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EFFECTS OF ADAPTED PHYSICAL ACTIVITY ON QUALITY OF LIFE, PHYSICAL FITNESS AND FEAR OF FALLING IN PEOPLE WITH OSTEOPOROSIS

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Acronyms

25OHD: 25-hydroxyvitamin D

6MWT: 6-Minute Walk Test

ACTLIFE: Physical ACTivity: the tool to improve the quality of LIFE in osteoporosis people

AHRQ: Agency for Healthcare Research and Quality

ALP: Alkaline Phosphatase

APA: Adapted Physical Activity

BALP: Bone Alkaline Phosphatase

BMD: Bone Mineral Density

BMI: Body Mass Index

BP: Bisphosphonates

BSP: Bone Sialoprotein

BW: Body Weight

Ca: Calcium

CG: Control Group

COMMS: Centro Osteoporosi e Malattie Metaboliche dello Scheletro

CR-10: Borg Category Ratio 10

CTSK: Cathepsin K

CTX-1: Carboxy-Terminal Crosslinked Telopeptide of type 1 collagen

DDK-1: Dickkopf-1

DPD: Deoxypyridinoline

DXA: Dual X-ray Absorptiometry

ECG: Electrocardiogram

ECOS-16: Evaluación de la Calidad de Vida en la Osteoporosis (Assessment of Health Related Quality of Life in Osteoporosis)

EG: Experimental Group

EQ-5D-3L: EuroQol Questionnaire 3-Level Version

ES: Effect Sizes

FES-I: Falls Efficacy Scale International

GGT: Gym Group Training

HRmax: Heart Rate Maximum

HRQOL: Health-Related Quality of Life

HRR: Hear Rate Reserve

HRT: Hormone Replacement Therapy

HYP: Hydroxyproline

IFAPA: International Federation of Adapted Physical Activity

IHT: Individual Home Training

IOF: International Osteoporosis Foundation

LPA: Light-Intensity Physical Activity

MCID: Minimal Clinically Important Difference

MCS: Mental Component Summary

MET: Metabolic Equivalent of Task

MPA: Moderate-Intensity Physical Activity

MVPA: Moderate-to-Vigorous Intensity Physical Activity

NOF: National Osteoporosis Foundation

NTS: Near Tandem Stand

NTX-1: Amino-Terminal Crosslinked Telopeptide of Type 1 Collagen

NYHA: New York Heart Association

OC: Osteocalcin

OP: Osteoporosis

OPG: Osteoprotegerin

P: Phosphorus

P1CP: Procollagen Type 1 C-Terminal Propeptide

P1NP: Procollagen Type 1 N-Terminal Propeptide

PA: Physical Activity

PAGA: Physical Activity Guidelines for Americans

PASE: Physical Activity Scale for Elderly

PCPs: Primary Care Providers

PCS: Physical Component Summary

PICO: Patients, Interventions, Comparators and Outcomes

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: International Prospective Register of Systematic Reviews

