; F: female; TT: time trial; ETT: exercise tolerance test; MIF: maximal isometric strength; CK: creatine kinase; TBARS: thiobarbituric acid reactive substance; PC: protein carbonils; UA: uric acid; TAS: total antioxidant status; METS: metabolic equivalents; EE: eccentric exercise; DOMS: delayed onset muscle soreness; P_i: inorganic phosphorus; cfPWV: carotid-femoral pulse wave velocity; OS: oxidative stress; MCV: maximal voluntary strength of isometric contraction; AC: atherogenic coefficient (triglyceride/HDL-c); The results are presented regarding taurine supplementation compared to pre-suppl and/or placebo group: * taurine in comparison to their own baseline levels; # in comparison to control/placebo group. Details of inclusion/exclusion criteria of studies are described in session Methods.

Some mechanisms by which taurine supplementation may improve performance and/or attenuating uncomfortable symptoms associated with the practice of heavily exercise are described below.

4.5.1 Fatigue

The ability of muscles to produce force through the metabolic challenges occurred in the tissues is directly linked to sport performance. Within these challenges are common agree that the depletion of energy substrate, accumulation of H^+ and inorganic Pi ions, and the metabolic acidosis as well, are already recognized a long time ago as foe of exercise performance. Evidence has shown the negative effects of oxidative stress and inflammation in the muscle's ability to produce (Reid, 2008). In this sense, in the recent years the premise that the accumulation of RONS and its relationship with the production of pro-inflammatory cytokines and hence the decrease in performance has been studied, especially considering the hypothetical benefit of dietary manipulation over these indices.

Taurine might have an important role to protecting cells from abnormal accumulation of ions during metabolic cellular stress, since the strenuous energy-demanding work may create a metabolic stress-like condition which in turn lead to compromised fueling of ion pumps, culminating in a disturbed cellular osmoregulation indicated by taurine efflux and cellular swelling (Branth *et al.*, 2009). In humans, alterations in the plasma taurine content during prolonged exercise are related to an osmoregulatory process (Cuisinier *et al.*, 2002). It seems that taurine is released by contracting muscles and taken up by other tissues, such as blood cells or brain (Ripps and Shen, 2012), which perform a key role in osmoregulation and hence in exercise performance. This is one of the several mechanisms by which taurine is considered to reduce the exercise-induced muscle fatigue (Yatabe *et al.*, 2009).

Taurine administration enhance the performance and reduce some aspects of muscle injury caused by exercise (Dawson *et al.*, 2002). The impaired contractile function in skeletal muscle of rodents are resulted from decreased taurine in muscles, and an increase in muscle taurine levels are associated with an improvement in contractile function (Spriet and Whitfield, 2015). The concentrations of taurine on skeletal muscle decrease significantly after exercise, specifically in the fast-twitch muscle fibers. Several hypotheses are related to this phenomenon, such as the synergistic action of taurine and cAMP during muscle contraction, thus contributing to the increase in glycolytic activity through a probable increase in catecholamine secretion, or due a decrease in Na^+ concentration and increased lactate in the blood, since the transport of taurine is facilitated by chlorine ions and inhibited by lactate and alanine (Matsuzaki *et al.*, 2002). In an exercising environment, this issue is primordial, once the maintaining muscle contraction is a basis for performance.

The mechanisms by whichtaurine supplementation interferes withthe exercise metabolism may be theinteraction with muscle membrane, the coordination or the force production capability of involved muscles (Balshaw *et al.*, 2013).

Animal studies reported that supplementation with Taurine around 100 to 500 mg/kg/day for 2 weeks increased running time to exhaustion (Miyazaki *et al.*, 2004). During high-frequency in vitro stimulation using Sprague-Dawley rats, Goodman and coworkers

(Goodman *et al.*, 2009) showed that administration of Taurine can protected muscle function.

During lipid peroxidation, peroxyl radical formation occurs and the hydroperoxide, substances that favor the formation of aldehydes. In this case, Tromm and co-workers (Tromm *et al.*, 2011) studied the effects of taurine supplementation after exercise on biomarkers of oxidative stress, and showed that supplementation reduces oxidative damage caused by physical exercise in rats. Taurine reduced oxidative damage, probably for his ability to capture the peroxyl, and to prevent the generation of superoxide by the mitochondrial system, thus reducing the deleterious effects on cellular constituents (Tromm *et al.*, 2011).

4.5.2 Taurine and Delayed Onset Muscle Soreness

The delayed onset muscle soreness (DOMS) occurs when an individual is exposed to high eccentric repetitions of muscle contractions and, sometimes, are attributed to reduction in performance such as strength and range of motion (Kim and Lee, 2014). In this way, several studies emerge to investigate the effectiveness of nutritional intervention to attenuate DOMS. Some studies also showed the effect of Taurine on DOMS, although the exact mechanism of their positive influence is not elucidated yet (Kim and Lee, 2014). The ingestion of 50mg of this amino acid decreased DOMS and oxidative stress markers after exercise, however, there was no effect on inflammatory response in healthy males (da Silva *et al.*, 2014).

The combined effect of ingestion of Taurine and BCAA also reduced DOMS and oxidation in 36 healthy males compared to the control group (Ra *et al.*, 2013).

