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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA MOTRICIDADE

EFFECT OF COMMUNITY-BASED PHYSICAL EXERCISE INTERVENTIONS CARRIED OUT IN PRIMARY HEALTH CARE ON PLASMA INFLAMMATORY BIOMARKERS AND CARDIORESPIRATORY FITNESS

CAMILA BOSQUIERO PAPINI

Tese apresentada ao Instituto de Biociências do Campus de Rio Claro, Universidade Estadual Paulista Júlio de Mesquita Filho, como parte dos requisitos para obtenção do título de Doutor em Ciências da Motricidade.

Maio - 2015

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TÍTULO: Effect of community-based physical exercise interventions carried out in primary health care on plasma inflammatory biomarkers and cardiorespiratory fitness

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I dedicate my thesis to all participants of the Saúde Ativa Rio Claro Program - especially the ones who participated in the study - and to all students, professionals and professors that work or worked in the Program and are part of this history.

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ABSTRACT

The study aims to verify the effect of community-based physical exercise interventions carried out in primary health care on plasma inflammatory biomarkers and cardiorespiratory fitness. It was performed a 1year quasi-experimental study with female participants of Physical Exercise Interventions carried out in Health Units in Rio Claro City, Sao Paulo State. Two different protocols were implemented. The Intervention 1 (two, 60 minute sessions/week) was based in the *Saude Ativa Rio Claro* Program (existing since 2001). The intervention 2 (three, 90 minute sessions/week) was based in the physical activity recommendation. In both interventions, aerobic, resistance muscle and stretching exercises were performed. The variables evaluated were: a) Anthropometric variables (body mass, stature, body mass index, waist and hip circumferences); b) Physical Activity level through pedometer; c) Cardiorespiratory fitness test (incremental ergoespirometric test); d) Inflammatory biomarkers (blood plasmatic dosage). The results are present in 3 articles. In the chapter 1, the results showed that the Intervention 1 was effective in reducing CRP and TNFa; and in maintaining the IL10, IL6 and insulin after 1 year of intervention. In the chapter 4, it was demonstrated that Intervention 2 decreased the LDL and glucose levels and improved the resistance insulin of participants. In chapter 5, the results indicated that participants of Intervention 2 developed a greater exercise tolerance and improved the energy cost during walking. These data suggest that cardiorespiratory fitness was enhanced. Some additional analyses indicated that participants of intervention 1 developed a greater exercise tolerance but they did not improve the energy cost during walking. Both interventions were able to improve health-related variables. The development of physical exercise community-based is can be a viable initiative to promote health of population.

Key-words: Physical exercise; Inflammatory biomarkers; Cardiorespiratory fitness; Community-based intervention; Primary health care.

RESUMO

O presente projeto tem como objetivo verificar o efeito de programas de exercício físico sobre biomarcadores de inflamação e a capacidade cardiorrespiratória em participantes de programas de exercícios físicos oferecidos em Unidades de Saúde do município de Rio Claro-SP. Para atingir os objetivos propostos foi realizado um estudo quase-experimental com duração de 12 meses, onde a amostra foi composta por mulheres participantes de programas de Intervenção com Exercício Físico em Unidades de Saúde. Foram implementados 2 Programas distintos. A Intervenção 1 foi baseada no Programa Saúde Ativa Rio Claro (já existente no Município desde 2001), composta de 2 sessões semanais de exercício físico com duração de 60 minutos. A intervenção 2 foi fundamentada nas recomendações preconizadas para a prática de atividade física, sendo oferecida 3 sessões semanais com duração de 90 minutos. Em ambas intervenções foram desenvolvidas atividades aeróbias, exercícios de força e flexibilidade. As variáveis avaliadas foram: a) Antropometria (Massa Corporal, Estatura, Cálculo do Índice de Massa Corporal, Circunferência da Cintura e Quadril); b) Pedometria; c) Aptidão Cardiorrespiratória (Teste Ergoespirométrico Incremental na esteira); d) Biomarcadores de Inflamação (Dosagem plasmática do sangue). Os resultados estão apresentados em forma de artigo. No capítulo 3, os resultados demonstram que a Intervenção 1 foi efetiva em reduzir concentrações de PCR e TNFα e manter concentrações de IL10, IL6 e insulina após 12 meses de intervenção. No capítulo 4, foi demonstrado que a Intervenção 2 reduziu concentrações de LDL e glicose e ainda melhorou o quadro de resistência à insulina das participantes. No capítulo 5 os dados indicaram que as participantes desenvolveram uma maior tolerância ao exercício e melhoraram o custo energético dos estágios do teste. Isso sugere que a aptidão cardiorrespiratória foi aprimorada. Análises adicionais mostraram que os participantes da intervenção 1 também desenvolveram uma maior tolerância ao exercício físico mas eles não melhoraram o custo energético durante a caminhada. Ambas intervenções se mostram efetivas em melhorar variáveis relacionadas com a saúde. O desenvolvimento de programas para a comunidade dentro da Saúde Pública pode ser uma iniciativa viável para promover saúde da população.

Palavras-chave: Exercício físico; Biomarcadores de inflamação; Aptidão cardiorrespiratória; Intervenção de base comunitária; Atenção básica de saúde.

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1. CHAPTER 1: Research Project Contextualization

1.1 General Introduction

Since the epidemiological transition of degenerative chronic diseases have begun, several studies have reported the physical activity as a way to promote health. Studies have demonstrated a positive correlation between the regular physical activity practice and the decrease in the incidence or mortality rate in various types of cancer and other chronic diseases. Thus, the physical exercise has been widely used as a preventive and therapeutic tool against many diseases, including obesity, cardiovascular disease and diabetes (PATE et al., 1995; KUJALA et al., 1998; FANG, et al., 2003; MELZER et al., 2004; OMS, 2010; WEN et al., 2011; LEE et al., 2012).

Nowadays it is well established that physical exercise improves the physical fitness; i.e., strength, aerobic resistance, among others, contributing to a better physical health and a better quality of life (GOBBI, et al., 2005; OMS, 2010). It is also known that the moderate-intensity physical exercise has a stimulating effect in the immune and anti-inflammatory functions of practitioners. This effect is mediated by several factors, including the reduced levels of pro inflammatory cytokines and the increased levels of anti-inflammatory cytokines (NIEMAN, 1997; PEDERSEN, 2006; HUANG et al., 2013). The physical exercise impact in the inflammatory biomarkers and in the immune function has been researched in healthy individuals and cardiac, obese and diabetic patients (FICHTLSCHERER et al., 2004; BALDUCCI et al., 2010; TEIXEIRA DE LEMOS et al., 2012). According to Pedersen (2006) the anti-inflammatory effect provided by physical exercise plays an important protecting role against cardiovascular diseases and type 2 diabetes.

Considering that, physical inactivity is the fourth leading cause of death in the world and is responsible for 6 to 10% of the major chronic diseases (KOHL et al., 2012; LEE et al. 2012) it is necessary to induce social, economic and environment changes and elaborate public policies to promote a more active life style.

Since 2001, a physical exercise intervention in primary health care has been offered to the population of Rio Claro City through the Program *Saúde Ativa Rio Claro* (SARC) (KOKUBUN et al., 2007). The SARC program has the objective to promote and maintain the physical activity levels of Rio Claro residents. The program reaches approximately 400 adults aged 35 years old or more. Since the SARC creation, several researches have been developed to evaluate its effectiveness focusing in variables related to the physical fitness, physical activity levels and quality of life.

In this way, the present study is intended to complement the range of evidence about the program effectiveness emphasizing the inflammatory biomarkers, hormones and cardiorespiratory fitness. The current intervention model was compared to another one that met the physical activity recommendation of 150 minutes of moderate-intensity per week (PATE et al., 1995) – both interventions were evaluated for one year.

1.2 Contextualization of *Saúde Ativa Rio Claro* Program

Since 2001, the *Saude Ativa Rio Claro* program has been developed in Rio Claro City, with a partnership between *Fundação Municipal de Saúde da Prefeitura de Rio Claro* and *Instituto de Biociências da Universidade Estadual Paulista (UNESP) – Campus Rio Claro.* Rio Claro is a midsize city (198 thousand inhabitants) located approximately 190 kilometers from the state of São Paulo, southeastern part of Brazil (IBGE, 2010).

The program has been designed to promote and maintain physical activity levels of residents in Rio Claro City, Brazil and has been developed by *Nucleo de Atividade Fisica, Esporte e Saude – UNESP.* The *Saude Ativa Rio Claro* program incorporates several strategies to achieve its aim:

- Physical Exercise Program carried out in Health Units – a community-based intervention in primary health care;
- Two annual Meetings with the participants of intervention – to socialize them and to make them aware of the benefits of an active lifestyle;
- The annual Meeting of Physical Activity and Health in Rio Claro – to promote the knowledge and discussion related to physical activity and health topics among academics, health professionals, post and undergraduate students;
- Epidemiological researches – to evaluate the factors associated to the physical activity levels of population.
- Effectiveness researches – to evaluate the effect of the physical exercise program in health-related variables.

The Physical Exercise Program is a community-based physical exercise intervention that reaches approximately 400 low-income adults (aged 35 years or more) and operates in Health Units of the city that are located in areas of greatest social vulnerability characterized by low economic income and low education level. The intervention offers 2 sessions per week with 60 minutes and comprises aerobic and neuromotor exercises (KOKUBUN et al., 2007; NAKAMURA et al., 2010).

The intervention is developed alternating aerobic and neuromotor exercises volume, as presented in figure 1.1. The neuromotor volume gradually decreases from the beginning to the end of the month (from 25 to 15 minutes per session), while the aerobic volume gradually increases (from 20 to 30 minutes per session). In the following month, the neuromotor and aerobic exercises start in the same volume reached in the last session. The neuromotor volume gradually increases (from 15 to 25 minutes per session), while the aerobic volume gradually decreases (from 30 to 20 minutes). This alternation is intended to provide a proportional volume in both exercises, without prioritizing only one (KOKUBUN et al., 2007).

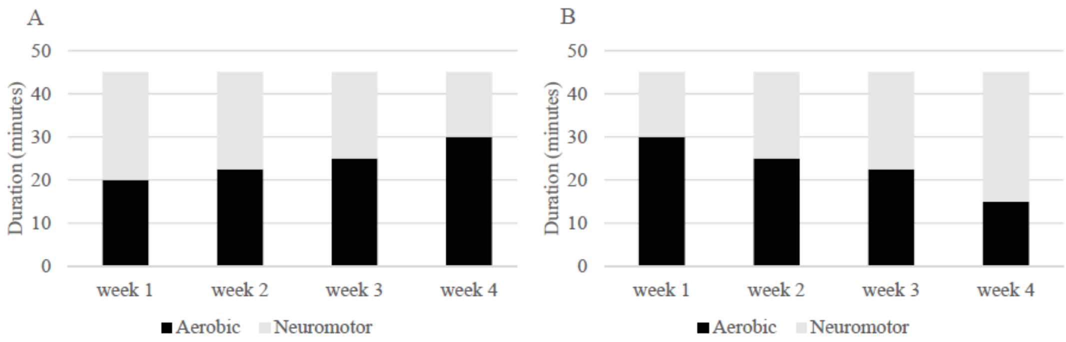

Figure 1.1: Periodization of the Physical Exercise Program

The sessions are divided in initial part (warm up activities), main part (moderate intensity aerobic, resistance muscles exercises, stretching and other activities) and final part (cool down activities). In addition, in each session, the participants received counselling designed to increase daily physical activity levels and encourage participation in physical exercise beyond the intervention (KOKUBUN et al., 2007; NAKAMURA et al., 2010).

Anthropometric variables and physical fitness are assessed every four months. Blood glucose and blood lipid profiles are evaluated twice a year. These data are used for individual feedback of each participant and for research purposes as well.

Some of the evidences accumulated along years of the intervention´s effectiveness are summarized in table 1.1.

Table 1.1: Summarized evidences of Physical Exercise Program carried out in Health Units in Rio Claro.

Author – year	**Main results**
Kokubun et al., 2007	In 6 years follow up, the Program improved health-related variables, such as the lipids and glucose metabolisms, functional capacity, states of mood and quality of life of participants.
Costa et al., 2009	The Program had a long-term permanence (average of 24 months) by participants.
Gomes et al., 2012	The participation in the Program was associated to greater physical activity levels, because it stimulates physical activity practice beyond program sessions.
Giraldo et al., 2013	In 3 years, the Program contributed to improve the levels of perceived health, to reduce the number of healthcare unit visits, the number of blood pressure measurements and to maintain the number and dose of drugs, as well as the number of diseases reports and the number of blood glucose measurements.
Nakamura et al., 2014	In 10 years, the Program improved the muscle strength, coordination, aerobic capacity, and agility and dynamic balance and maintained the flexibility in participants, reducing the effect of natural decline of physical fitness causes by aging.
Zorzetto et al., 2014	The Program´s protocol (Two 60-minute sessions/week) was compared to a protocol that reached the physical activity recommendation (Three 90-minute sessions/week). The adherence was higher for the 2 days intervention (47.2%) compared to 3 days (32. 6%). Both interventions promoted similar healthy benefits. The 2-days program may save money for public health agencies.

1.3 Aims

1.3.1 General Aim

Verify the effects of physical exercise programs carried out in Primary Health Care on inflammatory biomarkers and cardiorespiratory fitness in participants.

1.3.2 Specific aims

- Analyze the programs effect after 6 months and 1 year of intervention in interleukin 6 (IL6), interleukin 10 (IL10), C-reactive protein (CRP), leptin, insulin, tumor necrosis factor alpha (TNFα) and cardiorespiratory fitness;
- Compare the effects between both interventions in the variables described above.

1.4 Literature Review

1.4.1 Physical Exercise and Public Health

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or others (CASPERSEN et al., 1985). It is already established in the literature that physical activity practice is associated to health benefits (WARBURTON et al., 2010; OMS, 2010). However, to obtain these benefits it is recommended to accumulate 30 minutes or more of moderate physical activity in most days or preferentially all days in the week (PATE et al., 1995); or 20 minutes of vigorous physical activity at least 3 days in the week (HASKELL, et al. 2007; GARBER et al., 2011).

More than often, individuals are unable to meet the minimum recommendation of physical activity with work, transport and household activities; therefore, they need to exercise at leisure time. Physical exercise, a subset of physical activity, is planned, structured, and repetitive having as a final or an intermediate objective the improvement or maintenance of physical fitness (CASPERSEN et al., 1985). Considering the benefits of an active life style, the physical exercise performed during leisure time should be a priority.

A good physical fitness level provides the individual with a greater number of possibilities regarding leisure activities and improves the performance of such activities and domestic chores as well (GOBBI et al., 2005). The physical exercise is also a way of intervention to combat degenerative chronic diseases such as hypertension and diabetes, playing a preventive role and helping to minimize the symptoms.

A recent survey, carried out in the Federal District and 26 Brazilian capital cities, showed that the prevalence of insufficiently active individuals (less than 150 minutes of physical activity) is 49.9% of 53 thousands interviewed. This survey also showed that men are more sufficiently active in leisure time (41.2%) than women (27.4%) (VIGITEL, 2013). It is important to emphasize that the physical inactivity is considered a risk factor to several degenerative chronic diseases. It is responsible for 6% of coronary diseases, 7% of diabetes type 2 and 9% of premature mortality (LEE et al., 2012).

According to Kohl et al. (2012), the pandemic of physical inactivity should be a public health priority. Creative thinking allied with the development of partnerships and the implementation of National Politics and Actions plans are fundamental to build capacity and infrastructure in physical activity and public health (KOHL et al., 2012; BULL et al., 2004).

For the successful implementation of a population-wide approach to promote physical activity across the life course, some attributes were identified. These attributes include an evidence-based, consultative approach and integration across sectors and policies, national recommendations on physical activity levels, national goals and targets, an implementation plan including several strategies and evaluation based on a national surveillance system (KOHL et al., 2012).

Regarding an efficient Policy to promote physical activity, Kohl et al. (2012) state:

> "The mere existence of a national physical activity policy or action plan does not secure its functionality or implementation. Plans are not implementation, implementation is not strategy, and strategies are not evidence of population change. Nor does the existence of a national policy necessarily produce success. Ideally, national policies and action plans are designed not for implementation solely by governments, but rather for mobilization of both governmental and non-governmental collaboration towards advancement of physical activity and reduction of physical inactivity (KOHL et al., 2012).

In Brazil, there are important programs which promote physical exercise and healthy lifestyle habits. These programs are performed through a partnership between the public sector and Universities. Some of them are listed below:

- *Serviço de Orientação ao Exercício* – created in 1990 in Vitoria City, Espirito Santo State. It offers ten modules of physical exercise, located in squares, parks and places with a great flow of people (VENTURIM; MOLINA, 2005).

- *Agita Sao Paulo* – created in 1996 by *CELAFISCS* in São Caetano do Sul City, São Paulo State. The main goal is to increase the knowledge of population about the importance of physical activity as a way to promote health and to increase the physical activity level of population (MATSUDO et al., 2003).

- *CuritibAtiva* – created in 1998 in Curitiba City, Parana State. This program use shorts messages about physical activity and its benefits, face-to-face orientation, physical fitness evaluation, distribution of educational material to encourage physical activity, events organization and delivery of regular and sporadic oriented activities (KRUCHELSKI; RAUCHBACH, 2005).

- *Academia da Cidade* – created in 2002 in Recife City, Pernambuco State. It is developed through a partnership with the State Government and aims to renovate traditional green areas, providing the population with equipment for sports and encouraging healthy habits (SECRETARIA DE SAÚDE DO RECIFE, 2012).

- *Programa de Atividades Físicas para Pessoas com Necessidades Especiais* – created in 2002 in Sao Jose do Rio Pardo City, Sao Paulo State. It offers the physical activity program to degenerative chronic disease patients who are registered in the Family Health Units (PEREIRA-DA-SILVA et al., 2011).

- *Ação e Saúde Floripa "educar, conscientizar e praticar"* – created in 2006 in Florianopolis City, Santa Catarina State. It is carried out in Health Units and uses counseling as main tool (GOMES; DUARTE, 2008).

The successful implementation also depends on political commitment and sustainable funding, leadership and coordination, working in partnership, a network supporting professionals as well as ensuring links between policy and practice, a communication strategy and a clear program branding (KOHL et al., 2012). Thus, the *Saúde Ativa Rio Claro,* presented in the introduction of this research can be considered a successful example of an efficient implementation of an Action Politic in Rio Claro City.

1.4.2 The Public Health System in Brazil: SUS

In October 1988, the enactment of the new Federal Constitution completed the process of the return of democracy in Brazil. Within the context of the effort to set up a welfare state, the new constitution made the health a right of every citizen and launched the process of creating a public, universal and decentralized health system. It was responsible for a profound change in the organization of public health in Brazil (PAIVA; TEIXEIRA, 2014).

The Health Public System is Brazil, called SUS -*Sistema Único de Saúde)* was created by the Federal Constitution of 1988 (BRASIL, Law nº 8,080/1990 and Law nº 8,142 /1990). These laws established that “Health is a right of every citizen and a duty of State”. With the creation of SUS, all population have the right to an universal and free access to health, which is financed with resources from the budget of the Union, the States, the Federal District and Municipalities (BRASIL, Law nº 8,080/1990 and Law nº 8,142 /1990). The SUS´ aims to provide an embracing, universal, preventive and curative care through the decentralized management and delivery of health services, promoting community participation at all levels of government (PAIM et al., 2011).

According to the Ministry of Health (1990), the constitutional principles of SUS are:

- Universality: it is the health care guarantee for every citizen. With the universality, the individual has the right to access all public health services, as well as those hired by the government. Health is a right of citizenship and the duty of Municipal, State and Federal government.

- Integrality: the individual is an integral, bio-psycho-social being, and must be serviced by the health system with this comprehensive vision, focusing to promote, protect and restore their health.

- Equity: it is the implementation of actions and services at all health care levels, in accordance with the complexity required in each case, wherever the citizens live, without privileges and without barriers. All citizens are equal for the SUS and their needs will be examined, up to the limit of what the system can offer for everyone.

- Decentralization: it is understood as a redistribution of responsibilities regarding the actions and health services among the various levels of government. The comprehensiveness of a city shall be the responsibility of the Municipal government; the comprehensiveness included in a state region, should be under the State government's responsibility, and, what is the national comprehensiveness will be the Federal´s responsibility. There should be a profound redefinition of the powers of the various levels of government with a clear strengthening of the municipal government on health - The “Health Municipalization”. The municipality has the greatest responsibility to promote health actions directly targeting their citizens.

- Social participation: it is the constitutional guarantee that the population, through their representative organizations, participate in the process of health policies formulation and the control of its implementation at all levels, from the federal to the local. The community participation should be given in Health Councils, with representation of members, government, health professionals and service providers. Another form of participation is in periodic health conferences, to set priorities and guidelines on health.

- Solvability - is the demand that, when an individual seeks assistance or when there is a collective impact problem on health, the corresponding service is able to face it and solve it by the level of competence.