PRT: Progressive Resistance Training

PYD: Pyridoline

QoL: Quality of Life

RANKL: Receptor activator of NF-kB Ligand

RCT: Randomized Clinical Trial

RoB: Risk of Bias

SD: Standard Deviation

SE: Star Excursion Test

SERM: Selective Oestrogen Receptor Modulators

TRAP 5b: Tartrate-Resistant Acid Phosphatase 5b

VAS: Visual Analogue Scale

VPA: Vigorous-Intensity Physical Activity

WHA: World Health Assembly

WHO: World Health Organization

WHODAS: WHO Disability Assessment Schedule

Abstract

Undertaking regular physical activity is one of the major determinants of health. The benefits of exercise have been widely demonstrated through a wide range of studies, both in the treatment and prevention of almost every common medical problem seen today. Indeed, Physical Activity (PA), when adapted and in the right dosage, can be considered a protection and even a therapy for diseases conditions. Conversely, being physically inactive is associated with increased chronic disease risk. The prevalence of chronic conditions which affect the elderly population is bound to rise considerably due to a significant increase in life expectancy in the whole world. Among those, a relevant chronic condition includes Osteoporosis (OP) and the fragility fractures it causes. The clinical and social implications of the disease are mainly due to osteoporotic fractures that reach 1/3 of menopausal women. The number of individuals aged ≥50 years at high risk of osteoporotic fracture, worldwide in 2010, was estimated at 158 million and it is expected to double over the next 40 years. Among OP fractures, vertebral ones are associated with a significant decline in quality of life and disability. Therefore, OP and the associated fractures constitute a major public health concern. Exercise is a form of conservative non-pharmacological treatment that can be prescribed for the purpose of reducing pain and restoring motor functions in patients with osteoporosis. Regular PA, indeed, even taken up later in life, can help older women to prevent a decline in different components of Quality of Life (QoL), and even optimize muscle strength, balance, postural alignment and stability. Thus, preventing falls and reducing occurrence of fractures. However, in literature no definitive conclusions are available regarding benefits of exercise for individuals with OP and vertebral fractures. Furthermore, it is unclear which exercise is optimal for these patients. Lastly, there is no specific indication

on the best setting in which to exercise in. For these reasons, this present thesis aims to increase the knowledge on the type of exercise and training adapted for people with OP and its relative effects on QoL, physical fitness and fear of falling. Moreover, effects of exercise on bone biomarkers are investigated to deepen the topic.

In connection to this, the present thesis consists of two lines of study: the first part, from Chapter 1 to Chapter 4, focuses on introducing the topic by an overall state of the art regarding the benefits of PA in chronic disease particularly in OP, discussing also the results of a systematic review investigating the effects of exercise on bone biomarkers. The second part, Chapter 5 and Chapter 6 discusses two clinical trials, which differ in the type of target: the first one aims to evaluate the benefits and the feasibility of an Adapted Physical Activity (APA) middle-low impact program for postmenopausal women with OP and vertebral fractures, in terms of quality of life, physical performance, and fear of falling.

The second trial is focused on the evaluation of the efficacy of a 12-months exercise protocol for women with post-menopausal OP when administered as Individual Home Training (IHT) versus Gym Group Training (GGT) in terms of QoL, fear of falling, physical performance, joint mobility, muscle strength, and balance.

Concerning the first trial, results indicate that, due to its feasibility, safety and effectiveness, the APA program can be addressed to patients with osteoporosis-related vertebral fractures. Furthermore, the relationship between OP and QoL has been deepen and, most importantly, such programs showed to be a good strategy helping to improve particularly the quality of life of osteoporotic people. In view of this, findings from these studies can admittedly contribute in providing information on the beneficial effects of APA programs and also identifying the type of safe exercise to prescribe for the osteoporotic population. Moreover, it is worth pointing out the role of these studies in

defining possible future strategies to be applied by the involvement of health policy-makers, in order to primarily improve QoL in women with OP. Therefore, these indications are also intended to encourage the healthcare world to refer osteoporotic people to follow a healthy lifestyle, including adapted physical activity programs regularly administered by trainers able to deal with these conditions, especially for the prevention of fractures which represent the first cause of decline in terms of quality of life, physical fitness and fear of falling.

Keywords: physical activity; osteoporosis; exercise; quality of life; vertebral fractures; bone biomarkers.

1. Introduction

1.1 Benefits of Physical Activity in Chronic Disease

It is widely known that people, who engage in an active and fit way of life, live longer, healthier, and better lives. Indeed, undertaking regular Physical Activity (PA) is one of the major determinants of health (Marmot et al., 2019; Sallis, 2015). Moreover, studies have demonstrated the benefits of exercise in the treatment and prevention of most every chronic disease, including Osteoporosis (OP) (Sallis, 2015). A chronic disease can be defined as an illness that is not contagious, usually of long duration, progresses slowly, and is typically a result of genetics, environment, or poor lifestyle (WHO, 2018). Non-communicable diseases (NCDs) are a major burden worldwide (Andersen et al., 2016) with increasing prevalence in all age groups, genders, and ethnicities (Anderson et al., 2019).