The evidence around the reduced DOMS after high force eccentric exercise are showed and both ways of Taurine ingestions (alone and combined intake), and the possible explanation for these results are the reduction on oxidation levels in both cases (Kim and Lee, 2014). The confirmation for that are showed in rat model when 300mg/body weight/day of Taurine during fifteen days represented a significantly decrease on superoxide radical production after exercise practice (Silva *et al.*, 2011).

4.5.3 Sports beverages containing taurine – results and "lack" of conclusions

In humans, the evidence onpractice of exercise associated with supplementation of taurine are almost involved with their combined effect, since high levels of taurine are presence in sports beverage (Luckose, Pandey and Radhakrishna, 2013). Only a few number of publications involved administration of taurine alone in association with exercise. It is presently one of the most claimed functional ingredient in several commercialized "sports" drinks, and the concentration range around 1,000-2,000 mg of taurine per portion (Rutherford, Spriet and Stellingwerff, 2010). However, based on research investigating the effect of these beverages on performance, it is difficult to stablish their ergogenic benefit more precisely, since almost studies examine the effects of taurine on the combination of other ingredients that affect metabolism, such as guarana, carnitine, creatine and ginseng (Higgins, Tuttle and Higgins, 2010; Alsunni, 2015).

Taurine supplementation along with branched-chain amino acids (BCAA), creatine and caffeine increased physiological levels of growth hormone and insulin concentration in

trained men, also showing an increase in performance (Hoffman *et al.*, 2008). Supplementation with Taurine combined to others amino acids also enhanced the power performance and increased training volume during resistance training (Gonzalez *et al.*, 2011). Previously, was shown the effect of the combination of taurine and caffeine in sport beverages at the level of the heart and the brain during exercise, since taurine containing drink affected parameters of the cardiac contractility (Baum and Weiß, 2001). The same study also showed an increase on fractional shortening and in stroke volume after exercise on trained endurance athletes, results not observed in the group that ingested only caffeine containing drink, which can explain the combined effect of those on physiological mechanisms.

The effects of the ingestion of two energy drinks containing taurine in their composition confirmed an increase in maximal oxygen uptake (VO_{2max}) and time to exhaustion in athletes (Rahnama, Gaeini and Kazemi, 2010). Gonzalez and co-workers (Gonzalez *et al.*, 2011) also found that consumption of an energy drink containing taurine ten minutes before exercise significantly increased exercise time to exhaustion and strength production in type II fibers.

However, there are some evidence that shown no ergogenic effect of taurine containing beverages in performance, such as no change in time to exhaustion and exercise workload in young men (Dall'Agnol and Souza, 2009).

Thus, it is hard to determine whether any of those mentioned performance effects were caused exclusively by the taurine alone, or by a combination with other ingredients, or simply by the detail that some beverages used as placebo were not equally in calories to the taurine drink.

5. SAFETY OF TAURINE SUPPLEMENTATION IN HUMANS

There is no evidence that supplementation with Taurine may represent any kind of side effect, since it is an abundant and non-toxic amino acid. In this sense, we can also add that Taurine (in addition to no reported toxicity), contributes to alleviating the adverse cardiovascular symptoms associated with consumption of caffeine containing beverages (Schaffer *et al.*, 2014). None of the studies showed on Table 2 record any adverse effect of taurine, and the drop-outs observed in some of them were unrelated to the supplementation. The Observed Safe Level risk assessment indicate that, based on the available published human clinical trial data, the evidence for the absence of adverse effects is strong for taurine at supplemental intakes up to 3g/day (Shao and Hathcock, 2008). The dosage used in studies ranged from 1,5g to 6g/day. Only two studies used taurine intake according to the body mass of participants (da Silva *et al.*, 2014; McLeay, Stannard and Barnes, 2017).

6. CONCLUSIONS

Improving the immune system or performance in human living systems is very complex and life style aspects concur in determining the magnitude of changes in inflammation and oxidative stress response, in healthy, unhealthy or athletic subjects. A large part of studies investigating the effectiveness of taurine supplementation therapy in humans (either on health or performance) raised contrasting results. Taurine supplementation has been shown to be effective in promoting antioxidant and anti-inflammatory capabilities,

while improved sports performance. However, as is often the case in many studies involving supplementation in humans, a variety of methodological designs, the doses intake, the small sample size, and lack of investigations with dose-response mechanism make it difficult conclusively agree about the effects of long-term supplementation on the human body. In addition, many taurine trials should consider the regular diet of supplemented participants as an additive (or limiting) factor to the effects of supplementation itself. Taking in account some existing limitations on this literature topic, it is necessary further investigations on:

- The effects of dose-response of taurine supplementation on anti-inflammatory, antioxidant, and exercise capacities;

- the body responses to prolonged supplementation (> 2 weeks) in middle-aged and elderly adults;

- the effects of the combination of taurine supplementation and long term exercise (> 4 weeks), on immune parameters.

Supplementation with taurine, in fact, may be responsible for many beneficial effects in humans, promoting health and/or disease prevention. At the same time, it can promote the improvement of the sports performance of athletes, but this evidence need to be better explored in high controlled studies.

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