- Regionalization and hierarchization: the health services should be organized into levels of increasing technological complexity arranged in a defined geographical area and have the definition of the population to be served. This implies the ability to offer services to the population in all aid modalities, as well as to offer the access to all kinds of technology available, allowing a great degree of solvability (solution of their problems). The network of services - organized in hierarchical and regional basis - allow a better understanding of the health problems of the population in delimited areas, favoring epidemiological and health surveillances, vector control, health education, in addition to favoring the actions in the ambulatory and hospital care in all levels of complexity.

The development of primary health care – or basic attention as it is called in Brazil – has received great attention in SUS. The basic attention aims to offer the universal access to healthcare and embracing services, to coordinate and expand the coverage to the most complex healthcare levels (e.g. specialized assistance and hospital services), as well as to implement intersectoral actions to promote health and prevent diseases. Many strategies, e.g the *Programa de Agentes Comunitários de Saúde* and the *Programa de Saúde da Família* – PSF (Family Health Program) have been used to achieve theses aims (PAIM et al., 2011).

The PSF has been established as a crucial entry point to care for users into the health system. In this model, PSF´s staff works in specific geographic areas and are responsible for implementing actions for health promotion, disease prevention, treatment of common health conditions and rehabilitation (MINISTÉRIO DA SAÚDE, 2000). The PSF works through Family health staff, composed by one physician (general practitioner), one nurse, one auxiliary nurse and four to six community health agents. The PSF has been the main structuration strategy of basic attention since 1998. An innovative feature of PSF is its emphasis on reorganization of basic health units to focus on families and communities and integrate medical care with health promotion and preventive actions (PAIM et al., 2011).

In 2008, the *Núcleos de Apoio à Saúde da Família* –NASF (Centers of Support for Family Health) were created. They aim to give support to the basic attention in Brazil and to help the insertion of PSF in the network services, expanding its coverage, solvability, territorialization and regionalization. The NASF are composed by multidisciplinary professionals, such as social assistant, pharmacist, physiotherapist, audiologist, nutritionist, physical education professional, psychologist, occupational therapist, obstetrician, acupuncturist, homeopathics doctor, pediatrician, geriatrician medical and others. The professional composition must be defined by the municipal managers and the PSF staff, considering the local needs and the availability of professionals (MINISTÉRIO DA SAÚDE, 2009).

The NASF is not the system's gateway for users, but is a strategy to support PSF staff. The professionals operate together with the professionals of the PSF, sharing and supporting health practices in the territories under the responsibility of PSF. The NASF should work within some general guidelines for PSF, such as interdisciplinary and intersectoral action; continuing education for health professionals and the general public; development of the concept of territory; social participation, health promotion and humanization. Thus, the organization of the NASF´s work is always focused on the territory under its responsibility, and should be structured to prioritize the shared and interdisciplinary service care, with exchange of knowledge, training and mutual responsibilities, generating experience for all professionals involved through broad methodologies (MINISTÉRIO DA SAÚDE, 2009).

According to Paim et al. (2011), SUS was able to increase the healthcare access to the considerable part of Brazilian population in a time when the health system was being progressively privatized. There is many things to do to SUS become a universal system. Over the last years, there has been some progress such as the investment on human resources, on science and technology and on the primary care, as well as a great decentralization process, broader social participation and greater awareness regarding the right to health. The possibilities for financing a system on a universal scale still present difficulties that seem intractable (PAIVA & TEIXEIRA, 2014). The disarticulation among Branches (Municipal, State and Federal) reveals the importance of improving the balancing mechanisms and the dialog among public institutions which operate guaranteeing SUS principles. Regardless the advancements, it is still the State's great challenge, as a whole, to guarantee democracy and perform the role of mediator of interests and demands, establishing priorities and acting in a balanced manner, considering collective wellbeing and not only responding to the interests of specific groups (BAPTISTA et la., 2009). The greater political mobilization to restructure funding and redefine the roles of the public and private sectors is critical for the Brazilian Health System to overcome the current challenges (PAIM et al., 2011).

1.4.3 Physical Exercise and Biomarkers of Inflammation

The inflammatory process is the major way by which the immune system copes with infection and tissue damage The inflammation is a complex and intricate biological process involving cells of the innate and adaptive immunity systems. It is characterized by the accumulation of leukocytes and plasma proteins and can start in minutes to hours and last for days. The chronic inflammation is a process that occurs when the infection is not eliminated or in response to a prolonged tissue damage (ABBAS et al., 2011).

The cytokine secretion by cells is one of the first responses of the immune system and is very important to the inflammatory process (ABBAS et al., 2011). The cytokines are generated by different types of cells and constitute a large and heterogenic group of soluble proteins. They mediate and regulate many factors of adaptive and natural immunity. A cytokine can act in several cells and exert multiple biological effects. It can stimulate or inhibit the production of others and can antagonize one another and produce additive or synergistic effects (ABBAS et al., 2011).

The cytokines are grouped in categories, such as interleukins (IL), interferons (IFN), colony stimulating factor (CSF), transforming growth factor (TGF) and tumor necrosis factor (TNF). They are secreted by macrophages and mast cells, endothelial cells and adipose tissue. They can be classified in anti-inflammatory and pro-inflammatory cytokines. The IL4, I10 and IL3 belong to the anti-inflammatory group and TNFα, IL1, IL6 and IL8 belong to the pro-inflammatory group (VOLP et al., 2008; ABBAS et al., 2011).

In this research, the interleukin 10 (IL10), the interleukin (IL6) and TNF alpha (TNFa) were studied once the focus was in the effectiveness of physical exercise in the inflammation process. These cytokines seem to be the most studied ones in the literature when the study involves physical exercise intervention. They appear to be more susceptible to changes with physical exercise intervention. Furthermore, the C-reactive Protein (CRP) was also studied because it is directly associated to the inflammatory process and cardiac risk; the Leptin, since it seem to be linked with inflammatory responses; and the Insulin, for the reason that the hyperinsulinemia and the insulin resistance are deriving response by the inflammation process.

The IL6 is secreted by macrophages and lymphocytes in response to a tissue damage or infection and for this reason is associated to several diseases (PEDERSEN & TOFT, 2000; PEDERSEN, 2007; FISMAN & TENENBAUM, 2010). It presents local and systemic effects in response to inflammation, inducing the hepatic production of several inflammatory mediators (ABBAS et al., 2011). The IL6 is involved in the development of hyperinsulinemia and metabolic syndrome, once it plays an important role in carbohydrate and lipids metabolism. It increases the lipolysis and the release of free fatty acids and glycerol and decreases the insulin receptor substrate-1 expression and GLUT-4 in hepatic and muscle tissue (VOLP et al., 2008). It is suggested that IL6 plays both roles, anti and pro-inflammatory, depending on the circumstances. The increase of IL6 myokine - produced by muscle in response to physical exercise – can have an anti-inflammatory function. It has metabolic effects in the liver and adipose tissue (by activating glycogenolysis and lipolysis) and inhibits the production of TNFa (PEDERSEN et al., 2003; PRESTES et al., 2006).

Similarly to the IL6, the TNFa is the central mediator of the acute phase response in inflammation because it stimulates the synthesis of other cytokines and plays an important role in the same cascade of reactions (FRANCISCO et al., 2006). The TNFa is a cytokine with a wide range of pro inflammatory activities. As its name suggests, it causes tumor necrosis, resulting in local inflammation and thrombosis of blood vessels in the neoplasic area. The TNFa influences the atherosclerotic process once it causes metabolic disorders and increases the expression of cell adhesion molecules (VASSALI et al., 1992; ABBAS et al., 2011). It is also inversely related to glucose metabolism and positively correlated with the increase in the volume of adipocytes (RUAN & LODISH, 2003; WINKLER et al., 2003) and may result in insulin-resistance obesity.

The CRP is an acute phase plasma protein synthetized in the liver and regulated by cytokines such as TNFa and IL6 (AL ABDELLAOUI & KHAFFAF, 2007). Part of inborn immunity, the CRP binds to multiple species of bacteria and fungi. The CRP concentrations in the body are very low in healthy individuals, but can increase up to a thousand times during infection and in response to inflammatory stimuli (ABBAS et al., 2011). The CRP is triggered by several factors, such as cardiovascular disease, cancer and chronic arthritis. The plasma concentration above 3.0mg/L is associated with a high risk of cardiovascular disease (FICHTLSCHERER et al., 2004).

The IL10 is involved in the control of immune responses (inhibition of the function of activated macrophages and dendritic cells) and inhibits the expression and production of pro-inflammatory cytokines (ABBAS et al., 2011). Considered an anti-inflammatory cytokine, it has multiple functions including the reduction of TNFa and IL6 levels, inhibition of endothelial cell interactions, and plays a protective role against atherosclerosis (WANG et al, 1995;. SMITH et al., 2001).

The insulin is secreted by the beta cells of the pancreatic islets in response to the circulation of glucose and amino acids after meals. It regulates glucose homeostasis at multiple levels by reducing hepatic glucose production (via reduction in gluconeogenesis and glycogenolysis) and increasing peripheral glucose uptake, especially in muscle and adipose tissues. Insulin also stimulates lipogenesis in the liver and in the adipocytes, reduces lipolysis and inhibits protein degradation (GALLANT et al., 2002). The reduced insulin action in target tissues is associated with changes in its signaling contributing to insulin resistance which is a condition often associated with obesity and risk factor for type 2 diabetes (NEWSHOME et al., 2014).

Leptin is a substance secreted by adipocytes and it is responsible for the control of food intake, functioning on the neuronal cells of the hypothalamus in the central nervous system. In mammals, the action of leptin on the central nervous system promotes the reduction of food intake and the increase of energy expenditure, in addition to regulating the neuroendocrine function and the metabolism of glucose and fats (FRIEDMANN & HALAAS, 1998). Leptin concentrations are influenced by several factors. The increase in the level of leptin is associated with insulin levels, inflammatory cytokines and pro infectious conditions. On the other hand, reduced leptin concentrations are related to catecholamines, testosterone and stress conditions imposed on the body such as exposure to cold, starvation and intense exercise (FRIEDMANN & HALAAS, 1998; ROMERO & ZANESCO, 2006). It has pro-inflammatory effects in the body, triggering a sequence of reactions in monocytes and macrophages, inducing the synthesis of TNF-a and IL-6. Furthermore, there is evidence that leptin may enhance the growth of various cancer cells (TILG & MOSCHEN, 2006).

Studies in the literature have confirmed that chronic diseases are accompanied by inflammatory processes, and the presence of inflammation may precede the further development of these diseases (SAITO et al., 2000; PEARSON et al., 2003; KON et al., 2005).

The inflammatory process associated with chronic diseases is characterized by a disruption in the balance between pro- and anti-inflammatory cytokines, and is associated with several complications such as insulin resistance, endothelial dysfunction, atherosclerosis and metabolic and vascular disorders that represent a starting point in atherogenesis (CHAPMAN, 2004; LEE et al., 2012).

The increased permeability of the endothelium, the lipid infiltration and the formation of fat plaques on the intimal and medial layers of the arterial walls are followed by a complex sequence of events involving platelets, macrophages, smooth muscle cells and growth factors, adhesion of activated monocytes to endothelial wall and phagocytosis of oxidized low-density lipoprotein particle. This results in an increase in the production of pro-inflammatory mediators and the formation of foam cells that also produce TNFa inducing clot formation and acute coronary syndromes (SOCIEDADE BRASILEIRA DE CARDIOLOGIA, 2001). In this sense, plasma concentrations of some inflammation biomarkers seem to reflect the systemic inflammatory and the vessel wall status and have been associated with future cardiovascular risks (DANDONA ET AL., 2003).

Some studies indicate that physical exercise has an anti-inflammatory effect and is associated with the improvement of inflammation biomarkers concentrations (DAS, 2004; PETERSEN & PEDERSEN, 2005; STEWART et al, 2007; TIMMERMAN et al, 2008; AKPARPOUR, 2013; SOARES & DE SOUSA, 2013). According to Pedersen (2006), the anti-inflammatory process linked to the physical exercise plays an important role against diseases such as cardiovascular disease and type 2 diabetes.

Pedersen and Hoffman-Goetz (2000) state that several studies have demonstrated that exercise induces significant physiological changes in the immune system. The moderate intensity exercise is a procedure that favors the oxidative homeostasis of cells and tissues by reducing the basal levels of oxidative damage and increase the resistance to oxidative stress (NIESS et al. 1999; COOPER et al. 2002). Regular exercise results in adaptations in the antioxidant capacity, which protect cells against the deleterious effects of Oxygen Reactive Species, preventing cell damage (AGUILO et al. 2003). Some studies have found that the concentrations of certain biomarkers of inflammation is reduced by physical exercise, suggesting that it can modulate the cardiovascular health via anti-inflammatory effects (PISCHON, et al., 2003; BERLIN et al., 1990; DURSTINE & HASKELL, 1994; KRAUS et al., 2002; FORD, 2002; WANNAMETHEE et al., 2002). However, some studies have not found this association (MARCELL et al., 2005; ALBERT et al., 2004).

In the literature review by Teodoro et al. (2010), the authors concluded that chronic practice of physical exercise acts positively in cytokines. The TNFa operates mainly in the decrease of plasma concentration when physical activity becomes chronic, acting in this way, as an important tool for the prevention and treatment of chronic diseases. The IL6, in acute phase, increases in both aerobic and strength exercises. The significant increase of IL6 has a biological explanation, since it can induce the synthesis of anti-inflammatory factors, such as IL10, which protects from damage caused by excessive pro-inflammatory cytokines into the bloodstream. Chronically, both aerobic and strength exercises seem to decrease the basal plasma concentrations of IL6 (TEODORO et al., 2010).

According to Soares and De Sousa (2013), integrative interventions that includes healthy diet, physical exercise, counselling and health education appears to be effective strategies to improve the biomarkers inflammatory levels in women. The authors suggest that aerobic exercise (from 60% to 80% of maximum heart rate or from 50% to 60% of maximum oxygen uptake) and strength exercise (from 8 to 10 exercises, 8-12 repetitions) are more effective (SOARES & DE SOUSA, 2013).

Beavers et al. (2010) state that consistent data from observational studies show a link between levels of self-reported physical activity and inflammatory biomarkers. Some positive data from controlled and randomized studies indicate that increased aerobic physical activity could be effective to reduce chronic inflammation, especially in individuals with a chronic disease associated with an elevated inflammation status.

Table 1.2 summarizes some studies relating the effect of exercise and physical activity levels with biomarkers of inflammation. The studies described in Table 1.2 show that the CRP is the biomarker of inflammation more susceptible to changes due to physical exercise - aerobic, resistance or combined exercises. There is still no consensus on the effect of exercise on TNFa, IL10 and IL6 concentrations, perhaps for the methodological differences between the studies. In studies of association between physical activity and inflammation biomarkers, the results indicate that there is an inverse relationship with high-intensity activities.

Table 1.2: Studies about the effect of physical exercise and physical activity levels in inflammatory biomarkers

Authors - Year	Sample	Intervention design	Main results
Papini et al., 2014	13 female 56.8 years old	12 months Aerobic (30`) and resistance muscles (20`) exercises 2 sessions a week	↓ TNFa and CRP
Fisher et al., 2011	97 healthy and overweight female aged between 20 to 46 years old.	8 weeks Multidisciplinary treatment Diet group Diet group AND exercise group Diet group AND resistance exercise	↓ IL6, CRP and TNFa ↓ weight appears to be more efficient to reduce the biomarkers than physical exercise
Balducci et al., 2010	82 diabetes OR metabolic syndrome patients aged between 40 to 75 years.	12 months 2 sessions per week (60') Control group Counseling group for low intensity practice High intensity aerobic exercise group Combined exercise group (resistance AND aerobic)	↓ CRP in aerobic exercise group ↓ CRP and IL6 in combined group.

Donges et al., 2010	102 sedentary adults	10 weeks (aerobic OR resistance exercise) Resistance training in initial period with 5 exercises (2 sets/10 repetitions) and increased to 9 exercises (3 sets/8 repetitions) with 75% of 1RM. Aerobic training between 70 to 75% of HRmax, 30' and increased to 50' of duration.	↓ CRP in both exercises (aerobic and resistance).
Ferreira et al., 2009	14 healthy female aged between 33 to 45 years.	10 weeks Circuit training (resistance training) 9 exercises 3 laps on circuit. First lap, 15 – 20 repetitions (warm-up) Other two laps, 8 -12 maximum repetitions 3 times per week.	Did not found changes in IL6, IL10 e TNFa concentrations.
Olson et al., 2007	80 overweight or obese female aged between 22 to 25 years.	12 months Resistance exercise, to greater muscles groups. 2 times per week, 3 sets/8 – 10 repetitions.	↓ CRP

Devries et al., 2008	24 obese AND non-obese female aged between 20 to 50 years.	12 weeks Aerobic exercise, cycle ergometer Initially, 2 times per week, 50% VO_2peak and increased to 3 sessions per week with 65% VO_2peak	Did not found changes in IL6, IL10 e TNFa concentrations.
Esposito et al., 2003	112 obese female aged between 20 to 46 years.	2 years Multidisciplinary intervention Monthly sessions with nutritionist and trainer.	↓IL6 and PCR.
Pischon, et al., 2003	405 healthy male. 454 healthy female.	Prospective cohort Physical activity level measured by survey, with data transformed in energy expenditure (metabolic equivalents – METs)	Physical activity were inversely associated with insulin blood concentrations. Vigorous physical activity were associated with decreased IL-6, CRP and leptin concentrations.
Ford, 2002	13.748 subjects.	Last month physical activity levels analyzed by survey.	The elevated CRP concentration were inversely associated with vigorous physical activity levels.

1.4.4 Physical Exercise and Cardiorespiratory Fitness

The components which constitute physical fitness are important determinants to health. In addition to strength, flexibility and body composition, the cardiorespiratory fitness is a component related to health. The cardiorespiratory fitness corresponds to the capacity of cardiovascular and respiratory systems to provide oxygen during a continuous physical activity (CASPERSEN et al., 1985).

The Maximal Oxygen Consumption (VO_2max) is considered one of the most important parameters to identify the functional capacity of cardiorespiratory fitness and it constitutes an important predictor to cardiovascular diseases (ADEKUNLE & AKINTOMIDE, 2012). The VO_2max is defined as the maximum capacity of pulmonary, cardiovascular and muscular systems to collect, carry and use the oxygen in the oxidative biosynthesis of energy (ATP – Adenosine Triphosphate) (FLETCHER et al., 1990).

The VO_2max increases progressively to the chronological lifecourse and normal maturational process. Although boys have higher VO_2max values since 6 years old compared to girls, the profile between them does not show significant differences in the growth curves of VO_2max until 12 years old. After the age of 14 years old, the differentiation between genders is more evident. In this period, the girls reach a plateau and a slight drop subsequently. This occurs due to an increase of body mass. The boys continue to present increasing values until 18-20 years old. After complete maturation, the women present approximately 75% of VO_2max in relation to men. From to the third decade of life, the cardiovascular and respiratory systems start presenting reduced functionality with age, if they are not trained. With aging, the cardiorespiratory fitness decreases about 10% to each decade of life (GOBBI et al., 2005). In addition to age, the VO_2max is significantly related to other factors such as heredity, physical activity level, fitness training and clinic condition of cardiovascular system (FLETCHER et al., 1990).

According to Blair et al. (2001), there is a negative relation between cardiorespiratory fitness and mortality from coronary diseases, cerebrovascular accident or all the causes of mortality. The low cardiorespiratory fitness is also a strong predictor of metabolic syndrome (LAMONTE et al., 2005).

The potential benefits of a greater cardiorespiratory fitness should be considered in the primary health care of several diseases. Among the benefits, there is a decrease of risk factors related to cardio metabolic diseases such as an improvement of glucose tolerance, dyslipidemias, inflammatory biomarkers and body composition (GARBER, et al., 2011).

Therefore, the importance to maintain the cardiorespiratory fitness level across lifecourse is evident. The American College of Sport Medicine and the Heart American Association suggest VO_2max reference values for cardiorespiratory fitness classification separated by gender and stratified by age group (ACSM, 2010). These classifications are presented in Chart 1.1 (men) and Chart 1.2 (women).

Chart 1.1 – Cardiorespiratory fitness classifications for men (VO_{2max} values in ml.(kg.min)$^{-1}$), according to age group.

Age group	Very poor	Poor	Average	Good	Excellent
20 – 29	< 25	25 – 33	34 – 42	43 – 52	≥53
30 – 39	< 23	23 – 30	31 – 38	39 – 48	≥49
40 – 49	< 20	20 – 26	27 – 35	36 – 44	≥45
50 – 59	< 18	18 – 24	25 – 33	34 – 42	≥43
60 – 69	< 16	16 – 22	23 – 30	31 – 40	≥41

Source: American College of Sports Medicine ACSM's Guidelines for Exercise Testing and Prescription, 8th edition. (Philadelphia: Lippincott Williams & Wilkins, 2010).

Chart 1.2 – Cardiorespiratory fitness classifications for women (VO_{2max} values in ml.(kg.min)$^{-1}$), according to age group.

Age group	Very poor	Poor	Average	Good	Excelent
20 – 29	< 24	24 – 30	31 – 37	38 – 48	≥49
30 – 39	< 20	20 – 27	28 – 33	34 – 44	≥45
40 – 49	< 17	17 – 23	24 – 30	31 – 41	≥42
50 – 59	< 15	15 – 20	21 –27	28 – 37	≥38
60 – 69	< 13	13 – 17	18 – 23	24 – 34	≥35

Source: American College of Sports Medicine ACSM's Guidelines for Exercise Testing and Prescription, 8th edition. (Philadelphia: Lippincott Williams & Wilkins, 2010).