For the last two centuries life expectancy, has consistently risen, nevertheless, due to an increase in various chronic diseases such as obesity, cancer, diabetes, stroke, lower respiratory and cardiovascular disease, current estimations support a potential decline in life expectancy for future generations (Olshansky et al., 2005; GBD 2015; Murphy et al., 2017). In 1990, more than 28 million (57%) of all global deaths were caused by chronic disease (Murray et al. 1997). This number increased to 36 million (63%) of all global deaths in 2008 (Alwan et al., 2011) and 39 million (72%) of all global deaths in 2016 (Naghavi et al., 2016). Currently, the literature supports that the incorporation of daily PA and exercise into people's lifestyles will reduce risk of chronic diseases and mortality while providing a means for primary disease prevention (Lear et al., 2017). Furthermore, once a chronic illness is diagnosed, treatment is better managed when PA and exercise are part of the disease medical management plan. In either case of disease prevention or treatment, PA and regular exercise provide a higher Quality of Life (QoL) and can increased longevity (Pedersen et al., 2015). However, to date, health authorities still need to implement efficient strategies aim at improving chronic disease risk and management assessment as well as favour healthy choices of lifestyle, taking into account the beneficial role of PA, with a view of public health and QoL promotion. Particularly, strategies aimed at reinforcing prevention in the field of bone fragility, especially among postmenopausal women, are warranted on a National basis by designing strategies involving different components and providers (Cipriani et al., 2018). As far as concerned osteoporosis, a chronic condition and long-term, sometimes lifelong, management and treatment is required (Compston et al., 2019). However, individuals at high risk of fractures do not receive adequate treatment and strategies to address this disease. The discovery of key pathways regulating bone resorption and formation has identified new approaches to treatment with distinctive mechanisms of action. Therefore, also new assessment strategies represent important challenges for the future (Compston et al., 2019).

In light of this, the following chapters provide a state of the art concerning PA, QoL and OP, in order to better clarify the rationale behind the interventions. Subsequently, the present thesis encloses firstly a literature investigation of further method of assessment, secondly the evaluation of the effects of Adapted Physical Activity (APA) intervention specifically tailored to the study population with OP and finally the design of a PA promotion intervention in order to be implemented in different settings.

By proceeding the dissertation as far as concerned the importance of PA, the second edition of the Physical Activity Guidelines for Americans (PAGA) begins with the following statement that highlights the power of choosing to be active: *"Being physically* *active is one of the most important actions that people of all ages can take to improve their health"* (U.S. Department of Health and Human Services, 2018; Bushman 2019). Health promotion and disease prevention are two sides of the coin when it comes to PA and exercise; the dual benefits are an inspiration for everyone to seek ways to make movement part of daily routines (Bushman et al., 2020). Overall, exercise provides many primary prevention health benefits reducing the incidence of the disease and it is also useful in secondary prevention to avoid sequelae and finally in the tertiary as it facilitates recovery, reduces disability, limits the loss of autonomy and promotes socio-family reintegration (Olutende et al., 2015; Frangella et al., 2012; D'Amelio et al., 2013). Generally, engaging in regular physical activity display more desirable health outcomes across a variety of physical conditions. Similarly, participants in randomized clinical trials of PA interventions show better health outcomes, including better general and health-related quality of life, better functional capacity and better mood states (Penedo et al., 2005). Over the years, researchers have explored the potential effect of PA and exercise and the list of health benefits continues to grow for all ages and both males and females. Table 1 and 2, taken from the 2018 Physical Activity Guidelines for Americans (PAGA) show an extensive list of physical and brain benefits (U.S. Department of Health and Human Services, 2018).