Despite presenting a genetic factor, the components of physical fitness, including the cardiorespiratory one, can be influenced by external factors such as training and physical activity levels (BLAIR et al., 2001). Structured physical exercise interventions can bring significant and beneficial changes to cardiorespiratory fitness (DUNN et al., 1999).

The trainability of cardiorespiratory fitness in adults is more evident. The increase of VO_2max can range between 10-20% after an aerobic conditioning program during 2 to 4 months (GOBBI et al., 2005). The elderly individuals can also improve their VO_2max in response to exercise training and their adaptation capacity, in relative terms, is similar to younger individuals (HAGBERG, 1987). According to Hagberg (1987), elderly people can minimize the cardiorespiratory fitness decline resulting from aging process by keeping high levels of physical activity. Active elderly people decrease their VO_2max about 5% per decade, in contrast with 10% found in sedentary people.

To improve the cardiorespiratory fitness, aerobic exercises that involve large muscle groups are recommended (ACSM, 2010). The recommendation is that adults should accumulate at least 150 minutes of moderate-intensity aerobic physical activity per week; meeting preferentially the specification of 30-60 minutes/5 days a week or 20-60 minutes/3 days a week of vigorous-intensity activity. Exercises performed under the recommended intensity, duration and frequency result in an improvement of cardiorespiratory fitness. A gradual progression of time and intensity is recommend (GARBER et al., 2011). Greater volume of physical activity such as the performance of a physical exercise program with longer durations and more vigorous intensity causes additional benefits to health (ACSM, 2010).

The regular aerobic exercise practice promotes physiological adaptations resulting in an improvement of cardiovascular and respiratory functions. Some of the physiological adaptations are the increase of maximal oxygen uptake and exercise tolerance, the improvement in submaximal intensities (lactate threshold analyses), the decrease of minute ventilation, cardiac frequency and blood pressure for pre-established absolute submaximal exercise intensity (ACSM, 2010).

Thus, considering the close relationship between cardiorespiratory fitness and health and the benefits of a regular aerobic exercise practice on individuals, it is necessary to elaborate and implement physical exercise programs for children, adults and elderly people.

2. CHAPTER 2: Methods

A 1-year clinical study was performed to achieve the aims proposed by our research. The sample was composed by female participants of the Physical Exercise Programs carried out in Primary Health Care in Rio Claro City, Sao Paulo, Brazil.

2.2 Logistics and recruitment of participants

Three Health Units were selected to implement 2 different physical exercise protocols: *2 Unidades Basica de Saude (UBS)* and *1 Unidade de Saude da Familia (PSF*). These Health Units were selected due to the presence of appropriate and safe place for the performance of physical exercises and to keep the materials; and also because these Units did not offer any physical exercise intervention to residents around. The chart 1.1 presents the logistic of the programs offered.

Chart 2.1 – Logistic of Programs

Health Unit	Intervention	Sessions	Duration	Period
UBS 29 - Oreste Armando Giovani	1	2days/week	60 minutes	a.m.
UBS Jardim Chervezon Dr. Nicolino Maziotti	1	2days/week	60 minutes	p.m.
	2	3days/week	90 minutes	a.m.
USF Panorama Dr. Osvaldo Akamine	2	3days/week	90 minutes	p.m.

After the Health Unit selection, a divulgation (in June and July 2012) was performed inside the Health Units and in places nearby (e.g. commercial establishments) through flyers, newspaper ads and banners. The participant's registration was made in the Health Units by the researchers.

The following inclusion criteria were considered to select the sample: individuals aged 20 years old or over and without any limitation to the performance of physical exercises (being necessary to present a medical approval). Moreover, the following exclusion criteria were considered: 3 consecutive unjustified absences, 4 absences during a month and a attendance rate <75% of the total number of physical exercise session in the end of 1 year of intervention. The attendance was monitored through a name checklist in every session.

One hundred and forty participants registered in July 2012. Of this total, 87 met the inclusion criteria and attended the first evaluation. The male participants (n=5) were excluded from the sample due to the small number of participants. However, they were not excluded from the intervention. Thus, the initial sample was composed by 82 women (aged 52.6± 12 years old). They were placed by convenience considering the proximity of Health Unit from their residence. This distribution considers the regionalization principle of SUS. In the Health Unit that provided both interventions (in the morning and afternoon), the participants were also able to choose the timetable according to their availability.

In the beginning of the interventions, the program 1 was composed by 36 women (aged 55.4± 14.3 years old) and the program 2 was composed by 46 women (aged 50.45± 10.92 years old). The participants distribution is presented in figure 2.1.

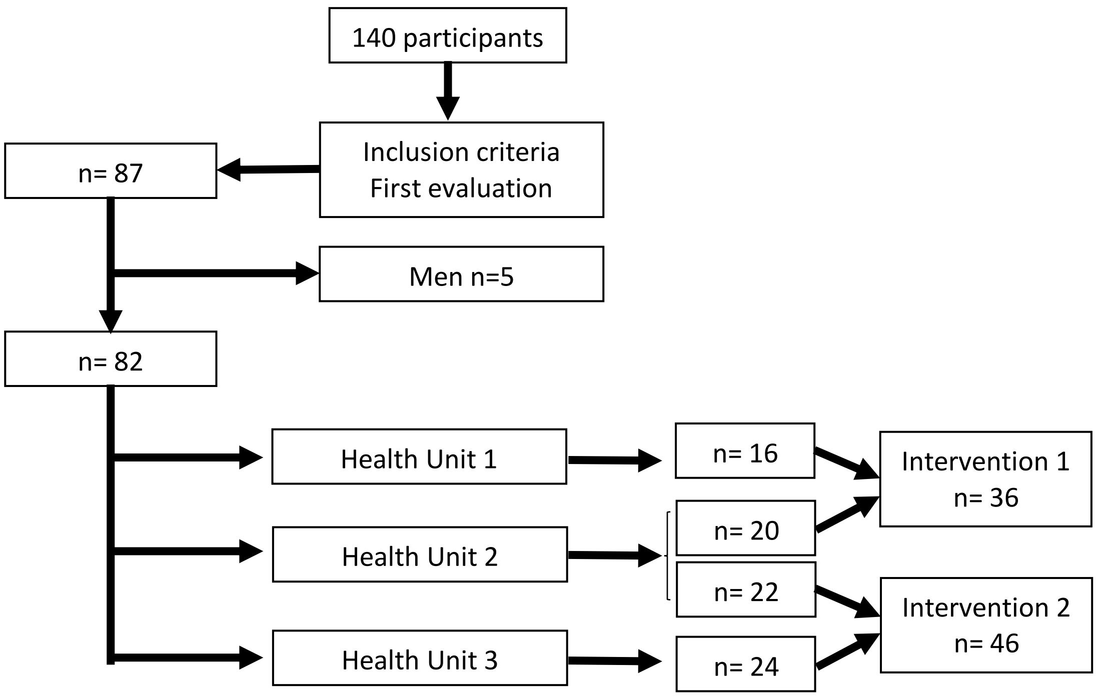

Figure 2.1: Distribution flowchart of participants in the beginning of interventions

The participants who were not eligible or did not achieve the necessary attendance were excluded from the sample; however, they remained in the intervention.

The figure 2.2 shows the female participation in the intervention 1 and 2 over 1 year. After 6 months, considering both voluntary dropout and failure to meet the inclusion criteria for the study (frequency of 75% attendance in the sessions), 25 participants remained in the interventions. After 1 year of intervention, the final sample consisted of 17 women (56.2± 11.9 years old) in intervention 1 and 20 women (57.2± 9.3 years old) in intervention 2. These final samples consider the women who completed 1 year of intervention with at least 75% attendance in sessions.

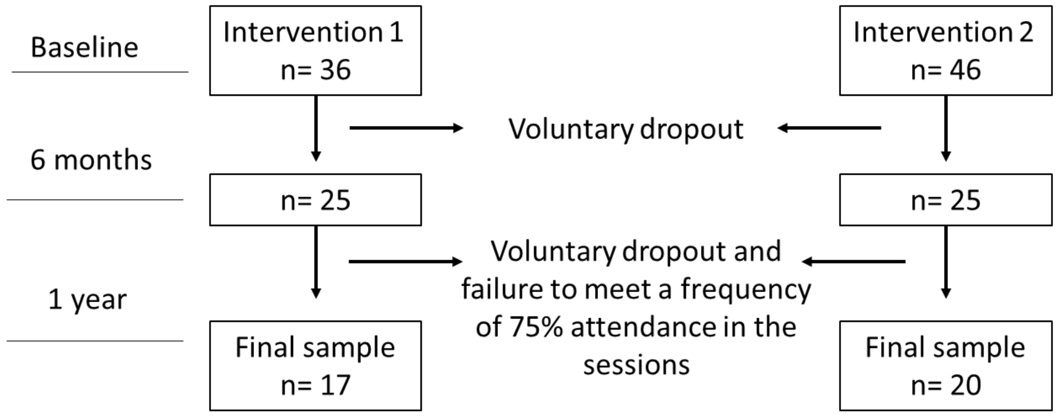

Figure 2.2: Flowchart of participation over 1 year of intervention.

Some of the participants who completed 1 year of intervention did not complete all evaluations, as illustrated in the chart 2.2. Thus, the final sample is 17 and 18 in the anthropometric evaluation; 16 and 15 in the pedometer evaluation; 15 and 20 in the cardiorespiratory fitness test; 13 and 11 in the biomarkers evaluation in intervention 1 and 2 respectively.

Chart 2.2: Final sample of participants in each evaluation.

Evaluation	**Intervention 1 (n)**	**Intervention 2 (n)**
Anthropometry	17	18
Pedometer	16	15
Cardiorespiratory fitness	15	20
Inflammatory biomarkers	13	11

The participants who did not meet at least 75% of attendance in sessions were excluded from the study but they were not excluded from the interventions. In the end of the 1-year interventions, 25 participants remained in the intervention 1 and 30 participants remained in the intervention 2.

2.3 Ethnic aspects

The study was approved by the Human Research Ethics Committee of Biosciences Institute, UNESP, protocol number: 2308. The participants were informed about the aims and procedures of study and signed the consent form (annexes session).

2.4 Interventions protocols and staff

Both interventions were performed from August 2012 to August 2013. They involved aerobic and neuromotor physical exercise practice targeting the development of cardiorespiratory fitness, muscle resistance, flexibility, agility, motor coordination and balance. In the first 6 months, the exercise sessions and the first and second evaluations were taught by 4 Physical Education Professionals (Bachelors in Physical Education). The last 6 months, 2 Physical Education Professionals conducted the exercise sessions and the last evaluation. We also have the participation of 4 nurses (one in each Health Unit) who conducted the blood sampling of participants; and 1 technical laboratory who performed the biochemical analysis.

2.4.1 Intervention 1

The intervention 1 comprised two 60-minute sessions/week of moderate physical exercises, totaling 120 minutes per week. The sessions were divided in: a) initial part (5 minutes), intended for monitoring of blood pressure and glucose, followed by warm-up activities; b) main part (50 minutes), composed by aerobic activities (30 minutes) and strength exercises (20 minutes); c) final part (5 minutes) composed by stretching and cool-down activities. The intervention 1 totalized 60 minutes of aerobic activities, 40 minutes of strength exercises and 10 minutes of stretching activities per week (figure 2.3). Furthermore, during each session, the participants received counseling designed to increase daily physical activity levels and encourage participation in physical exercise outside the intervention. The importance of meeting the physical activity levels recommendation was exposed during the counselling sessions. However, the counseling and advices offered to participants of intervention 1 cannot be considered a structured counseling session.

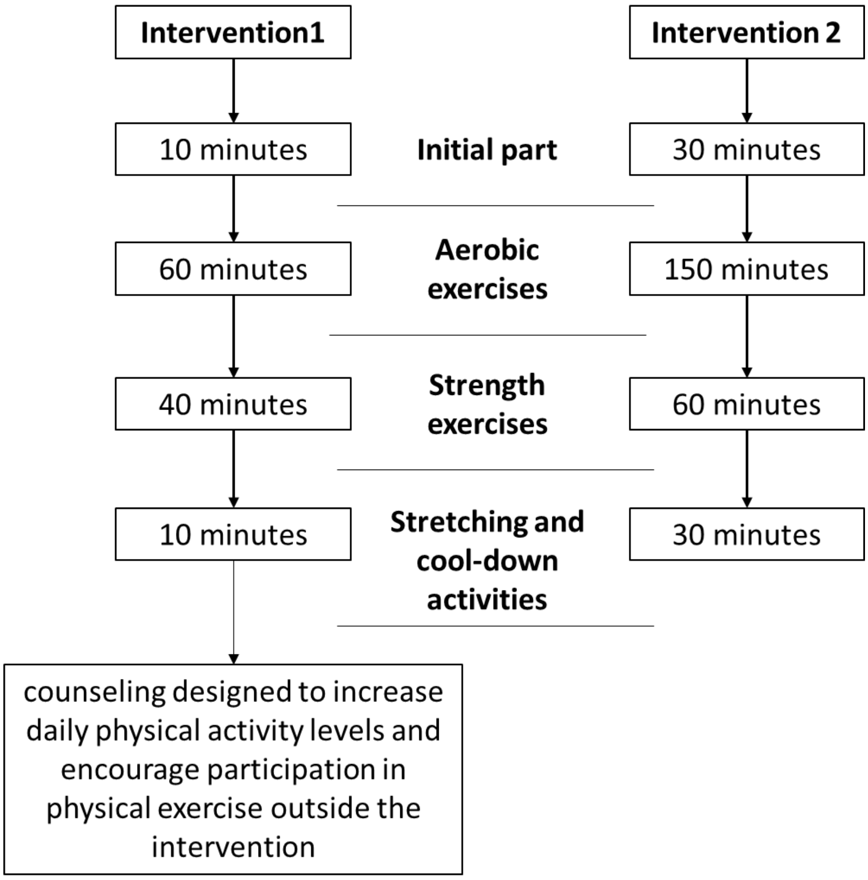

Figure 2.3 Weekly time of activities performed in each intervention

2.4.2 Intervention 2

The intervention 2 comprised three 90-minute sessions/week of moderate physical exercises, totaling 270 minutes per week. The sessions were divided in: a) initial part (10 minutes), intended for monitoring of blood pressure and glucose, followed by warm-up activities; b) main part (70 minutes), composed by aerobic activities (50 minutes) and strength exercises (20 minutes); c) final part (10 minutes) composed by stretching and cool-down activities. The intervention 2 totalized 150 minutes of aerobic activities, 60 minutes of strength exercises and 30 minutes of stretching activities per week (figure 2.3). The participants did not receive any counseling related to the practice of physical exercise in addition to the intervention.

2.4.3 Physical Exercise and Intensity monitoring

In both interventions, the blood pressure of participants was monitored once a week using a digital equipment (Fuzzy LOGIC®, BioLand model: 3001); the blood glucose of insulin-dependents diabetics was measured once per week and for non-insulin-dependents diabetics and healthy participants was measured once a month using a portable blood glucose meter (Advantage®, Eli Lilly do Brasil Ltda). The blood pressure and glucose were not measured in all participants on the same day, being distributed throughout the week and month, according to the number of participants. This strategy was adopted to avoid overloading the responsible professional and also avoid interference in the time allotted for this action and compromise the session progress. The blood pressure and glucose measurements were documented in the list of attendance in each intervention. These measurements aimed to raise the participants´ - especially hypertensive and diabetic - concern in relation to safety and care.

The session was initiated with warm-up activities and static stretching of large muscle groups. The aerobic exercises consisted of walking at moderate intensity (60–70% of peak heart rate). The target zone for exercise was calculated using the equation HR peak = 206 − (0.88 × age), as suggested by Gulati et al. (2010). All participants were instructed to maintain a subjective effort between 13 and 15 on the Borg scale while walking (BORG, 1982). Four participants were randomly selected to measure the intensity of their activity twice a month using a cardiac rate monitor (Polar, FS1) and the subjective effort scale. This evaluation aimed to control the intensity of exercise, ensuring that participants remained on a moderate range.

The neuromotor activities comprised stretching and strength resistance exercises, in addition to activities that develop coordination, balance and agility. The strength resistance exercises were performed in each session with the support of free weights, exercise mats, and latex exercise bands. Exercises included all major muscle groups and were performed in 3 sets of 30 seconds, followed by one minute of recovery; the overload was obtained by increase the number of sets or repetitions of exercises. The static stretching exercises were performed in each session and a minimum period from 15 to 30 seconds was maintained, twice for each muscle group. The participants were advised to sustain a muscle stretch that did not cause pain. The cool-down activities consisted of relaxation, massage or recreational activities.

Although the groups presented healthy individuals and with chronic diseases, both interventions were designed with moderate intensity activities. It is also important to note that both interventions were carried out in Heath Units, which attend most individuals in these conditions, thus individuals with chronic disease were not excluded from our research. To minimize possible risks or any health damage, all participants had to present a medical report certifying appropriate physical condition to perform physical exercises.

2.5 Evaluations

The evaluations occurred in 3 stages: pre intervention (baseline), after 6 months and after 1 year of intervention. Except for the cardiorespiratory fitness, which occurred at baseline and after 1 year of intervention due to technical problems with the gas analyzer in the evaluation of six months. The evaluations were conducted in the *Nucleo de Atividade Fisica, Esporte e Saude – UNESP Rio Claro.*

2.5.1 Clinical history and Questionnaires

All participants answered to a clinical history questionnaire in order to give general health information, readiness for physical activity, lifestyle habits, amount of leisure time physical activity and exercise performed in the last 7 days.

2.5.2 Anthropometric Evaluation

The anthropometric measurements (body mass weight, stature, waist and hip circumferences) were evaluated in the 3 moments (baseline, after 6 months and after 1 year of intervention).

A scale (Welmy®) was used to measure the body mass weight. The participants were oriented to take off the shoes and sweat suit and to remain in the center of the scale, with corporal weight distributed in both feet (LOHMAN et al., 1991).

The stature was measured by a stadiometer and participants were advised to remain with their back turned to it. The measurement was performed with participants barefoot, corporal weight distributed in both feet and the head positioned parallel to the ground. The arms remained extended along the trunk with the palms resting on lap and the heels remained together. The participants remained in upright position and sustained an inspiration in the moment of the measurement (LOHMAN et al., 1991).

The waist and hip circumferences were taken with participants standing in upright position, with relaxed abdomen and the heels together. For waist measurement, the participants were asked to lift the shirt for the direct measurement on the skin. The metric tape was positioned at the natural waist (midpoint between the anterior superior iliac spine and the last rib). For the hip measurement, the metric tape was positioned in the horizontal plan at the largest circumference point of the gluteal region (LOHMAN et al., 1991). A inextensible metric tape (Sanny®) with 1mm accurate was used. The tape was maintained under the skin, without compressing the tissue.

2.5.3 Pedometer

The pedometer measurement was performed at baseline and after 1 year of intervention using the Digi-Walker SW700®. The pedometer was distributed to participants and returned within 6-7 days. They were instructed to use it on three different days: (1) on a weekday (Monday to Friday) when there was no intervention; (2) on a weekday (Monday to Friday) when there was intervention; (3) on a weekend day (Saturday or Sunday) (TUDOR-LOCKE et al., 2005).

The results were calculated to obtain the physical activity level during week. Different calculations were applied for the intervention 1 and intervention 2, using the number of steps in each day:

- Intervention 1 = (day with intervention x 2) + (day without intervention x 3) + (weekend day x 2)

- Intervention 2 = (day with intervention x 3) + (day without intervention x 2) + (weekend day x 2)

The daily physical activity level was calculated by dividing the values found by 7. The participants received the pedometer with a set of written instructions to be followed:

- Place the pedometer at the right hip, as soon as you wake up;
- Remove the pedometer only when you go to bed, before taking a shower or before performing water activities;
- Note the number of steps shown on display at the end of the day (bed time) and remember to reset it for use on the next day.

The number shown on the display was registered in the instruction sheet, which also contained the day it should be used and a space to write this number. The instruction sheet was returned with the pedometer.

2.5.4 Blood Analysis

The blood analysis examined the levels of Interleukin 6 (IL-6), Interleukin 10 (IL-10), Tumor Necrosis factor alpha (TNFα), C-reactive Protein (CRP), Glucose, Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Leptin and Insulin at baseline, after 6 months and after 1 year of intervention. The analysis was conducted in the *Laboratorio de Biodinamica da UNESP - Rio Claro.*

A 10 mL venous blood sample was collected in the morning after 12 hours of fasting by a nurse from a Health Unit. The blood sample was transported under refrigeration to the laboratory within 30 minutes, centrifuged for 10 minutes with the serum immediately separated following centrifugation. All variables were analyzed in duplicate using commercial kits. To minimize the analytics variation, the samples were analyzed by the same technician.

The CRP, Glucose, TG, TC, LDL, HDL were analyzed using the colorimetric-enzymatic method. The IL-10, IL-6, TNFα, leptin and insulin were analyzed using Luminex technology assay (Luminex).

2.5.5 Cardiorespiratory Fitness Test

The cardiorespiratory fitness was measured via submaximal incremental treadmill test (ATL3®, Inbrasport, Brasil) through indirect calorimetry using a gas analyzer (VO2000, Medgraphics, St. Paul, Minnesota, USA) and a medium flow pneumotachograph (6 – 120 L/min). The test data was collected in each 3 breathings by Aerograph Software. The participants answered the Readiness Activity PAR-Q questionnaire before the test and performed an adaptation on the treadmill; the use of neoprene masks and the use of the perception of exertion scale (BORG, 1982).

The test initiated in 4km/h with no incline. In the second stage, the speed was increased to 5.6 km/h with no incline. In the next stages, the speed was maintained and the incline was increased 2.5% in each stage. Each stage lasted 3 minutes.

The Maximum Heart Rate (HRmax) was calculated according to the Karvonen et al., (1975) equation: HRmax = 220 - age. The heart rate was monitored during test (Polar® model FS1, Polar Electro Oy, Finland). The scale BORG was also used – every minute – to monitor the subjective effort perception.

The test was interrupted when participants reached 85% of HRmax previously estimated by equation (HR85%= (HRmax x 85)/100); or when participants reached the BORG 15 (in case of participants medicated with beta-blocker); or by voluntary exhaustion (before reaching the 85% of HRmax).

The final VO_2, the final time and the final stage reached in the test were evaluated. The participants performed the test at baseline and after 1 year of intervention.

3. CHAPTER 3: The Effect of a Community-Based, Primary Health Care Exercise Program on Inflammatory Biomarkers and Hormone Levels.

This Chapter contains the paper "The Effect of a Community-Based, Primary Health Care Exercise Program on Inflammatory Biomarkers and Hormone Levels" – published in the Journal *Mediators of Inflammation* (http://dx.doi.org/10.1155/2014/185707). It was originated from the analysis of Intervention 1.

Introduction

It is well established that chronic diseases are the leading cause of mortality in the world. According to the World Health Organization (2011) 60% of all death is attributed to cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases. The inflammatory process related to chronic diseases, characterized by dysregulation in the balance between pro- and anti-inflammatory processes, ispaned linked with several complications such as insulin resistance, endothelial dysfunction, atherosclerosis, and vascular and metabolic disorders (KING, 2008; GOLDBERG, 2009; FERNÁNDEZ-BERGÉS et al., 2014; VINAGRE et al., 2014).

Regular physical exercise has been increasingly viewed as an effective therapeutic strategy for the management of chronic diseases (LEE et al., 2012). It has long been known that regular physical activity induces multiple adaptations within skeletal muscles and the cardiorespiratory system, providing positive outcomes for the prevention and treatment of chronic diseases (HAWLEY, 2004; PEDERSEN, 2006). Some studies have indicated that regular physical activity has anti-inflammatory effects and is associated with improvement in inflammatory biomarkers such as a reduction in levels of the pro inflammatory cytokines (DAS, 2004; PETERSEN & PEDERSEN, 2005; STEWART et al., 2007; TIMMERMAN et al., 2008; AKPARPOUR, 2013; SOARES & DE SOUSA, 2013). According to Pedersen (2006), the anti-inflammatory processes provided by physical exercise play important roles in the protection against diseases associated with low-grade inflammation such as cardiovascular diseases and type 2 diabetes.

Considering that physical inactivity is the fourth leading cause of death worldwide] and causes 6–10% of the major non communicable diseases (KOHL et al., 2012; LEE et al. 2012), it is necessary to induce social, economic, and environmental changes and multiple strategies that promote public policies related to physical active life style. "Saude Ativa Rio

Claro" (SARC) is a community-based exercise intervention in primary care designed to promote and maintain physical activity levels of residents in Rio Claro City, Brazil. Since 2001, SARC operates in basic health care units and reaches approximately 400 low-income adults aged 35 years or older (NAKAMURA et al, 2014). Evidence suggests that this program improves blood cholesterol, LDL, HDL, and glucose profiles (KOKUBUN et al., 2007; ZORZETTO, 2013). However, it is unknown whether the SARC intervention can improve inflammatory biomarkers and thus potentially aid in the prevention of chronic disease and associated complications. Therefore, the aim of this study was to assess the impact of SARC on a range of common inflammatory biomarkers and hormone levels in adult women, including leptin, insulin, C-reactive protein (CRP), interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), and interleukin 10 (IL10). It was hypothesized that there would be an increase in IL10 and a decrease in inflammatory markers (CRP, IL6, and TNFα) and hormone (leptin and insulin) levels after 1 year of SARC intervention.

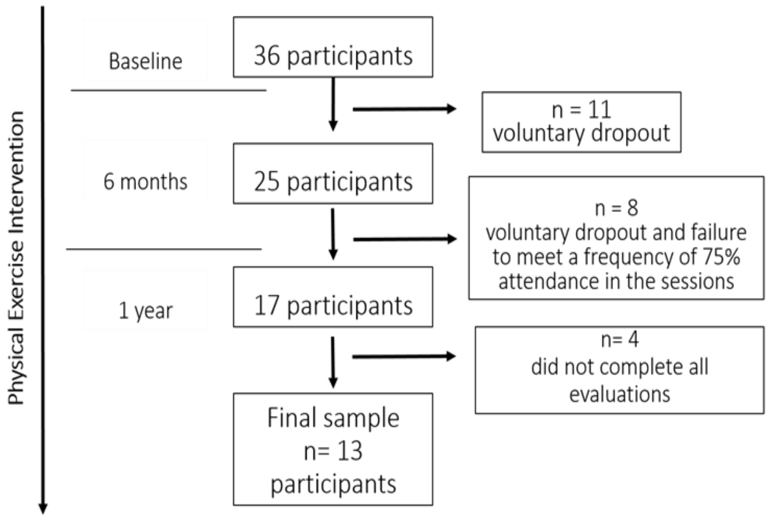

Figure 3.1: Recruitment of participants for the study. Evaluations were done at baseline, 6 months, and 1 year of SARC intervention.

Methods

Participants

This 1-year quasi experimental study was developed in two basic health care units in Rio Claro City, Brazil. Adult females were recruited via flyers and newspaper advertisements. Participants were assigned to the intervention group based upon proximity from their residence. Thirty-six participants were recruited at the beginning of intervention. As a result of either voluntary dropout or failure to meet the inclusion criterion for the study (frequency of 75% attendance in the sessions), 25 participants remained in the intervention after 6 months. Although 17 participants completed the 1 year intervention, four participants did not complete all evaluations; thus the final sample size was 13 women (mean age = 56.8 ± 11.4 years, Figure 1). The study was approved by the Human Research Ethics Committee of Biosciences Institute, UNESP, protocol number: 2308.

Physical Exercise Intervention

SARC is a community based exercise intervention comprised of two 60-minute sessions/week of physical exercises. The sessions were divided in warm-up activities (5 minutes), moderate intensity aerobic exercise (30 minutes), strength-training exercises (20 minutes), and cool-down activities (5 minutes). Furthermore, during each session, the participants received counseling designed to increase daily physical activity levels and encourage participation in physical exercise outside of the intervention.

The warm-up and cool-down activities included static stretching exercises and articular movements. Static stretching was maintained for a minimum period of 15 to 30 seconds, twice for each muscle group. The participants were advised to sustain a muscle stretch that did not cause pain (ACSM, 2010; JUNIOR, 2010). The aerobic exercises consisted of walking at moderate intensity (60–70% of peak heart rate). The target zone for exercise was calculated using the equation HR peak = 206 − (0.88 × age), as suggested by Gulati et al. (2010). All participants were instructed to maintain a subjective effort between 13 and 15 (GARBER et al., 2011) on the Borg scale (BORG, 1982) during walking. Four participants were randomly selected to measure the intensity of their activity twice a month using a cardiac rate monitor (Polar, FS1) and the subjective effort scale. The strength-training exercises were performed using free weights, exercise mats, and latex exercise bands. Exercises included all major muscle groups and were performed in 3 sets of 30 seconds, followed by one minute of recovery.

Inflammatory Biomarkers Measures

A 10 mL venous blood sample was collected at baseline, after 6 months, and after 1 year of intervention, in the morning after 12 hours of fasting. The blood sample was transported under refrigeration to the laboratory within 30 minutes, centrifuged for 10 minutes with the serum immediately separated following centrifugation. The inflammatory biomarkers were analyzed in duplicate using commercial kits. C-reactive protein (CRP) was analyzed using an enzyme-linked immune sorbent assay (ELISA). Interleukin 10 (IL10), interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), leptin, and insulin were analyzed using Luminex technology assay (Luminex). Intra assay coefficients were all <10%. To minimize analytical variations, the same technician tested all samples without changing reagent lots, standards, or control materials.

Statistical Analyses.

Descriptive data are reported as means and standard deviations. The ratio of IL-10 to TNFα (IL10/TNF-α) was calculated and compared in 1 year. A repeated measures ANOVA was used to analyze the changes in anthropometric variables, inflammatory biomarkers, and hormones levels over time (baseline, 6 months, and 1 year). Significant differences were determined by Bonferroni post hoc tests. Statistical analyses were conducted using SPSS 20.0, with the alpha level set at $p < 0.05$.

Results

Table 3.1 shows the anthropometric characteristics of the participants (n = 13, mean age of 56.8 ± 11.4) at baseline, 6 months, and 1 year. No changes in weight, body mass index (BMI), or waist to hip ratio (WHR) were seen over time ($P > 0.05$). The prevalence of diseases was 7.7% (n = 1) for diabetes, 30.7% (n = 4) for obesity, and 38.5% for hypertension ($n = 5$). The prevalence of participants having at least 1 disease was 46.1% ($n = 6$). Table 3.2 and Figure 3.2 illustrate the inflammatory biomarkers and hormone concentration levels and indicate the outcomes of statistical analyses between time at baseline, 6 months, and 1 year. CRP levels significantly decreased after 1 year of intervention (1.5 ± 1.0 $mg \cdot L^{-1}$) compared to baseline (3.4 ± 1.2 $mg \cdot L^{-1}$, p = 0.001) and 6 months (3.0 ± 1.2 $mg \cdot L^{-1}$, p = 0.003). A significant decrease in TNFα levels was shown after 1 year of intervention (56.6 ± 3.0 $pg \cdot mL^{-1}$) compared to baseline (10.6 ± 5.6 pg·mL−1, p = 0.001) and 6 months (7.6 ± 4.0 pg·mL−1, p = 0.004). IL10, IL6, and insulin did not change over 1 year ($p > 0.05$). Leptin levels were significantly increased after 1 year (7.6 ± 4.89 $pg \cdot mL^{-1}$) of intervention compared to baseline (2.69 ± 2.25 pg·mL−1, p = 0.016) and 6 months (2.3±1.66 pg·mL−1, p = 0.003). The IL10/TNFα ratio increased after 1 year of intervention (BL = 0.59 ± 0.4; 6 M = 0.64 ± 0.2; 1Y = 0.85 ± 0.3).

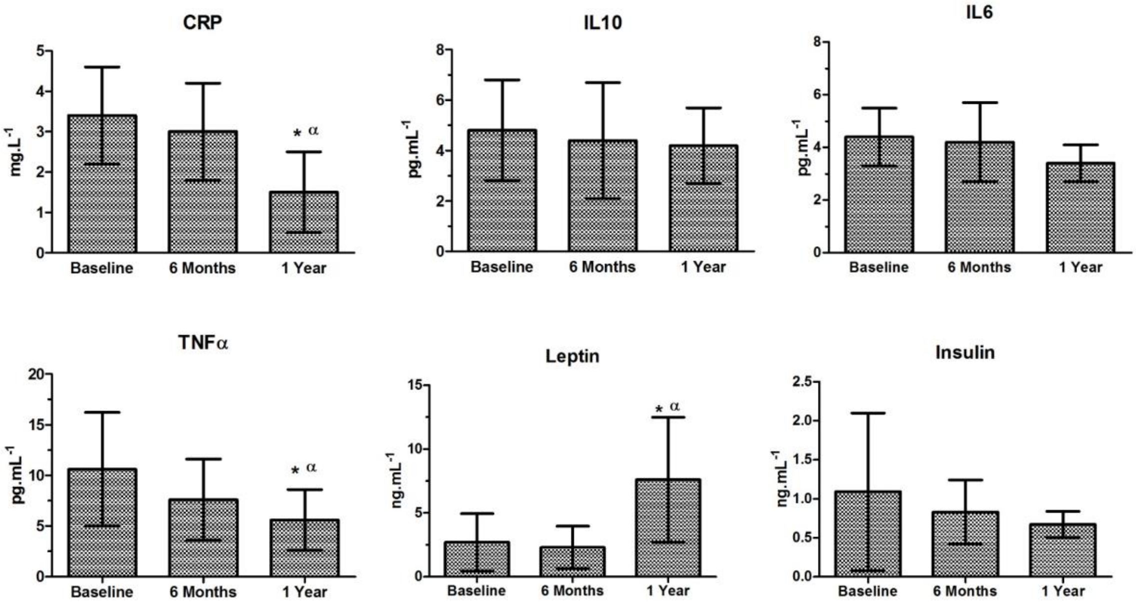

Figure 3.2: Levels of C-Reactive Protein (CRP), Interleukin 10 (IL10), Interleukin 6 (IL6), Tumor Necrosis factor alpha (TNFα), leptin and insulin at baseline, after 6 months and after 1 year of exercise intervention.

*Statistically significant difference from baseline.
$^{\alpha}$ Statistically significant difference from 6 months

Table 3.1: Anthropometric characteristics (mean, standard deviation) of participants at baseline, after 6 months, and after 1 year of exercise intervention.

	Baseline	6 months	1 year	*P* value BL versus 6M	*P* value BL versus 1Y	*P* value 6M versus 1Y
Weight (kg)	67.3 ± 11.5	66.8 ± 11.4	67.2 ± 10.9	0.541	0.631	1.000
BMI (kg/m^2)	27.5 ± 5.6	26.8 ± 6.0	27.9 ± 5.6	0.500	0.316	1.000
WHR	0.88 ± 0.8	0.86 ± 0.8	0.89 ± 0.7	0.863	0.326	1.000

BL: baseline; 6 M: 6 months; 1 Y: 1 year; BMI: body mass index; WHR: waist and hip ratio.

Table 3.2: Inflammatory biomarkers and hormone concentration levels (mean, standard deviation) at baseline, after 6 months, and after 1 year of exercise intervention.

Biomarker	BL	6 M	1 Y	*P* value BL versus 6M	*P* value BL versus 1Y	*P* value 6M versus 1Y
CRP ($mg.L^{-1}$)	3.4 ± 1.2	3.0 ± 1.2	1.5 ± 1.0$^{*\alpha}$	0.999	0.001	0.003
IL10 ($pg.mL^{-1}$)	4.8 ± 2.0	4.4 ± 2.3	4.2 ± 1.5	0.988	0.681	0.602
IL6 ($pg.mL^{-1}$)	4.4 ± 1.1	4.2 ± 1.5	3.4 ± 0.7	0.999	0.236	0.163
TNFα ($pg.mL^{-1}$)	10.6 ± 5.6	7.6 ± 4.0	5.6 ± 3.0$^{*\alpha}$	0.082	0.001	0.004
Leptin (ng/mL^{-1})	2.69 ± 2.25	2.30 ± 1.66	7.60 ± 4.89$^{*\alpha}$	0.999	0.016	0.003
Insulin (ng/mL^{-1})	1.09 ± 1.01	0.83 ± 0.41	0.67 ± 0.17	0.898	0.405	0.642
IL10/TNFα	0.59 ± 0.4	0.64 ± 0.2	0.85 ± 0.3	—	—	—

BL: baseline; 6 M: 6 months; 1 Y: 1 year; CRP: C-reactive protein; IL10: interleukin 10; IL6: interleukin 6; TNFα: tumor necrosis factor alpha. *Statistically significant difference from baseline. $^\alpha$Statistically significant difference after 6 months.

Discussion

Chronic inflammation is an important pathophysiological factor in the development of several diseases and complications, through the effects of pro inflammatory cytokines such as TNFα and IL6, among others (KING, 2008; GOLDBERG, 2009; FERNÁNDEZ-BERGÉS et al., 2014; VINAGRE et al., 2014). On the contrary, anti-inflammatory cytokines, such as adiponectin and IL-10, seem to be protective against pathological conditions (WANG et al., 1995; SMITH et al., 2001).

Analyses indicate that the SACR intervention was effective in decreasing CRP and TNFα levels and maintaining IL10, IL6, and insulin levels over 1 year. However, leptin levels increased over 1 year. Several studies show that inflammatory biomarkers are reduced following longer term lifestyle modification involving reduced food intake and increased physical activity (DAS, 2005). Thus, the effects of regular physical activity on basal levels of inflammatory markers have been used to recommend exercise as an anti-inflammatory therapy. According to Soares and de Souza (2013) integrative interventions, including diet, moderate aerobic exercise (60% to 80% of HRmax or 50% to 60% of VO2max) and circuit resistance training (8 to 10 exercises, 8 to 12 repetitions), health education, and counseling, used together, appeared to be effective strategies to improve inflammatory biomarkers in women.

Our results (Table 2 and Figure 2) indicated that SARC was effective in decreasing CRP levels after 1 year compared to baseline and 6 months. These findings are in agreement with other studies in the literature indicating that a physical lifestyle can reduce CRP levels (FORD, 2002; ELOUSA et al., 2005; KADOGLOU et al., 2008; WALTER et al., 2008; AKPARPOUR, 2013). CRP has a long plasma half-life (>96 h), no variation of diurnal or seasonal, and no age or gender dependence (MEIER-EWERT et al., 2001; FROHLICH et al., 2002). It plays a pivotal role in the innate immune response, is released in response to a variety of pro inflammatory cytokines, and is triggered by many factors such as cardiovascular diseases, trauma, malignancy, and chronic arthritis (FICHTLSCHERER et al., 2004). In our study, the 56% decrease in CRP is clinically relevant because the value changed from a level considered "high risk" for cardiovascular disease at baseline (above 3.0 mg/L) to an "average risk" (1.0 to 3.0 $mg.L^{-1}$) after 1 year of the SARC intervention.

According to You et al. (YOU et al., 2013), findings about the relationship between physical exercise and inflammatory biomarkers are more consistent for CRP than for other biomarkers. However, the SARC intervention was effective in reducing TNFα (Table 2 and Figure 2) after 1 year compared to baseline and after 6 months. Studies have indicated that regular physical activity is associated with a reduction or no change in TNFα (ELOUSA et al., 2005; KADOGLOU et al., 2007; BALDUCCI et al., 2010; COLBERT et al., 2013). TNFα is a cytokine with a varied range of pro inflammatory activities, such as influencing the atherosclerotic process both by causing metabolic perturbations and by increasing the expression of cellular adhesion molecules (VASSALLI, 1992).

No changes were detected in IL10 following 1 year of intervention (Table 2). IL10 has multifaceted anti-inflammatory properties. It is able to reduce serum levels of TNFα and IL6 and plays a protective role against atherosclerosis (WANG et al., 1995; SMITH et al., 2001). There is lack of consensus in the literature as to whether physical activity can improve IL10 levels. Kadoglou et al. (2007) demonstrated in their study that a higher volume of aerobic exercise (four times/week, 45–60 min/session) was effective in increasing IL10 levels after 6 months. Similarly, Jankord and Jemiolo (2004) compared groups performing different amounts of physical activity volume and concluded that the higher volume was associated with an increase of IL-10. Thus, it appears that 2 sessions per week of physical exercise delivered by SARC may be insufficient to improve IL10 levels. However, the IL10/TNFα ratio increased after 1 year of intervention. This result indicates that physical exercise was able to improve the proportion of anti- to proinflammatory cytokines after 1 year.

The SARC intervention did not change IL6 levels following 1 year of intervention (Table 2). Some studies have reported that physical exercise is correlated with lower IL6 levels (TAAFFE et al., 2000; REUBEN et al., 2003; COLBERT et al., 2004; JANKORD & JEMIOLO, 2004; NICKLAS et al., 2008). However, our results are in agreement with other studies. Olson et al. (2007) found that an intervention consisting of at least two training sessions per week was not effective in reducing IL6 levels after 1 year.

Campbell et al. (2009) and Donges et al. (2010) did not also find lower levels of IL6 following physical exercise interventions. Different cells produce IL6 and this cytokine plays both "good" and "bad" roles depending on the circumstances. It has been suggested that an elevation in IL6 in response to physical exercise can exert an anti-inflammatory role. Myokine, the IL6 from muscle, can increase during physical exercise. It wields metabolic effects on liver and adipose tissues (activating glycogenolysis and lipolysis) and inhibits the production of TNFα (PEDERSEN et al., 2003; PRESTES et al., 2006)**.** On the other hand, IL6 is also secreted by macrophages and lymphocytes in response to injury or infection [46] and has been associated with several pathological conditions as a marker of low-grade inflammation (PEDERSEN, 2010; FISMAN & TENENBAUM, 2010). Thus, the maintenance of IL6 levels during a 1-year intervention could be considered a positive outcome.

It is currently well accepted that regular physical exercise is an effective therapeutic intervention to reduce the risk of developing insulin resistance by improving glucose tolerance and insulin action in individuals predisposed to developing type 2 diabetes (HAWLEY, 2004). It has been hypothesized that insulin resistance increases with age due to increased adiposity, decreased lean muscle mass, changes in dietary habits, and reduced physical activity (SCHEEN, 2005). Although there was not a statistically significant change in insulin in the present study (Table 2), insulin levels decreased by 38.4% after 1 year of the intervention, suggesting that insulin sensitivity may have improved, although an insulin sensitivity test in participants would be needed to confirm this.

In the present study, leptin levels were maintained until 6 months and then increased significantly after 1 year of the intervention (Table 2 and Figure 2). Despite these changes, leptin levels remained in the normal range (2.5–21.8 ng/mL). According to Mota and Zanesco [50], the relationship between physical activity and plasma leptin is unclear, with some studies showing a reduction in their levels while others fail to find any change. Recently, Akbarpour (2013) demonstrated that 12 weeks of physical exercise was able to reduce leptin levels, BMI, and IL6, and in contrast to our findings they did not find any changes in TNFα.

Plasma levels of leptin can increase as the result of obesity (TIRYAKI-SONMEZ et al., 2013); in the present study we saw no changes in body weight, BMI, or WHR after 1 year. In addition, TNFα and CRP have been shown to be related to high levels in adipose tissue, and its level in the circulation indicates the production of these biomarkers in adipose tissue (TIRYAKI-SONMEZ et al., 2013) . In the present study, although no decrease in BMI and weight was observed, the levels of TNFα and CRP were decreased, supporting the effect of exercise on these biomarkers independent of weight loss. Current evidence supports that exercise training reduces chronic inflammation and this effect is independent of the exercise induced weight loss (YOU et al., 2004).

The mechanisms related to physical exercise as a therapy in changing inflammatory biomarkers are not clear, despite studies showing positive outcomes. The discrepancy between the results from various studies in the literature can be attributed to the differences among the groups studied, training period, volume, intensity, duration, and type of training.

This study has a number of limitations that should be considered. The small sample size that resulted in the study has low statistical power and was a result of the difficulty in maintaining a 75% participation rate in the intervention sessions over the 1-year intervention period. We attempted to reduce dropout by assigning participants to an intervention groups geographically near their home. In addition, this study employed a quasi experimental design, and thus we are not able to state with confidence that the changes in inflammatory markers are due to participation in the SARC intervention. We attempted to include a control group (doing no physical exercise over 1 year) to allow us to conduct a controlled trial, but the university ethics committee would not approve this study design.

Considering the fact that 46.1% of participants already had at least 1 disease related with the inflammation process, this study illustrates that a public health exercise intervention delivered in low-income communities has the potential to exert a beneficial effect and improve or maintain inflammatory biomarkers profiles, assisting in the prevention of chronic diseases. However, a larger randomized controlled trial needs to be conducted to confirm or refute these suggestive findings.

Conclusion

The major finding of the present study was that a public health exercise intervention was effective in decreasing CRP and TNFα levels and maintaining IL10, IL6, and insulin levels over 1 year. Developing and delivering a community-based, public health exercise intervention like SARC could be a viable initiative to promote health at the public health level.

4. CHAPTER 4: Effects of six-month community-based physical exercise intervention carried out in Primary Health Care on plasma inflammatory biomarkers and metabolic profile in obese women.

This Chapter contains the paper "Effects of six-month community-based physical exercise intervention carried out in Primary Health Care on plasma inflammatory biomarkers and metabolic profile in obese women". It was originated from the analysis of Intervention 2. The final version of the paper will be approved by all authors before submission. The scientific journal is to be chosen by the authors.

Introduction

A range of studies has demonstrated that physical exercise induces considerable physiological changes in the immune system. The mechanism underlying this effect are multifactorial and include multiple neuroendocrinological aspects and alterations in metabolic factors (PEDERSEN & HOFFMAN-GOETZ, 2000). Moderate intensity physical exercise results in adaptations in antioxidant capacity, which protects the cells against the deleterious effects of reactive oxygen species preventing cellular damage (NIESS et al. 1999; PEDERSEN & HOFFMAN-GOETZ, 2000; COOPER et al. 2002; AGUILO et al. 2003). In addition, some studies indicates that physical exercise has an anti-inflammatory effect and is associated with the improvement of levels of biomarkers of inflammation (DAS, 2004; PETERSEN & PEDERSEN, 2005; STEWART et al., 2007; TIMMERMAN et al., 2008; AKPARPOUR, 2013; HUANG et al., 2013; SOARES & DE SOUSA, 2013).

The inflammatory process related to chronic diseases is characterized by a dysregulation between pro- and anti-inflammatory cytokines, and is associated with several complications such as insulin resistance, endothelial dysfunction, atherosclerosis, and metabolic and cardiovascular disorders that represent an initial landmark in atherogenesis (CHAPMAN, 2004; VOLP et al., 2008; LEE et al., 2012). Studies in the literature have confirmed that chronic diseases are associated with an inflammatory process, and that this inflammatory process can predict the development of these diseases (SAITO et al., 2000; PEARSON et al., 2003; KON et al., 2005).

Thus, studies have been conducted in order to understand this relationship and to establish potential targets for treatment and prevention of chronic diseases and low-grade inflammation. A lifestyle characterized by lack of exercise and a poor diet is the most likely factor related to this complication and may contribute directly to the development of low-grade inflammation. Physical exercise plays an important role in the prevention and treatment of chronic diseases such as cardiovascular and type 2 diabetes (PEDERSEN, 2006). It has been suggested that skeletal muscle acts as an endocrine organ by influencing metabolism and modifying immune system message production in other tissues including endothelial and adipose tissues (BRUUNSGAARD, 2005). However, the relationship between physical exercise and its anti-inflammatory influence is still somewhat controversial.

The pandemic of physical inactivity must be a priority in public health, as it is the fourth leading cause of death worldwide and causes 6–10% of the major non-communicable diseases (KOHL et al., 2012; LEE et al. 2012). In order to reverse this problem it is necessary to induce social, economic, and environmental changes that promote public policies related to ensuring a physical active lifestyle. Physical exercise interventions in primary health care settings can be a good strategy, as they offer access to programs for low-income and low-education populations in developing countries. The evaluation of these interventions is a fundamental tool to motivate the agents and political forces to support and carry out community-based programs.

Considering that physical exercise is viewed as an effective non-pharmacological strategy for the prevention and management of chronic diseases, and its possible effect on the improvement of inflammatory processes and one's metabolic profile, the present study aimed to analyze changes in these variables in obese women following a six-month community-based physical exercise intervention carried out in Primary Health Care.

Methods

Participants

This six-month quasi-experimental study was developed in two Primary Health Care Units in Rio Claro City, Brazil. Adult females were recruited by flyers and newspaper advertisements. Participants were assigned to the intervention group based upon proximity from their residence. Forty-six participants were recruited at the beginning of intervention. As a result of either voluntary dropout or failure to meet the inclusion criterion for the study (frequency of 75% attendance in the sessions in 1 year), 25 participants remained in the intervention after 6 months with only 19 participants completing all evaluations. Only participants with obesity were included in analyses; thus the final sample was 13 women, with a mean age = 57.0 ± 8.3 years and mean Body Mass Index (BMI) = 34.5 ± 4.4 kg/m^2. Nine women reported having hypertension and 2 reported having type 2 diabetes. The study was approved by the Human Research Ethics Committee of Biosciences Institute, UNESP, protocol number: 2308.

Physical Exercise Intervention

The community based exercise intervention used in this study was comprised of three, 90 minute sessions/week of physical exercises. The intervention was designed to meet current recommendations for physical activity (PATE et al., 1995). The sessions were divided into warm-up activities (10 minutes), moderate intensity aerobic exercise (50 minutes), strength-training exercises (20 minutes), and cool-down activities (10 minutes).

The warm-up and cool-down activities included static stretching exercises and articular movements. Static stretching was maintained for a minimum period of 15 to 30 seconds, twice for each muscle group. The participants were advised to sustain a muscle stretch that did not cause pain. The strength-training exercises were performed using free weights, exercise mats, and latex exercise bands. Exercises included all major muscle groups and were performed in 3 sets of 30 seconds, followed by one minute of recovery.

The aerobic exercises consisted of walking at moderate intensity (60–70% of peak heart rate). The target zone for exercise was calculated using the equation HR peak = 206 − (0.88 × age), as suggested by Gulati et al. (2010). All participants were encouraged to maintain a subjective effort of a rating of perceived exertion between13 and 15 on the 20-point Borg scale (BORG, 1982) during walking. Four participants were randomly selected to measure the intensity of their activity twice a month using a cardiac rate monitor (Polar- FS1) and the subjective effort scale.

Blood Analysis

A 10 mL venous blood sample was collected at baseline (BL) and at six months (6M) of the intervention, in the morning after 12 hours of fasting. The blood sample was transported under refrigeration to the laboratory within 30 minutes, centrifuged for 10 minutes with the serum immediately separated following centrifugation. The blood variables (biomarkers of inflammation, glucose and lipid profile) were analyzed in duplicate using commercial kits. Glucose, triglycerides, total cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and C-reactive protein (CRP) were analyzed using colorimetric-enzymatic method. Interleukin 10 (IL10), Interleukin 6 (IL6), Tumor Necrosis Factor alpha (TNFα), leptin and insulin were analyzed using Luminex technology assay (Luminex). Intra assay coefficients were all <10%. To minimize analytical variations, the same technician tested all samples without changing reagent lots, standards, or control materials. The ratio of IL10 to TNFα (= IL10/TNFα) and the Homeostasis model assessment-Insulin Resistance (HOMA-IR= fasting glucose x 0.0555 x fasting insulin / 22.5) were also calculated.

Statistical Analyses

Descriptive data were reported as means and standard deviations. The paired Student´s t-Test was used to compare the changes in anthropometric measures, inflammatory biomarkers, glucose and lipid profiles and hormones levels over time (BL and 6M). Statistical analyses were conducted using SPSS 17.0, with the alpha level set at $p < 0.05$.

Results

The BL and 6M post intervention characteristics are shown in Table 1. There were no significant differences over time in weight (p= 0.241), BMI (p= 0.753) and waist to hip ratio (WHR, p= 0.348). After six-month of the physical exercise intervention, the women remained in the Obese class I category (BMI= 34.07 kg/m^2) with a WHR indicative of increased cardiovascular risk (WHR= 0.93).

Table 4.1: Anthropometric characteristics, biochemical parameters, biomarkers of inflammation and hormone levels (mean, standard deviation) of participants at baseline and after six months of a physical exercise intervention.

Variables	Baseline	6 month	Paired Student´s t-Test- p value
Anthropometric parameters			
Weight	82.18 ±12.55	81.76 ±12.82	0.241
BMI (kg/m^2)	34.15 ±4.37	34.07 ±1.27	0.753
WHR	0.95 ±0.05	0.93 ±0.06	0.348
Metabolic profiles			
Fasting glucose (mg/dl)	106.74 ±34.84	90.61 ±29.18	0.036*
Triglycerides (mg/dl)	120.34 ±54.45	134.84 ±37.13	0.319
Cholesterol (mg/dl)	179.70 ±31.62	159.00 ±53.94	0.137
LDL (mg/dl)	135.08 ±31.30	99.61 ±44.85	0.046*
HDL (mg/dl)	52.13 ±15.21	68.84 ±37.42	0.138
HOMA-IR (mUI/ml)	3.40 ±1.40	2.48 ±1.08	0.021*
Inflammatory Biomarkers			
CRP (mg/l)	3.90 ±1.94	3.30 ±1.62	0.290
IL10 (pg/ml)	5.80 ±4.87	7.24 ±5.04	0.403
IL6 (pg/ml)	3.73 ±2.60	4.00 ±4.51	0.850
TNFα (pg/ml)	4.06 ±3.00	3.71 ±2.44	0.778
IL10/TNFα	9.12 ±17.47	13.61 ±26.58	0.648
Hormones			
Leptin (ng/ml)	3.55 ±2.04	3.12 ±1.81	0.616
Insulin (ng/ml)	0.51±0.13	0.44 ±0.09	0.111

Legend: BMI= Body Mass Index; WHR= Waist and Hip Ratio; LDL= Low Density Lipoprotein; HDL= High Density Lipoprotein; HOMA-IR= Homeostasis model assessment-Insulin Resistance; CRP= C-reactive Protein; IL10= Interleukin 10; IL6= Interleukin 6; TNFα= Tumor Necrosis Factor alpha; IL10/TNFα= ratio of IL10 to TNFα.

No changes in triglycerides ($p= 0.319$), total cholesterol ($p= 0.137$) or HDL ($p= 0.138$) were seen over time. Fasting glucose (BL= 106.74 ±34.84 and 6M= 90.61 ±29.18 mg/dl; $t(12)=2.366$, $p= 0.036$), LDL levels (BL= 135.08 ±31.30 and 6M= 99.61 ±44.85 mg/dl; $t(12)=2.224$, $p= 0.046$) and HOMA-IR (BL= 3.40 ±1.40 and 6M= 2.48 ±1.08; $t(12)=2.661$, $p=0.021$) decreased significantly after six months of the physical exercise intervention.

The physical exercise intervention did not induce significant changes in inflammatory biomarkers CRP ($p=0.290$); IL10 ($p= 0.403$); IL6 ($p= 0.850$); TNFα ($p= 0.778$), or the IL10/TNFα ratio ($p= 0.648$). Leptin ($p= 0.616$) and insulin ($p= 0.111$) also did not change following the intervention.

Discussion

The physical exercise intervention implemented in this study did not induce significant changes in triglycerides, total cholesterol or HDL following six-months of intervention. It is important to note that these levels were in the normal range at baseline and remained so following the intervention. LDL levels decreased significantly at six-months. At baseline the LDL levels (BL= 135mg/dl) were above recommended level (< 100mg/dl), and following the six-month physical exercise intervention mean LDL decreased to within the normal range (99mg/dl). High levels of LDL are associated with increased risk for coronary artery disease (GORDON et al., 1997). According to Kraus et al (2002), regular exercise with minimal weight change has broad beneficial effects on the lipoprotein profile, with the amount of exercise suggested to be more important than the intensity.

Kannan et al. (2014) reported improvements in total cholesterol, HDL and LDL levels in obese adults engaging in either moderate or high intensity exercise for 15 weeks. In the Kannan et al. (2014) study, the moderate intensity group performed 40 minutes/day of exercise for 5 days/week and the high intensity group performed 20 minutes/day of exercise for 3 days/week. In our study, the exercise volume was lower than that of Kannan et al. (2014) and this could explain the differences between the outcomes. Considering that in the present study triglycerides, total cholesterol and HDL remained in the normal range after six month and that the high level of LDL decreased to within the normal range, the physical exercise intervention appeared to have some positive impact on the blood metabolic profile in these obese women.

No significant changes were observed in inflammatory biomarkers (CRP, IL10, IL6 and TNFα) following six-months of the intervention. Some studies have reported that biomarkers of inflammation are associated with physical exercise, suggesting that an active lifestyle can modulate cardiovascular health via anti-inflammatory effects (PISCHON, et al., 2003; BERLIN et al., 1990; DURSTINE & HASKELL, 1994; FORD, 2002; WANNAMETHEE et al., 2002; KADOGLOU et al., 2007). Kadoglou et al. (2007) found that a six-month aerobic exercise intervention (four times/week, 45-60 min/session) improved glucose control, the lipid profile, CRP and IL10 in overweight patients with type 2 diabetes. However, others studies corroborate our results indicating no effect of physical exercise on biomarkers of inflammation (MARCELL et al., 2005; ALBERT et al., 2004; ZOPPINI et al., 2006).

Research suggests that the cytokines CRP and TNFα are more sensitive to change as a result of engaging in regular physical exercise (YOU et al., 2013). Nonetheless, in the present study CRP and TNFα did not change after 6 months of physical exercise intervention. Some studies have indicated that regular physical activity is associated with either a reduction or no change in CRP and TNFα (ELOUSA et al., 2005; KADOGLOU et al., 2007; COLBERT et al, 2004; BALDUCCI et al., 2010). Zoppini et al (2006) reported results similar to the finding of the present study, in that the aerobic exercise (performed twice per week) was not effective in inducing changes in CRP and TNFα following six-months of exercise in overweight, older patients with type 2 diabetes (ZOPPINI et al., 2006).

Our group has previously demonstrated that a physical exercise program developed in primary health care was effective in reduce CRP and TNFα levels after 1 year of intervention in overweight women, but no change were observed after 6 months (PAPINI et al., 2014). In that study, the decrease in CRP after one year was clinically relevant because the value changed from a level considered "high risk" for cardiovascular disease at baseline to an "average risk" after 1 year of intervention (PAPINI et al., 2014). Maybe for this type of intervention with overweight and obesity woman, the adaptations in CRP and TNFα may take a longer period of time to manifest. More studies are needed to confirm these findings.

No significant changes in IL10 and IL6 were found over time. According to the literature, changes in IL10 is dependent on a higher volume of physical activity, especially aerobic exercise (KADOGLOU et al., 2007; JANKORD & JEMIOLO, 2004). In the study of Kadoglou et al. (2007), 180-240 minutes of aerobic exercise per week was effective in increasing IL10 levels after 6 months. In our previous study, 60 minutes of aerobic exercise per week did not change IL10 and IL6 after 6 months or after 1 year of intervention (PAPINI et al., 2014). In the present study, 150 minutes of aerobic exercise combined with 60 minutes of strength exercise per week was also not effective in changing IL10 and IL6 after 6 months. The IL10/TNFα ratio also did not change significantly as a result of the intervention.

Our results demonstrate that six-month of combined aerobic and strength exercise did not reduce weight, BMI and WHR. This result is not surprising, we did not control the dietary intake of participants and the study was not designed to reduce energy intake. Studies indicate that exercise alone is not particularly effective in decreasing body weight (add in a few references here to support this statement). Interestingly, current evidence indicates that exercise training can reduce chronic inflammation independent of exercise-induced weight loss (YOU et al., 2013).

Exercise training has been shown to modulate the secretion of leptin; however, the reduction in body weight arising from the exercise seems to be responsible for this adaptation more than the effect of the exercise per se (SARTORIO et al., 2003). In the current study, the leptin levels did not change after six-month of intervention, and remained in the normal range (2.5–21.8 ng/ml). Hickey et al (1997) reported that obese woman that trained for 9 months (four times/week) also did not reduce adiposity or leptin levels independently of an increase in physical fitness (HICKEY et al., 1997). It may be that improvements in leptin and the lipid profile are more significant when exercise is combined with weight loss. However, even without controlling the diet, the maintenance of profile levels that were within a normal range and the improvement of LDL levels in obese women after six-month of physical exercise is a good outcome.

Analyses indicated that insulin levels were maintained after 6 month. However, HOMA-IR and plasma glucose levels were significantly decreased after six-months of intervention, with HOMA-IR decreasing from 3.40mUI/ml to 2.48mUI/ml. Geloneze et al. (2006; 2009) investigated the cut-off values for HOMA-IR to identify insulin resistance in 1,203 healthy and non-healthy Brazilians and established a HOMA-IR value >2.7 as the optimal cut-off. Thus, the women participants in our study reduced HOMA-IR below this cut point for insulin resistance. The improvement of insulin sensitivity was associated with a reduction in fasting blood glucose (from 106mg/dl to 90mg/dl). Our results confirm that regular physical exercise is an effective therapeutic intervention to ameliorate and reduce the risk of developing insulin resistance by improving glucose tolerance and insulin action in individuals predisposed to developing type 2 diabetes (HAWLEY, 2004).

The physical exercise intervention in our study incorporated the recommendation of 150 minutes/week of moderate aerobic exercise combined with 60 minutes/week of strength-training exercises (GARBER et al., 2011). The improvements observed in LDL, glucose and HOMA-IR and the maintenance of anthropometric variables, lipid profile, biomarkers of inflammation and leptin and insulin levels after six-months are a good outcome, considering that the participants are obese and the most of them reported having hypertension and/or type 2 diabetes. The discrepancy between the results from various studies in the literature can be attributed to the differences among the groups studied, training period, volume, intensity, duration, and type of training. Thus, the amount of exercise training required for optimal benefit is unknown.

Beavers and Nicklas (2011) found strong evidence for the role of lifestyle interventions (diet and/or exercise) on the improvement of inflammatory biomarkers and metabolic profiles. Soares and de Souza suggest that integrative interventions, including diet, moderate aerobic exercise and circuit resistance training, health education, and counseling, used together, appeared to be an effective strategy to improve inflammatory biomarkers in women.

This study has a number of limitations. The small sample size resulted in low statistical power, and was a result of the difficulty in maintaining a 75% participation rate in the intervention sessions over the 6-month intervention period. We attempted to reduce dropout by assigning participants to an intervention group geographically near their home. We attempted to include a control group (doing no physical exercise over 1 year) to allow us to conduct a controlled trial, but the university ethics committee would not approve this study design. In addition, this study employed a quasi-experimental design in a specific place and population, and thus we are not able to state with total confidence that this intervention per se was what resulted in the positive changes observed, or that the outcomes observed are generalizable to other populations. However, we feel it is essential that physical exercise interventions are adapted to the specific context of the place and population in order to meet the needs and public health strategies of the local community.

Conclusion

We conclude that a public health exercise intervention was effective in maintaining biomarkers of inflammation, leptin and insulin levels and lipid plasma profile in obese women. The intervention reduced the LDL and glucose levels and improved insulin resistance. Developing and delivering this community-based, public health exercise intervention to a much larger sample of participants could be a relevant initiative to promote health on low-income communities.

5. CHAPTER 5: Changes in cardiorespiratory fitness variables in woman after 1 year of physical exercise program carried out in Health Units.

This Chapter contains the paper "*Changes in cardiorespiratory fitness variables in woman after 1 year of physical exercise program carried out in Health Units*". It was originated from the analysis of cardiorespiratory fitness data of Intervention 2. The final version of the paper will be approved by all authors before submission. The scientific journal is to be chosen by the authors.

Introduction

The physical fitness components are important determinants of health. In addition to strength, flexibility and body composition, the cardiorespiratory fitness is a component that constitutes the health-related physical fitness. The cardiorespiratory fitness is defined as the capacity of cardiovascular and respiratory systems to provide oxygen during a continuous physical activity (CASPERSEN et al., 1985). The oxygen consumption (VO_2) is considered the most important parameter to identify the functional capacity of cardiorespiratory system and it is used as an important predictor to cardiovascular diseases. The VO_2 is defined as the capacity of respiratory, cardiovascular and muscle systems to capture, transport and utilize oxygen for oxidative biosynthesis of energy (ATP - adenosine triphosphate (FLETCHER et al., 1990; ADEKUNLE; AKINTOMIDE, 2012).

The cardiorespiratory fitness have a genetic component and it is significantly related to gender, age group and clinic condition of cardiovascular system. However, it can be influenced by external factors as such as physical activity and fitness training levels (FLETCHER et al., 1990; BLAIR et al., 2001). Structured physical exercise interventions cause significant and beneficial changes in cardiorespiratory fitness (DUN et al., 1999).

Aerobic exercises that involve the large muscle groups are recommended to improve the cardiorespiratory fitness (ACSM, 2010). The regular practice of aerobic exercises promotes physiological adaptations that result in the improvement of cardiovascular and respiratory systems. Some of the physiological adaptations are the increase of maximal oxygen uptake and exercise tolerance, the improvement in submaximal intensities (lactate threshold analyses), the decrease of minute ventilation, cardiac frequency and blood pressure for pre-established absolute submaximal exercise intensity (ACSM, 2010).

The recommendation is that adults should perform at least 150 minutes of moderate intensity aerobic activities weekly. Preferably, they should meet the specification of 30 to 60 minutes of moderate intensity activities per day, 5 days a week or 20 to 60 minutes of vigorous intensity activities per day, 3 days a week (PATE et al., 1995; HASKELL et al., 2007). Lager amount of physical activity, e.g. participation in a physical exercise program that has longer duration and is more vigorously performed, results in additional health benefits (ACSM, 2010). However, the number of individuals who meet the physical activity recommendation is insufficient (HALLAL et al., 2012).

According to Blair et al. (2001), there is an inverse relation between cardiorespiratory fitness levels and mortality by coronary disease, cerebral vascular accident or all mortality causes. The low levels of cardiorespiratory fitness is also an important predictor for metabolic syndrome (LAMONT et al., 2005). The potential benefits of increased cardiorespiratory fitness should be considered for primary prevention of numerous diseases related to metabolic syndrome. Some potential benefits are a decrease of factors related to cardio-metabolic diseases, such as the improvement of glucose tolerance, insulin resistance, dyslipidemias, inflammatory biomarkers and the decrease of body mass and LDL levels (GARBER, et al., 2011). Thus, the importance of maintaining or improving the cardiorespiratory fitness levels in life course is evident.

Considering both the high prevalence of physical inactivity and the relation between cardiorespiratory fitness and health, it is necessary to elaborate, implement and evaluate physical exercises programs focused on adults, elderly and children.

The development of physical exercise programs in Primary Health Care can be considered a good strategy to increase the physical activity levels and quality of life in the population. More specifically, in the Brazilian context, this kind of programs can reach individuals with low socioeconomic and schooling level once the Health Units are located in areas of great vulnerability. Thus, the present study aims to evaluate the effect of 1 year of physical exercise program carried out in Health Units concerning the variables related to cardiorespiratory fitness in woman.

Methods

Participants

This 1 year quasi-experimental study was developed in two Primary Health Care Units in Rio Claro City, Brazil. Adult females were recruited by flyers and newspaper advertisements. Participants were assigned to the intervention group based upon proximity from their residence. Forty-six participants were recruited at the beginning of intervention (50.45 ± 10.92 years old). As a result of either voluntary dropout or failure to meet the inclusion criterion for the study (frequency of 75% attendance in the sessions), 20 participants remained in the intervention after 1year of intervention (56.35 ± 9.25 years old). The study was approved by the Human Research Ethics Committee of Biosciences Institute, UNESP, protocol number: 2308.

Intervention

The community based exercise intervention used in this study was comprised of three, 90 minute sessions/week of physical exercises. The intervention was designed to meet current recommendations for physical activity (PATE et al., 1995). The sessions were divided into warm-up activities (10 minutes), moderate intensity aerobic exercise (50 minutes), strength-training exercises (20 minutes), and cool-down activities (10 minutes). Thus, the participants performed 150 minutes of aerobic exercises, 60 minutes of strength exercises and 30 minutes of stretching exercises weekly.

The warm-up and cool-down activities included static stretching exercises and articular movements. Static stretching was maintained for a minimum period of 15 to 30 seconds, twice for each muscle group. The participants were advised to sustain a muscle stretch that did not cause pain. The strength-training exercises were performed using free weights, exercise mats, and latex exercise bands. Exercises included all major muscle groups and were performed in 3 sets of 30 seconds, followed by one minute of recovery.

The aerobic exercises consisted of walking at moderate intensity (60–70% of peak heart rate). The target zone for exercise was calculated using the equation HR peak = 206 − (0.88 × age), as suggested by Gulati et al. (2010). All participants were encouraged to maintain a subjective effort of a rating of perceived exertion between13 and 15 on the 20-point Borg scale (BORG, 1982) during walking. Four participants were randomly selected to measure the intensity of their activity twice a month using a cardiac rate monitor (Polar- FS1) and the subjective effort scale.

Cardiorespiratory Fitness Test

The cardiorespiratory fitness was measured via submaximal incremental treadmill test (ATL3®, Inbrasport, Brasil) through indirect calorimetry using a gas analyzer (VO2000, Medgraphics, St. Paul, Minnesota, USA) and a medium flow pneumotachograph (6 – 120 L/min). The ergoespirometric test data was collected in each 3 breathings by Aerograph Software. The participants answered the Readiness Activity PAR-Q questionnaire before the test and performed an adaptation on the treadmill; the use of neoprene masks and the use of the perception of exertion scale (BORG, 1982). The participants performed the test at baseline (BL) and after 1 year (1Y) of intervention.

The test initiated in 4km/h with no incline. In the second stage, the speed was increased to 5.6 km/h with no incline. In the next stages, the speed was maintained and the incline was increased 2.5% in each stage. Each stage lasted 3 minutes.

The Maximum Heart Rate (HRmax) was calculated according to the Karvonen et al., (1975) equation: HRmax = 220 - age. The heart rate was monitored during test (Polar® model FS1, Polar Electro Oy, Finland). The scale BORG was also used – every minute – to monitor the subjective effort perception.

The test was interrupted when participants reached 85% of HRmax previously estimated by equation (HR85%= (HRmax x 85)/100); or when participants reached the BORG 15 (in case of participants medicated with beta-blocker); or by voluntary exhaustion (before reaching the 85% of HRmax). The final VO_2, BORG and HR reached in the test were used to verify if the test interruption was the same in pre and post evaluation.

The variables used to verify the changes in cardiorespiratory fitness were: final time/stage and energy cost for each stage. The energy cost for stage was calculated through Delta (absolute difference of VO_2 ($ml.kg.min^{-1}$) between pre and post tests, using the equation: D= VO2 pre – VO2 post) and after the corresponding difference was calculated in percentage (%).

Statistical Analyses

The data normality was verified through Shapiro-Wilk test. Descriptive data were reported as means and standard deviations. The paired Student´s t-Test was used to compare the changes in final VO_2 and final HR. The paired Wilcoxon test was used to compare the final BORG, stage and time reached in the tests. Statistical analyses were conducted using SPSS 17.0, with the alpha level set at $p < 0.05$.

The VO_2 Delta values (energy cost) in BL and 1Y were compared through a descriptive analysis. The stages from 5 to 7 were not analyzed due to the small number of participants who reached these stages.

Results

The statistical analyses showed no differences ($p > 0.05$) between BL and 1Y for final HR, VO_2 and BORG, as presented in table 5.1. Significant differences were indicated between tests for final time (BL= 6.36 ± 3.2 and 1Y= 10.80 ± 5.0 minutes; p= 0.004), final stage (BL= 2.2 ± 1.2 e 1Y= 3.6 ±1.7, p= 0.004) reached in the ergoespirometric test (table 5.1).

Table 5.1: Comparison between ergoespirometric variables related to cardiorespiratory fitness at baseline and after 1 year of intervention.

	Baseline	**1 year**	**p value**
HR_{final} - bpm	140.45 ±14.88	140.68 ±15.89	0.869
VO_{2final} - $ml.kg.min^{-1}$	19.28 ±3.37	19.30 ±3.45	0.972
$BORG_{final}$	14.5 ±2.17	15.35 ±1.38	0.115
Final Time - minutes	6.36 ±3.45	10.80 ±5.00	0.004*
Final stage	2.2 ± 1.2	3.6 ±1.7	0.004*

Legend: HR_{final}= final heart rate; bpm= beats per minute; VO_{2final}= final oxygen uptake; $BORG_{final}$= subjective effort scale reached in the end of test.

The figure 5.1 illustrates the final time and stage reached in the end of the test at baseline and after 1 year of intervention. The statistical analysis indicated significant changes for both variables (table 5.1).

The table 5.2 shows the Delta value (absolute changes) and the percentage changes (%) for energy cost, and the number of participants that completed each stage in baseline and after 1 year of intervention. Few participants could complete more than three or four stages at baseline; however, most participants completed the three stages and some of them completed from four to seven stages.

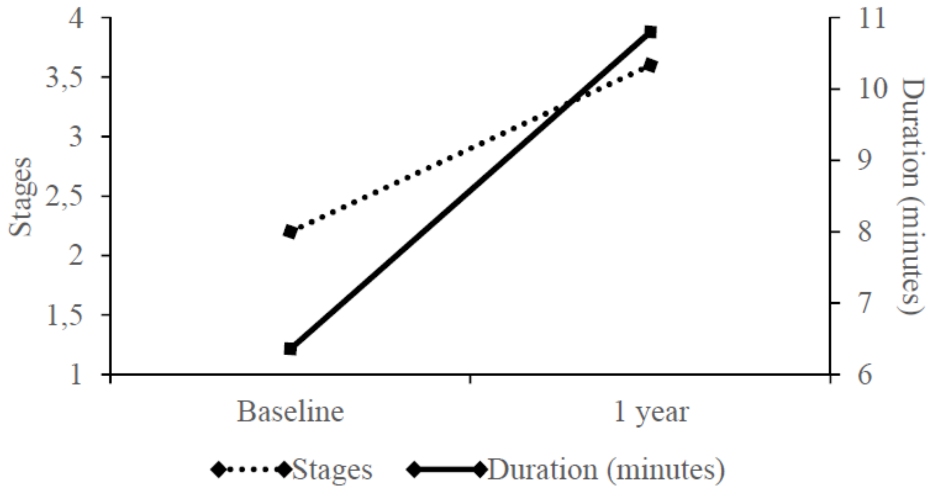

Figure 5.1: Final time and stage reached in ergoespirometric test at baseline (BL and after 1 year (1Y) of intervention.

Table 5.2: Energy cost (VO_2 – ml.kg.min^{-1}), Delta (absolute changes) and percentage changes (%) for each stage at baseline and after 1 year of intervention.

	Baseline	N	1 year	N	Delta	%
Stage 1	14.56 ±2.77	20	11.63 ±3.10	20	-2.93	20.1
Stage 2	18.41 ±3.13	16	16.03 ±3.62	20	-2.38	12.9
Stage 3	20.61 ±2.23	8	16.83 ±3.73	13	-3.78	18.3
Stage 4	22.01 ±2.16	3	17.69 ±3.83	9	-4.32	19.6
Stage 5	22.99	1	17.55 ±2.51	7	-	-
Stage 6	-	0	21.27 ± 1.98	3	-	-
Stage 7	-	0	22.91	1	-	-

It is possible to note in table 5.2 that the negative Delta in each stage indicates that a decrease of VO_2 after 1 year of intervention occurred (also illustrated in figure 5.2). The decrease in Delta value ranged around 12-21% as shown in table 5.2.

In figure 5.2, the VO_2 from stage 1 to stage 4 and the final VO_2 (gray line) are illustrated. It is possible to see considerable decrease in the VO_2 reached in the four first stages after 1 year of intervention when compared to the same stages at baseline.

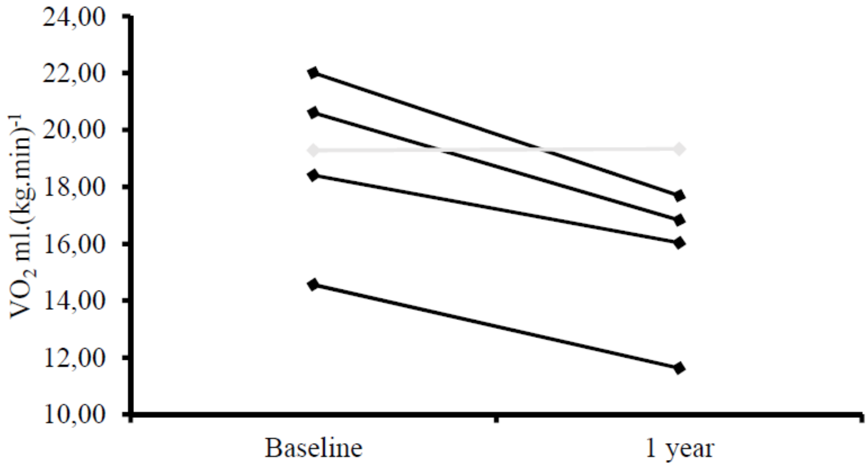

Figure 5.2: VO_2 values in stage 1 to 4 and VO_2 reached in the test at baseline and after 1 year of intervention.

Legend: The black lines represent the VO_2 in stages 1 to 4 (the following stages were not compared due the small number of participants); the gray line represents the final VO_2 reached (average of participants) in each test.

Discussion

The results indicate that the intervention carried out in primary health care was effective to improve the variables related to cardiorespiratory fitness.

The similar values for final VO_2, HR and BORG in baseline and after 1 year indicates that both tests were performed until the same criteria interruption (85% of HRmax e BORG 15). The significant difference for final time and stage between tests indicates that participants developed a greater exercise tolerance.

Belli et al. (2011) evaluated 9 sedentary participants (53.4 ±2.3 years old) that performed 12 months of intervention consisting in walking 3 times a week, from 20 to 60 minutes. The results corroborate our study once an increase of the final speed and final time reached in the incremental test was observed. Additionally, the VO_2pico had a significant increase after 12 months of intervention. Although, the VO_2max was not evaluated in our study, the increase in final time and stage between tests can suggest a possible increase in it.

Moreover, the increase in participant´s exercise tolerance was confirmed by the low energetic cost presented in each stage at baseline and after 1 year of intervention. It was also observed that at baseline, few participants completed more than 3 or 4 stages, while most participants completed the 3 stages and others completed from 4 to 7 stages after 1 year. These results indicate an improvement in functional capacity in walking and greater endurance.

Nakamura et al. (2014) evaluated the effect of a 10-year physical exercise program carried out in primary health care in 409 females (50.0 ± 26 years old) and 64 males (64.0 ±10 years old). The authors concluded that the cardiorespiratory fitness was improved once participants significantly decreased the time to perform the walking test over 10 years.

The walking energy cost has an association with functional capacity in elderly individuals. Being functionality independent within the community and having quality of life are 2 commons objectives among adults with advanced age. However, some physiological alterations which occur with aging can make it difficult to achieve these objectives. Additionally, the relative decline of functional capacity with aging decreases the total energy available to perform the daily physical activities among elderly individuals (WERT et al., 2013). Therefore, it is evident the importance of improving or maintaining the cardiorespiratory fitness levels in life course.

The intervention offered in our study incorporated the physical activity recommendation (150 minutes of moderate aerobic exercise combined to 60 minutes of resistance muscle exercises weekly) (PATE et al., 1995). It can have influenced physiological adaptations in participants resulting in an improvement of cardiovascular and respiratory functions and consequently an increase in exercise tolerance.

The cardiorespiratory fitness presents a progressive increase with the course of chronological age and from the third decade of life, the cardiovascular and respiratory systems suffer a decrease with age, about 10% every decade, if not trained (GOBBI et al., 2005). According to Hagberg (1987), elderly people who maintain great levels of physical activity can minimize the natural cardiorespiratory fitness decline. Physically active elderly have their cardiorespiratory fitness decreased at a rate of 5% per decade – half decline in relation to sedentary people (HAGBERG, 1987). Thus, the increase or maintenance of physical activity levels such as the participation in physical exercise programs are key points for a healthy aging.

One of the study limitations was not to perform the maximum effort test until the voluntary exhaustion to verify directly the improvement of cardiorespiratory fitness. The submaximal effort test had to be performed once the guidelines recommend that when some risk health factors are presented by individuals (e.g. hypertension and diabetes), advanced age and when there is not the presence of a doctor, the maximum effort test should not be performed (GUIMARÃES et al., 2003; ACSM, 2010; HARRIS E WHITE, 2007; MENEGHELO et al., 2010; GHORAYEB et al., 2013).

Some studies in the literature show that physical exercise programs carried out in primary health care are effective to increase the VO_2max in mature adults and in elderly individuals (PETRELLA et al., 2003; MONTEIRO et al., 2007).

Petrella et al. (2003) evaluated 131 healthy participants (> 65 years old) of an intervention carried out in primary health care (counselling and exercise prescription) during 1 year. The results indicated that VO_2max increased significantly in 11% after 6 months and 12% after 1 year of intervention. Monteiro et al. (2007) investigated the effect of a physical exercise program carried out in primary health care in 16 participants (56 ±3 years old) during 4 months. The program was effective to improve the VO2max in 42%.

The test protocol choice with incremental incline was made considering the physical conditions of the participants. Some of them did not have mobility to walk very quickly and/or run on the treadmill. Although the VO_2max of participants was not assessed during test, the variables studied showed that there was a decrease in energy cost and a increase in exercise tolerance. Being able to walk at 5.6km/h with some incline is a very good improvement for their life. Elderly people do not need to reach advanced stages in the treadmill test considering the amount of effort needed to perform their daily activities.

It is important to discuss other limitations of the study. The small sample of participants after 1 year of intervention is due to the difficulty to maintain 75% of attendance in sessions. Although the participants who did not meet 75% of attendance were excluded from statistical analyses, they were not excluded from the program. The non-randomization of Health Units and participants was a strategy to avoid the voluntary dropout. The choice of the 2 Health Units was made because in these place no physical exercise program was being offered; and the participants were allocated in the Health Unit near their residence to facilitate the participation.

Considering the relation between cardiorespiratory fitness with health and the benefits that regular aerobic physical exercise promote in participants - in physiological and functional point of view - it is necessary to design, implement and evaluate community-based physical exercise. The development of physical exercise programs in primary health care, especially in Health Units in Brazil, is a good strategy to reach more vulnerable populations, in terms of low socioeconomic status and schooling.

Conclusions

The physical exercise program carried out in primary health care was effective to promote an improvement in cardiorespiratory fitness variables. The significant increase of final time and stage indicates that participants developed a great exercise tolerance. Moreover, the decrease obtained in energy cost reflects an economy of movement during walking, in other words, less physical effort for the same intensity exercise. These improvements may possibly have a positive impact in the daily physical activities and in the quality of life of participants.

6. CHAPTER 6: Additional Analyses

Some additional analyses were performed to answer the aims proposed in this study. First, the cardiorespiratory data of intervention 1 was analyzed to verify the effect of intervention in variables related to the cardiorespiratory fitness. In this analysis we included 3 participants (n=18) who completed 1 year of intervention but did not perform the treadmill test at the end of the study (Intention-to-treat analysis). The imputation of data for these participants was made using the baseline value.

The data normality was verified through Shapiro-Wilk test. Descriptive data were reported as mean and standard deviation. The paired Student´s t-Test was used to compare the changes in final VO_2 and final HR. The paired Wilcoxon test was used to compare the final BORG, stage and time reached in the tests. Statistical analyses were conducted using SPSS 17.0, with the alpha level set at $p < 0.05$. The VO_2 Delta values (energy cost) in BL and 1Y were compared through a descriptive analysis. The stages from 5 to 7 were not analyzed due to the small number of participants who reached these stages.

The statistical analyses showed no differences ($p > 0.05$) between BL and 1Y for final HR, BORG, final time and final stage reached in the ergoespirometric test, as presented in table 6.1. Significant differences were indicated between tests for final VO_2 (BL= 20.8 ± 4.2 and 1Y= 19.1 ± 3.6 $ml.kg.min^{-1}$; p= 0.025) reached in the ergoespirometric test (table 6.1).

Table 6.1: Comparison between ergoespirometric variables related to cardiorespiratory fitness at baseline and after 1 year of intervention.

	Baseline	1 year	p value
HR_{final} - bpm	142.7 ±9.1	138.68 ±1.12	0.079
VO_{2final} - $ml.kg.min^{-1}$	20.8 ± 4.2	19.1 ± 3.6	0.025*
$BORG_{final}$	13.5 ±2.4	14.8 ±1.9	0.006
Final Time - minutes	8.50 ± 4.9	10.00 ± 5.3	0.075
Final stage	2.8 ± 1.6	3.3 ±1.8	0.075

Legend: HR_{final}= final heart rate; bpm= beats per minute; VO_{2final}= final oxygen uptake; $BORG_{final}$= subjective effort scale reached in the end of test.

The table 6.2 shows the Delta value (absolute changes) and the percentage changes (%) for energy cost, and the number of participants that completed each stage in baseline and after 1 year of intervention. Few participants could complete more stages at 1 year compared to baseline. The Delta value did not change either after 1 year of intervention 1.

Table 6.2: Energy cost (VO_2 – $ml.kg.min^{-1}$), Delta (absolute changes) and percentage changes (%) for each stage at baseline and after 1 year of intervention.

	Baseline	N	1 year	N	Delta	%
Stage 1	14.8 ±3.8	18	13.9 ±3.7	18	-0.9	6
Stage 2	17.6 ±3.2	15	16.8 ±3.7	17	-0.8	4
Stage 3	19.0 ±3.2	9	19.1 ±4.0	11	0.1	0.5
Stage 4	20.3 ±1.4	5	20.2 ±3.1	6	-0.1	0.4
Stage 5	22.5	1	21.2 ±2.7	3	-	-
Stage 6	22.7	1	22.7 ± 2.9	3	-	-
Stage 7	27.5	1	25.8± 2.3	1	-	-
Stage 8	29.8	1	25.4	1		
Stage 9	-	0	28.1	1	-	-
Stage 10	-	0	29.8	1	-	-

Comparison of cardiorespiratory fitness variables between interventions

The two-way repeated measures ANOVA was used to compare the cardiorespiratory variables between intervention 1 and 2. The Wilcoxon signed-rank test was performed in the variables with significant difference between time (Baseline x 1 year). Descriptive data were reported as mean and standard deviation. The table 6.3 shows the values of final VO_2, time and stage reached in the treadmill test at baseline and after 1 year of interventions. The values of VO_2 in stages 1, 2, 3 and 4 at baseline and after 1 year are also showed in the table 6.3

Table 6.3: Comparison between ergoespirometric variables related to cardiorespiratory fitness at baseline and after 1 year of interventions 1 and 2.

	Intervention 1 (2x/week)		**Intervention 2 (3x/week)**		**p value**	**p value**
	BL	**1Y**	**BL**	**1Y**	**Intervention**	**Time**
VO_{2final} - $ml.kg.min^{-1}$	20.79 ±4.2	21.43 ±4.3	19.23 ±3.3	19.04 ±3.4	0.090	0.623
Final Stage	2.8 ±1.6	4.3 ±2.2	2.3 ±1.3	3.5 ± 1.7	0.193	0.000*
Final Time - minutes	8.5 ±4.9	13.0 ± 6.8	6.9± 4.1	10.6 ±5.1	0.193	0.000*
VO_2 - Stage 1	14.7 ±3.8	13.9 ±3.7	14.4 ±2.6	11.6 ±3.1	0.143	0.004*
VO_2 - Stage 2	17.6 ±3.2	16.62 ±3.4	18.23 ±3.1	16.16 ±3.9	0.938	0.028*
VO_2 - Stage 3	19.80 ±2.3	19.63 ±4.0	20.26 ±2.9	16.46 ±4.0	0.267	0.162
VO_2 - Stage 4	20.35 ±1.4	21.18 ±3.1	20.87 ±2.8	19.26 ±4.8	0.649	0.810

Legend: VO_{2final}= final oxygen uptake; BL= baseline; 1Y= 1 year.

The statistical analyses showed no differences ($p > 0.05$) between interventions for all variables analyzed. Significant differences were indicated between time (BL and 1Y) for final stage ($p = 0.000$) and final time ($p = 0.000$) reached in the treadmill test. Changes in the VO_2 values in the stages 1 ($p = 0.004$) and 2 ($p = 0.028$) were also significant, as showed in table 6.3. Both intervention significantly increase the final stage (intervention 1, $p = 0.003$ and intervention 2, $p = 0.006$) and the final time (intervention 1, $p = 0.003$ and intervention 2, $p = 0.006$) reached in the test after 1 year compared to the baseline. The analysis indicated that the changes in VO2 in stage 1 and 2 were significant in intervention 2 ($p = 0.000$ for both stages) but not significant in intervention 1 (stage 1, $p = 0.248$, stage 2, $p = 0.191$).

Comparison of inflammatory biomarkers between interventions

The two-way repeated measures ANOVA was used to compare the inflammatory biomarkers between intervention 1 and 2. The Wilcoxon signed-rank test was performed in the variables with significant difference between time (Baseline x 1 year). Descriptive data were reported as mean and standard deviation.

Table 6.4: Comparison between inflammatory biomarkers at baseline, after 6 months and after 1 year of interventions 1 and 2.

	Intervention 1 (2x/week)			**Intervention 2 (3x/week)**			**p value**	**p value Time**		
	BL	**6M**	**1Y**	**BL**	**6M**	**1Y**	**Intervention**	**BL versus 6M**	**BL versus 1Y**	**6M versus 1Y**
CRP ($mg.L^{-1}$)	4.1 ±2.3	3.5 ±1.4	2.5 ±1.8	3.8 ±2.0	3.4 ±1.5	2.2 ±1.6	0.648	0.480	0.000	0.000
IL10 ($pg.mL^{-1}$)	5.1 ±2.1	3.7 ±2.3	10.2 ±17.3	7.1 ±6.0	5.6 ±3.7	5.9 ±3.0	0.928	0.297	1.000	0.297
IL6 ($pg.mL^{-1}$)	7.3 ±9.3	4.3 ±2.5	4.0 ±1.2	3.2 ±2.0	3.7 ±3.9	4.0 ±3.8	0.143	0.908	0.813	1.000
TNFα ($pg.mL^{-1}$)	11.7 ±6.2	6.9 ±4.0	5.4 ±3.1	4.5 ±3.0	3.1 ±2.4	4.5 ±2.8	0.000	0.006	0.000	1.000
Leptin (ng/mL^{-1})	2815 ±2244	2457 ±1653	10625 ±8452	3745 ±2567	3301 ±2169	11032 ±8050	0.533	0.953	0.000	0.000
Insulin (ng/mL^{-1})	1739 ±3284	733 ±389	676 ±221	485 ±132	454 ±91	531 ±128	0.043	0.551	0.600	1.000

The table 6.4 shows the values of inflammatory biomarkers at baseline, 6 months and after 1 year of interventions. The analyses indicated no differences between interventions ($p > 0.05$) for CRP, IL10, IL6 and leptin. Significant differences between interventions were found for TNFa ($p = 0.000$) and insulin levels ($p = 0.043$). In the beginning of study and also at 6 months, the levels of TNFa and insulin of participants of intervention 1 were significantly higher compared to participants of intervention 2. After 1 year of intervention no significant differences were seen between interventions.

No significant changes and differences were seen for insulin, IL10 and IL6 over time and between interventions. The statistical analyses indicated significant changes in some variables over time. The CPR and TNFa were significantly reduced after 6 months and after 1 year compared to baseline in both intervention. The leptin levels significantly increased after 1 year of both intervention compared to baseline and 6 months.

7. CHAPTER 7: General Conclusions

The results showed that both interventions improve health-related variables. The intervention 1 was able to reduce the CRP and TNFα levels after 1 year of intervention. The intervention 2 reduced the levels of LDL and glucose and improved the insulin resistance after 6 months of intervention. The comparison between interventions showed similar results for both. They were able to reduce CRP and TNFa levels after 1 year of intervention.

Both interventions promoted the improvement of cardiorespiratory fitness-related variables which reflects in a greater exercise tolerance. The intervention 2 was able to decrease the energy cost during walking. However, these benefits were not seem in intervention 1. The different results could be explained by the difference between the time intended for the walking activities. The women performed 60 minutes per week in intervention 1 and 150 minutes in intervention 2. To develop exercise tolerance and energy cost during walking the time intended to this activity should be more than 30 minutes in each session.

Some limitations of this study are the small number of participants (due to the difficulty to maintain 75% of attendance in sessions), the non-randomization of Health Units (they were chosen because any physical exercise program was being offered in these places), the non-randomization of participants (they were allocated in the Health Unit near their residence considering the regionalization principle of SUS). The study had a small number of participants, because they did not meet the inclusion criteria, however some of participants remained in the intervention up to 1 year of intervention.

The present study should be considered as a clinical study design once it aimed to test the effect of 2 interventions in variables related to health. Few clinical and longitudinal studies are developed in the real world in Brazil. The samples analyzed in the present study are the users of SUS (Public Health System) who represent 60% of the Brazilian population. The interventions carried out in this study can be used as a model to be applied in other parts of Brazil and the world.

The community-based physical exercises carried out in primary health care is a good strategy to help people change their behaviors and to improve health and quality of life. It is essential to adapt the intervention to each place context. The set of strategies to implement interventions should be thought according to local needs. The last 13 years, the

Saude Ativa Rio Claro program is offered to population and it show effective in promote several benefits in its participants, even not meeting the physical activity recommendations preconized by American College of Sports Medicine.

8. CHAPTER 8: References

ABBAS, A.K.; LICHTMAN, A.H.; PILLAI, S. **Imunologia Celular e Molecular**. Rio de Janeiro: Rio de Janeiro, 2005.

ABDELLAOUI, A.; AL-KHAFFAF, H. C-reactive protein (CRP) as a marker in peripheral vascular disease. **European journal of vascular and endovascular surgery**, v. 34, n. 1, p. 18-22, 2007.

ACSM - American College of Sports Medicine. **ACSM's Guidelines for Exercise Testing and Prescription.** 8th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2010. p. 366.

ADEKUNLE, A. E.; AKINTOMIDE, A.O. Gender differences in the variables of exercise treadmill test in type 2 diabetes mellitus. **Ann Afr Med,** v.11, n.2, p.96-102, 2012.

AGUILO, A.; TAULER, P.; PILAR GUIX, M. et al. Effect of exercise intensity and training on antioxidants and cholesterol profile in cyclists**. J Nutr Biochem**, v.14, n.6, p.319-25. 2003.

AKBARPOUR, M. The effect of aerobic training on serum adiponectin and leptin levels and inflammatory markers of coronary heart disease in obese men. **Biology of Sport,** v. 30, n.1, p. 21-27, 2013.

ALBERT M.A.; GLYNN, R.J.; RIDKER, P.M. Effect of physical activity on serum C-reactive protein. **The American Journal of Cardiology**, v. 93, n°2, p. 221-5, 2004.

BALDUCCI, S.; ZANUSO, S.; NICOLUCCI , A. et al., Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. **Nutrition, Metabolism & Cardiovascular Disease***,* v. 8, pp. 608–17, 2010.

BAPTISTA, T.W.F et al. State responsibility and right to health in Brazil: a balance of the Branches' actions. **Ciência & Saúde Coletiva,** v. 14, n.3, 2009.

BERLIN, J.A.; COLDITZ, G.A. A meta-analysis of physical activity in the prevention of coronary heart disease. **American Journal of Epidemiology**, v.132, p. 612–628, 1990.

BEAVERS, K.M.; BRINKLEY, T.E.; NICKLAS, B.J. Effect of exercise training on chronic inflammation. **Clinica Chimica Acta**, v. 411, n. 11, p. 785-793, 2010.

BELLI, T. et al. Effects of 12-week overground walking training at ventilatory threshold velocity in type 2 diabetic women. **Diabetes Research and Clinical Practice,** v. 93, n. 3, p. 337-343, 2011.

BLAIR, S.N.; CHENG, Y.; HOLDER, J.C. Is physical activity or physical fitness more important in defining health benefits? **Med Sci Sports,** v.33, p. S379-S99, 2001.

BRASIL. Constituição da República Federativa do Brasil. Brasília, DF: Senado Federal, 1988.

BRASIL, Lei nº 8.142 de 28 de dezembro de /1990.

BRASIL, Lei nº 8.080 de 19 de setembro de 1990.

BRUUNSGAARD, H. Physical Activity and modulation of systemic low-level inflammation. **Journal of Leukocyte Biology,** v.78, p. 819-835, 2005.

BORG, G.A. Psychophysical bases of perceived exertion. **Medicine & Science in Sports & Exercise,** v. 14, n. 5, p. 377-81, 1982.

BULL, F.C.; BELLEW, B.; SCHOEPPE, S. et al. Developments in national physical activity policy: an international review and recommendations toward better practice. **J Sci Med Sport**, v. 7 (suppl 1), p. 93–104, 2004.

CAMPBELL, P. T.; Campbell, K. L.; Wener, M. H., et al. A yearlong exercise intervention decreases CRP among obese postmenopausal women. **Medicine and Science in Sports and Exercise**, v. 41, n. 8, p. 1533–1539, 2009.

CASPERSEN, C.J.; POWELL, K.E.; CHRISTENSON, G.M. Physical activity, exercise end physical fitness: definitions and distinctions for health-related research. **Public Health Reports,** v. 100, n. 2, p. 126-131, 1985.

CAVALHEIRA, J.B.C; ZECCHIN, H.G; SAAD, M.J.A. Vias de sinalização da insulina. **Arquivos Brasileiros de Endocrinologia & Metabologia,** v.46, n.4, p. 419-425, 2002.

CHAPMAN, M.J.; ASSMANN, G.; FRUCHART, J.C. et al. European Consensus Panel on HDL-C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid – A position paper developed by the European Consensus Panel on HDL-C. **Curr Med Res Opin**, v.20, p. 1253-68, 2004.

COLBERT, L. H.; VISSER, M.; SIMONSICK, E. M.; et al. Physical activity, exercise, and inflammatory markers in older adults: findings from the health, aging and body composition study. **Journal of the American Geriatrics Society**, v. 52, n. 7, p. 1098–1104, 2004.

COOPER, C.E. et al. Exercise, free radicals and oxidative stress. **Biochemical Society Transactions**, v.30, p.280-5, 2002.

COSTA, B.V. et al. Aderência a um programa de atividade física e fatores associados. **Motriz,** v. 15, p. 25-36, 2009.

DANDONA, P. et al. The potential influence of inflammation and insulin resistance on the pathogenesis and treatment of atherosclerosis-related complications in type 2 diabetes. **Journal of Clinical Endocrinology & Metabolism**, v. 88, p. 2422–2429, 2003.

DAS, U.N. Anti-inflammatory nature of exercise. **Nutrition,** v. 20, n. 3, p. 323–326, 2004.

DEVRIES, M. C.; M. J. HAMADEH, A. W.; GLOVER, S. et al. Endurance training without weight loss lowers systemic, but not muscle, oxidative stress with no effect on inflammation in lean and obese women. **Free Radic Biol Med**, v. 45, n. 4, p.503–11, 2008.

DONGES, C.E.; DUFFIELD, R.; DRINKWATER, E.J. Effects of resistance or aerobic exercise training on interleukin-6, C-reactive protein, and body composition. **Medicine & Science in Sports Exercise**, v. 42, n. 2, p. 304-13, 2010.

DUNN, A.I.; MARCUS, B.; KAMPERT, J.B. et al. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness. **JAMA,** v.281, n.4. p. 327-334, 1999.

DURSTINE, J.L; HASKELL, W.L. Effects of exercise training on plasma lipids and lipoproteins. **Exercise and Sports Science Review**, v. 22, p. 477–521, 1994.

ELOSUA, R.; BARTALI, B.; ORDOVAS, J. M. et al. Association between physical activity, physical performance, and inflammatory biomarkers in an elderly population: the InCHIANTI study. **Journals of Gerontology A: Biological Sciences and Medical Sciences,** v. 60, n. 6, p. 760– 767, 2005.

ESPOSITO, K.; PONTILLO, A.; DI PALO, C. et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. **JAMA**, v.289, n.14. p.1799-1804, 2003.

FANG J.; WYLIE-ROSETTT, J.; COHEN H.W. et al. Exercise, body mass index, caloric intake, and cardiovascular mortality. **Am J Prev Med**, v. 25, p. 283-9, 2003.

FERNANDEZ-BERGES, D.; CONSUEGRA-SANCHEZ, L.; PENAFIEL, J. et al. Metabolic and inflammatory profiles of biomarkers in obesity, metabolic syndrome, and diabetes in a Mediterranean population: DARIOS inflammatory study. **Revista Espanola de Cardiologia**, 2014.

FERREIRA, F. C.; A. I. DE MEDEIROS, C.; NICIOLI, J. E. et al. Circuit resistance training in sedentary women: Body composition and serum cytokine levels. **Appl Physiol Nutr Metab**, v. 35, n. 2, p 163–71, 2009.

FICHTLSCHERER, S.; HEESCHEN, C.; ZEIHER, A.M. Inflammatory markers and coronary artery disease. **Current Opinion in Pharmacology**, v. 4, pp.124-131, 2004.

FISHER, G.; HYATT, T.C.; HUNTER, G.R. et al. Effect of diet with and without exercise training on markers of inflammation and fat distribution in overweight women. **Obesity,** v. 19, n. 6, p. 1131–6, 2011.

FISMAN, E.Z.; TENENBAUM, A. The ubiquitous interleukin-6: a time for reappraisal. **Cardiovascular Diabetology**, v. 9, n.1, p.62, 2010.

FLETCHER, G.F.; FROELICHER, V.F.; HARTLEY, L.G. et al. Exercise standards. A statement for health professionals from the American Heart Association. **Circulation**, v. 82, p. 2286-322, 1990.

FORD, E.S. Does exercise reduce inflammation? Physical activity and C-reactive protein among US adults. **Epidemiology**, v. 13, p. 561–568, 2002.

FRANCISCO, G.; HERNÁNDEZ, C.; SIMÓ R. Serum markers of vascular inflammation in dyslipidemia. **Clin Chim Acta**, v.369, p. 1-16, 2006.

FRIEDMANN, J.M.; HALAAS J.L. Leptin and the regulation of body weight in mammals. **Nature**, v. 395, n.22, p. 763-70, 1998.

FROHLICH, M.; SUND, M.; THORAND, B.; et al. Lack of seasonal variation in C-reactive protein. **Clinical Chemistry**, v. 48, n. 3, p. 575–577, 2002

GARBER, E.C.; BLISSMER, B.; DESCHENES, M.R. et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for Prescribing Exercise, **Medicine & Science in Sports & Exercise,** v. 43, no7, p. 1334-59, 2011.

GHORAYEB, N. et al. Diretriz em Cardiologia do Esporte e do Exercício da Sociedade Brasileira de Cardiologia e da Sociedade Brasileira de Medicina do Esporte. **Arquivos Brasileiros de Cardiologia,** v. 100, n. 1, p. 1-41, 2013.

GIRALDO, A. et al. Influence of a physical activity program on the use of Primary Care services in the city of Rio Claro, SP. **Revista Brasileira de Atividade Física e Saúde**, v. 18, p. 186-196, 2013.

GOBBI, S.; VILLAR, R.; ZAGO, A.S. **Educação física no ensino superior:** bases teórico-práticas do condicionamento físico. Rio de Janeiro: Editora Guanabara Koogan, 2005.

GOLDBERG, R. B. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. **Journal of Clinical Endocrinology and Metabolism**, v. 94, n. 9, p. 3171– 3182, 2009.

GOMES, M.A., DUARTE, M.F.S. Efetividade de uma intervenção de atividade física em adultos atendidos pela estratégia Saúde da Família: Programa de Ação e Saúde Floripa – Brasil. **Revista Brasileira de Atividade Física & Saúde,** v.13, n.1, p. 44-56, 2008.

GOMES, G.A.O. **Participação em um programa de exercícios físicos em unidades de saúde e níveis de atividade física de adultos e idosos.** Tese de Doutorado, Instituto de Biociências, Campus Rio Claro Campus, Universidade Estadual Paulista, 2012, como parte dos requisites para obtenção do título de Doutor em Ciências da Motricidade, na área de concentração de Atividade Física e Saúde.

GORDON, T. et al. High density lipoprotein as a protective factor against coronary heart disease. **The American Journal of Medicine,** v.62, n.5, p.707-714, 1977.

GUIMARÃES, J. I.; STEIN, R.; VILAS-BOAS, F. Normatização de técnicas e equipamentos para realização de exames em ergometria e ergoespirometria. **Arquivos Brasileiros de Cardiologia,** v. 80, p. 457-464, 2003.

GULATI, M. et al. Heart Rate Response to Exercise Stress Testing in Asymptomatic Women: The St. James Women Take Heart Project**. Circulation,** n. 122, p. 130 -137, 2010.

HAGBERG, M.J. Effect of training on the decline of VO2max with aging. **Fed Proc,** v.46, n.5, p.1830-3, 1987.

HALLAL, P.C. et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. **The Lancet,** v. 380, n. 9838, p. 247-257, 2012.

HARRIS, G. D.; WHITE, R. D. Exercise stress testing in patients with type 2 diabetes: when are asymptomatic patients screened? **Clinical Diabetes,** v. 25, n. 4, p. 126-130, 2007.

HASKELL, W. L. et al. Physical Activity and public health: update recommendation for adults from the American College of Sports Medicine and the American Heart Association. **Medicine Science Sports and Exercise,** v. 39, n.8, p.1423-1434, 2007.

HAWLEY, J. A., Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. **Diabetes/Metabolism Research and Reviews,** v. 20, n. 5, p. 383– 393, 2004.

HICKEY, M.S.; HOUMARD, J.A; CONSIDINE, R.V et al. Gender-dependent effects of exercise training on serum leptin levels in human, **Am J Physiol,** v.272, p.E562-6, 1997

HUANG, C.J; ZOURDOS, M.C.; JO, E. et al. Influence of physical activity and nutrition on obesity-related immune function. **The Scientific World Journal,** v. 2013, p. 1-12, 2013.

IBGE. Instituto Brasileiro de Geografia e Estatística. Censo demográfico. 2010.

JANKORD, R.; JEMIOLO, B. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. **Medicine and Science in Sports and Exercise**, v. 36, n. 6, p. 960–964, 2004.

JUNIOR, A. A. **Exercícios de alongamento: Anatomia e Fisiologia**, chapter 7, Manole, 3rd edition, 2010.

KADOGLOU, N. P. E.; ILIADIS, F.; ANGELOPOULOU, N. et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. **European Journal of Cardiovascular Prevention and Rehabilitation**, v. 14, n. 6, p. 837–843, 2007.

KANNAN, U.; VASUDEVAN, K.; BALASUBRAMANIAM, K. et al. Effect of exercise intensity on lipid profile in sedentary obese adults. **J Clin Diagn Res,** v. 8, p. BC08-10, 2014.

KING, G. The role of inflammatory cytokines in diabetes and its complications. ***Journal of Periodontology***, v. 79, n. 8, p. 1527–1534, 2008.

KOHL, H.W; CRAIG, C.L.; LAMBERT, E.V. The pandemic of physical inactivity: global action for public health. **The Lancet**, v. 380, n. 9838, p. 294-305, 2012.

KOKUBUN, E.; LUCIANO, E.; SIBUYA, C.Y. et al., Programa de atividade física em unidades básicas de saúde: relato de experiência no município de Rio Claro-SP. **Revista Brasileira de Atividade Física e Saúde,** v.12, no.1, pp.45-53, 2007.

KON, K.K.; HAN, S.H.; QUON, M.J. Inflammatory markers and metabolic syndrome. **J Am Coll Cardio**, v.46, n.11, p. 1978-85, 2005.

KRAUS, W.E. et al. Effects of the amount and intensity of exercise on plasma lipoproteins. **The New England Journal of Medicine**, v. 347, p. 1483–1492, 2002.

KRUCHELSKI, S.; RAUCHBACH, R**. Curitibativa gestão nas cidades voltada à promoção da atividade física, esporte, saúde e lazer**: Avaliação, prescrição e orientação de atividades físicas e recreativas, na promoção de saúde e hábitos saudáveis da população curitibana. R Rauchbach: Curitiba. p. 149, 2005.

KUJALA, U.M. et al. Relationship of leisure-time physical activity and mortality: The Finnish Twin Cohort. **JAMA**, v. 279- n. 6, p. 440-444, 1998.

LAMONT, M.J; BARLOW, C.E.; JURCA, R. et al., Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. **Circulation**, v.112, n.4, p. 505-512, 2005.

LEE, I.M; SHIROMA, E.J.; LOBELO, F. et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. **The Lancet**, v. 380, n. 9838, p. 219-229, 2012.

LOHMAN, T. G.; ROCHE, A. F.; MARTORELL, R. **Anthropometric Standardization Reference Manual:** Abridged Edition. Illinois: Human Kinetics Books, p.90, 1991.

MALTA, D.C. et al. Presentation of the strategic action plan for coping with chronic diseases in Brazil from 2011 to 2022. **Epidemiol. Serv. Saúde,** v.20, n.4, 2011.

MARCELL, T.J. et al. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. **Metabolism**, v. 54, n. 4, p. 533-41, 2005.

MATSUDO, S.M.; MATSUDO, V.R.; ARAÚJO, T.L. et al. The Agita São Paulo Program as a model for using physical activity to promote health. **Rev Panam Salud Publica/Pan Am J Public Health,** vol. 14, n. 4, p. 265-72, 2003.

MEIER-EWERT, H. K.; RIDKER, P. M.; RIFAI, N.; et al. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. **Clinical Chemistry**, v. 47, n. 3, p. 426–430, 2001.

MELZER, K. et al. Physical activity: the health benefits outweigh the risks. **Current Opinion in Clinical Nutrition and Metabolic Care,** v. 7, n. 6, p. 641-647, 2004.

MENEGHELO, R. S. et al. III Diretrizes da Sociedade Brasileira de Cardiologia sobre teste ergométrico. **Arquivos Brasileiros de Cardiologia,** v. 95, n. 5, p. 1-26, 2010.

MINISTÉRIO DA SAÚDE. **ABC do SUS: doutrinas e princípios.** Brasília: Ministério da Saúde; Secretaria Nacional de Assistência à Saúde, 1990.

MINISTÉRIO DA SAÚDE. **Cadernos de atenção básica: a implantação da Unidade de Saúde da Família**. Brasília: Ministério da Saúde; Secretaria de Políticas de Saúde, Departamento de Atenção Básica, 2000.

MINISTÉRIO DA SAÚDE. **Cadernos de atenção básica: diretrizes do NASF – Núcleo de Apoio à Saúde da família.** Brasília: Ministério da Saúde; Secretaria de Atenção à Saúde, 2009.

MONTEIRO, Henrique L. et al. Efetividade de um programa de exercícios no condicionamento físico, perfil metabólico e pressão arterial de pacientes hipertensos. **Rev Bras Med Esporte,** v. 13, n. 2, p. 107-12, 2007.

MOTA, G.; ZANESCO, A. Leptina, Grelina e Exercício Físico. **Arquivos Brasileiros de Endocrinologia & Metabologia**, v. 51, n. 1, p. 25–33, 2007.

NAKAMURA, P.M. et al. Programa de intervenção para a prática de atividade física: Saúde Ativa Rio Claro. **Revista Brasileira de Atividade Física e Saúde**, v. 15, p. 128-132, 2010.

NAKAMURA, P.M. et al. Effect of a 10-year physical activity intervention in primary health care settings on physical fitness. **Journal of Physical Activity and Health**, 2014.

NEWSHOLME, P.; CRUZAT, V.; ARFUSO, F. et al. Nutrient regulation of insulin secretion and action. **Journal of Endocrinology,** v.201, n.3, p. R105-R120, 2014.

NIEMAN, D.C. Exercise immunology: practical applications. **Int J Sports Med**, v. 18, p.S91-S100, 1997.

NIESS, A.M. et al. Free radicals and oxidative stress in exercise – imunological aspects. **Exercise Immunology Review**, v. 5, p. 22-56, 1999.

NICKLAS, B. J.; HSU, F.; BRINKLEY, T. J.; et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. **Journal of the American Geriatrics Society**, v. 56, n. 11, p. 2045–2052, 2008.

OLSON, T. P.; DENGEL, D. R.; LEON, A. S.; et al. Changes in inflammatory biomarkers following one-year of moderate resistance training in overweight women. **International Journal of Obesity**, v. 31, n. 6, p. 996–1003, 2007.

OMS. **Global recommendations on physical activity for health**. Geneva: World Health Organization, 2010.

PAIVA, C.H.A; TEIXEIRA, L.A. Health reform and the creation of the Sistema Único de Saúde: notes on context and authors. **História, Ciências, Saúde – Manguinhos,** v.21, n.1, 2014.

PALM, J. et al. The Brazilian health system: history, advances, and challenges. **The Lancet**, v. 377, n. 9779, 2011.

PAPINI et al. The Effect of a Community-Based, Primary Health Care Exercise Program on Inflammatory Biomarkers and Hormone Levels. **Mediators of Inflammation**, v. 2014, p.1-7, 2014.

PATE, R.R. et al. Physical Activity and public health. A recommendation from the CDC and ACMS. **Journal of American Medical Association,** Chicago, v. 273, n. 5, p. 402-407, 1995.

PEARSON, T.A.; MENSAH, G.A.; ALEXANDER, R.W. et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice. **Circulation**, v. 107, p. 499-511, 2003.

PEDERSEN, B.K. The anti-inflammatory effect of exercise: its role in diabetes and cardiovascular disease control. **Essays in Biochemistry**, v. 42, p. 105–117, 2006.

PEDERSEN, B.K. IL-6 signalling in exercise and disease. **Biochemical Society Transactions**, v. 35, n. 5, p. 1295– 1297, 2007.

PEDERSEN, B.K.; TOFT, A.D. Effects of exercise on lymphocytes and cytokines. **British Journal of Sports Medicine**, v.34, p. 246-251, 2000.

PEDERSEN, B.K.; HOFFMAN-GOETZ, L. Exercise and the immune system: regulation, integration, and adaptation. **Physiol Rev**, v.80, p. 1055-81, 2000.

PEDERSEN, M.; BRUUNSGAARD, H.; WEIS, N. et al. Circulating levels of TNFα and IL6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with Type-2 diabetes**. *Mechanism of Ageing and Development,*** v. 124. n. 4, p. 495-502, 2003.

PETERSEN, A.M.; PEDERSEN B.K. The anti-inflammatory effect of exercise. **J Appl Physiol**, v.98, p. 1154-62, 2005.

PETRELLA, Robert J. et al. Can primary care doctors prescribe exercise to improve fitness?: The step test exercise prescription (STEP) project**. American Journal of Preventive Medicine,** v. 24, n. 4, p. 316-322, 2003.

PISCHON, T. et al., Leisure- time physical activity and reduce plasma levels of obesity-related inflammatory markers. **Obesity Research**, v.11, n.9, 2003.

PRESTES, J.; DONATO, F.F.; DIAS, R. et al. Papel da interleucina-6 como um sinalizador de diferentes tecidos durante o exercício físico. **Fitness & Performance Journal,** v.5, n. 6, p. 348-353, 2006.

REUBEN, D. B.; JUDD-HAMILTON, L.; HARRIS, T. B.; et al. The associations between physical activity and inflammatory markers in high-functioning older persons: macArthur studies of successful aging. **Journal of the American Geriatrics Society**, v. 51, n. 8, p. 1125–1130, 2003.

ROMERO, C.E.M; ZANESCO, A. O papel dos hormônios leptina e grelina na gênese da obesidade. **Rev. Nutr**, v. 19, n. 1, p.85-91, 2006.

RUAN, H.; LODISH, H.F. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alfa. **Cytokine Growth Factor Rev**, v.14, p. 447-55, 2003.

SAITO, I.; FOLSOM, A.R.; BRANCATI, F.L. et al. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the atherosclerosis risk in communities (ARIC) study. **Ann Intern Med**, v.133, n.2, p. 81-91, 2000.

SARTORIO, A. et al. Effects of a 3-week integrated body weight reduction program on leptin levels and body composition in severe obese subjects. **Journal of Endocrinological Investigation**, v. 26, n. 3, p. 250-256, 2003.

SCHEEN, A. J. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? **Diabetes and Metabolism**, v. 31, n. 2, p. 5S27–5S34, 2005.

SECRETARIA DE SAÚDE DO RECIFE. Academia da Cidade. Disponível em: <http://www2.recife.pe.gov.br/projetos-e-acoes/projetos/academia-da-cidade/> Acesso em: 06 Abr. 2012.

SMITH, D.; IRVING, S.; SHELDON, J. et al. Serum levels of the antiinflammatory cytokine interleukin-10 are decreased in patients with unstable angina. **Circulation**, v. 104, p.746–749, 2001.

SOARES, F.H.R.; SOUSA, M.B.C. Different types of physical activity on inflammatory biomarkers in women with or without metabolic disorders: a systematic review. **Women & Health,** v.53, n.3, p. 298-316, 2013.

SOCIEDADE BRASILEIRA DE CARDIOOLGIA. III Diretrizes Brasileiras Sobre Dislipidemias e Diretriz de Prevenção da Aterosclerose do Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia. **Arq Bras Cardiol,** v.77, Supl III:1-48, 2001.

STEWART, L.K.; FLYNN, M.G.; CAMPBELL, W.W. et al. The influence of exercise training on inflammatory cytokines and C-reactive protein. **Medicine and Science in Sports and Exercise**, v. 39, n. 10, p. 1714–1719, 2007.

TAAFFE, D. R.; HARRIS, T. B.; FERRUCCI, L.; et al. Cross-sectional and prospective relationships of interleukin6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. **Journals of Gerontology A: Biological Sciences and Medical Sciences**, v. 55, n. 12, p. M709–M715, 2000.

TEIXEIRA DE LEMOS, E. et al. Regular physical exercise as a strategy to improve antioxidant and anti-inflammatory status: benefits in type 2 diabetes mellitus. **Oxidative medicine and cellular longevity**, v. 2012, 2012.

TEODORO, B.G. et al. Respostas das citocinas ao exercício físico. **Efdeports- Revista Digital – Buenos Aires,** ano 15, n. 144, maio de 2010.

TILG, H.; MOSCHEN, R.A. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity**. Nat Rev Immunol**, vol6, p. 772-783, 2006.

TIMMERMAN, K.L.; FLYNN, M.G.; COEN, P.M. et al. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? **Journal of Leukocyte Biology**, v. 84, n. 5, p. 1271–1278, 2008.

TIRYAKI-SONMEZ, G.; OZEN, S; BUGDAYCI, G. et al. Effect of exercise on appetite-regulating hormones in overweight women. **Biology of Sport**, v. 30, n. 2, p. 75–80, 2013.

TUDOR – LOCKE , C.; BURKETT, L.; REIS, M. S.; AINSWORTH, B. E.; M. P. H.; MACERA, C. A.; WILSON, D. K. How many days of pedometer monitoring predict weekly physical activity in adults? **Preventive Medicine**, v.40, n.3, p. 293-98, 2005.

VASSALLI, P. The pathophysiology of tumor necrosis factors. **Annual Review of Immunology**, v.10, p.411-452, 1992.

VENTURIM, L. M. D. V. P.; CADE, N. V. Efeitos do Programa — "P.E.S.O" (Promoção de Estilo de Vida Saudável na Obesidade) sobre variáveis antropométricas, hemodinâmicas e bioquímicas. **Revista Brasileira de Atividade física & Saúde**, v.12, n.1, p. 19-26, 2007.

VIGITEL. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Ministério da Saúde: 2013.

VOLP, A.C.P.; ALFENAS, R.C.; COSTA, N.M.B. et al. Capacidade dos biomarcadores inflamatórios em predizer a síndrome metabólica. **Arq Bras Endocrinol Metab,** v.52, n.3, p.537-549, 2008.

WALTER, R. E.; WILK, J. B.; LARSON, M. G. et al. Systemic inflammation and COPD: the Framingham heart study. **Chest Journal**, v. 133, n. 1, p. 19–25, 2008.

WANG, P.; WU, P.; SIEGEL, M.I et al. Interleukin (IL)-10 inhibits nuclear factor kappa B (NF kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. **The Journal of Biological Chemistry**, v. 270, p. 9558-9563, 1995.

WANNAMETHEE, S.G. et al. Physical activity and hemostatic and inflammatory variables in elderly men. **Circulation**, v. 105, p. 1785–1790, 2002.

WARBURTON, D.E.; CHARLESWORTH, S.; IVEY, A. et al. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. **Int J Behav Nutr Phys Act,** v.7, n.1, p. 39, 2010.

WEN, L.M.; THOMAS, M.; JONES, H.; ORR, N.; MORETON, R.; KING, L.; HAWE, P.; BINDON, J.; HUMPHRIES, J.; SCHICHT, K.; CORNE, S.; BAUMAN, A. Promoting physical activity in women: evaluation of a 2-year community-based intervention in Sydney, Australia. **Health Promotion International**, v. 17, n. 2, p. 127–37, 2002.

WERT, D. M. et al. The association between energy cost of walking and physical function in older adults**. Archives of gerontology and geriatrics,** v. 57, n. 2, p. 198-203, 2013.

WHO, **Noncommunicable Diseases Country Profiles**, World Health Organization, 2011.

WINKLER ,G.; KISS, S.; KETSZTHELYI, L. et al. Expression of tumor necrosis factor (TNF-alfa) protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell volume, serum TNF-alfa, soluble serum TNF- receptor-2 concentrations and C-peptide level. **Eur J Endocrinol**, v.149, n.2, p. 129-35, 2003.

YOU, T.; ARSENIS, N. C.; DISANZO, B. L., et al. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. **Sports Medicine**, v. 43, n. 4, p. 243–256, 2013.

ZOPPINI, G. al. Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. **Nutrition, Metabolism and Cardiovascular Diseases**, v. 16, n. 8, p. 543-549, 2006.

ZORZETTO, L.P. **Comparação entre modelos de intervenção de exercício físico em em unidades de saúde e suas influências na aderência e variáveis relacionadas a saúde**. Dissertação de Mestrado, Instituto de Biociências, Campus Rio Claro Campus, Universidade Estadual Paulista, 2013, como parte dos requisites para obtenção do título de Mestre em Ciências da Motricidade, na área de concentração de Atividade Física e Saúde.

9. ANEXXES SESION

9.1 Consent form

Termo de Consentimento Livre e Esclarecido

(Conselho Nacional de Saúde, Resolução 196/96)

Convidamos a senhora a participar de uma pesquisa intitulada: "Efeito de um programa de exercício físico em usuários de unidades de saúde sobre biomarcadores de inflamação e suas associações com doenças crônicas". Esse projeto de pesquisa é de responsabilidade da aluna de Pós-graduação, nível de Doutoramento, Camila Bosquiero Papini sob supervisão do orientador Prof. Dr. Eduardo Kokubun, professor titular da Universidade Estadual Paulista – UNESP – Campus Rio Claro, situada à Avenida 24-A, 1515 – Bela Vista, CEP: 13506-900, telefone (19) 3526-4331.

A sua participação é de grande importância, pois, através das informações colhidas poderemos avaliar a efetividade de um Programa de Promoção de Exercício Físico na Atenção Básica de Saúde em parâmetros relacionados à saúde. Caso a senhora aceite participar desse estudo como voluntária será convidada a participar de um programa de Exercício Físico oferecido na Unidade de Saúde próxima a sua residência Serão avaliadas medidas relacionadas à saúde no início do programa e a cada 6 (seis) meses, sendo: medidas antropométricas, testes de capacidade funcional (flexibilidade, força, agilidade, coordenação), tese submáximo de caminhada na esteira), análise da bioquímica sanguínea. A sua participação é voluntária e a eventual recusa em participar, seja ela em qualquer momento da pesquisa não lhe provocará nenhum dano ou punição. Informamos também que a senhora não terá despesa bem como não será remunerada para participação da pesquisa

Durante a realização da pesquisa, os riscos levantados são durante as sessões e exercício físico e/ou avaliação, entre eles: desconforto, quedas, quadro de hipoglicemia, queda de pressão arterial, torções, mal estar, etc. Caso aconteça algum imprevisto, todos envolvidos com a pesquisa são orientados a chamarem o resgate. Como prevenção as hipertensas terão sua pressão arterial aferida antes do início das aulas e as diabéticas terão a glicemia medida uma vez por mês para controle e minimização de riscos. A pressão arterial também será controlada durante toda a realização dos testes. Dentre os benefícios, estão aqueles relacionados à saúde como redução de peso, controle e prevenção da hipertensão e diabetes, melhora da aptidão física e melhora da qualidade de vida. Além disso, cada participante terá acesso a sua evolução durante a pesquisa de forma individualizada.

Os dados coletados serão confidencialmente estudados e serão utilizados somente para fins de pesquisa. Se a senhora se sentir suficientemente esclarecida sobre os objetivos, os eventuais riscos e os benefícios dessa pesquisa convido-a a assinar esse Termo, elaborado em duas vias, sendo que uma ficará com a senhora e outra com os pesquisadores.

Dados do participante da pesquisa:

Nome:____RG:_____________

Data de Nascimento: _____/_____/______ Telefone: ( )_______________________

Endereço: ____

Dados do pesquisador:

Título da pesquisa: "Efeito de um programa de exercício físico em usuários de unidades de saúde sobre biomarcadores de inflamação e suas associações com doenças crônicas".

Pesquisador Responsável: Camila Bosquiero Papini

RG: 30.218.947-6

CREF: 067053 G/SP

Orientador: Prof. Dr. Eduardo Kokubun

Instituição: Universidade Estadual Paulista – UNESP- Rio Claro

Endereço: Avenida 24A, 1515 – Bela Vista

Fone: 3526-4331

Rio Claro, _____________________ de 2013.

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Assinatura do participante Camila Bosquiero Papini

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Eduardo Kokubun