Table 1. Health Benefits Associated with Regular Physical Activity

Children and Adolescents
• Improved bone health (ages 3 through 17 years)
• Improved weight status (ages 3 through 17 years)
• Improved cardiorespiratory and muscular fitness (ages 6 through 17 years)
• Improved cardiometabolic health (ages 6 through 17 years)
• Improved cognition (ages 6 to 13 years)
• Reduced risk of depression (ages 6 to 13 years)
Adults and Older Adults
• Lower risk of all-cause mortality
• Lower risk of cardiovascular disease mortality
• Lower risk of cardiovascular disease (including heart disease and stroke)
• Lower risk of hypertension
• Lower risk of type 2 diabetes
• Lower risk of adverse blood lipid profile
• Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach
• Improved cognition
• Reduced risk of dementia (including Alzheimer's disease)
• Improved quality of life
• Reduced anxiety
• Reduced risk of depression
• Improved sleep
• Slowed or reduced weight gain

- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain following initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)
- Lower risk of fall-related injuries (older adults)

Note: *The Advisory Committee rated the evidence of health benefits of physical activity as strong, moderate, limited, or grade not assignable. Only outcomes with strong or moderate evidence of effect are included in this table.*
Note: From *Physical Activity Guidelines for Americans. 2nd ed. Washington (DC): U.S. Department of Health and Human Services; 2018*

Table 2. Benefits of Physical Activity for Brain Health

Outcome	**Population**	**Benefit**	**Acute**	**Hab itual**
Cognition	Children ages 6 to 13 years	Improved cognition (performance on academic achievement tests, executive function, processing speed, memory)	*x*	*x*
	Adults	Reduced risk of dementia (including Alzheimer’s disease)		*x*
	Adults older than age 50 years	Improved cognition (executive function, attention, memory, crystallized intelligence*, processing speed)		*x*

Quality of life	Adults	Improved quality of life		*x*
Depressed mood and depression	Children ages 6 to 17 years and adults	Reduced risk of depression Reduced depressed mood		*x*
Anxiety	Adults	Reduced short-term feelings of anxiety (state anxiety)	*x*	
	Adults	Reduced long-term feelings and signs of anxiety (trait anxiety) for people with and without anxiety disorders		*x*
Sleep	Adults	Improved sleep outcomes (increased sleep efficiency, sleep quality, deep sleep; reduced daytime sleepiness, frequency of use of medication to aid sleep)		*x*
	Adults	Improved sleep outcomes that increase with duration of acute episode	*x*	

Note: *The Advisory Committee rated the evidence of health benefits of physical activity as strong, moderate, limited, or grade not assignable. Only outcomes with strong or moderate evidence of effect are included in this table.*

**Crystallized intelligence is the ability to retrieve and use information that has been acquired over time. It is different from fluid intelligence, which is the ability to store and manipulate new information.*
Note: From *Physical Activity Guidelines for Americans. 2nd ed. Washington (DC): U.S. Department of Health and Human Services; 2018*

As reported above, exercise can represent a very powerful tool for the treatment, prevention and harmful effects mitigation of non-communicable disease. In fact, there is a linear relationship between activity level and health status: people who are able to maintain an active and fit way of life, can feel better from all points of view: physical and also mental (Physical Activity Guidelines Advisory Committee 2009; Warburton et al., 2010; WHO, 2010; Sallis et al., 2016; ISPAH, 2017). This strong connection between PA and health was also highlighted in a series of articles that the Journal Lancet published in 2012. The series reached this conclusion: *"In view of the prevalence, global reach, and health effect of physical inactivity, the issue should be appropriately described as pandemic, with far-reaching health, economic, environmental, and social consequences"* (Kohl et al., 2012). In recognition of that, member states of WHO agreed to set as one of the nine global targets, a relative reduction of 10% in the prevalence of insufficient PA by 2025, to improve the prevention and treatment of non-communicable diseases (WHO, 2013). In fact, additionally to fosters healthy growth and aging, preventing the occurrence of many chronic diseases, regular PA can reduce the risk of mortality (Hupin et al., 2015). Indeed, while the study's results consistently show that those who are active and fit are healthier, at the same time, being physically inactive can imply a long list of harmful effects on health. Indeed, sedentary and unfit people very predictably begin to suffer prematurely from chronic disease and die at a younger age. This association between disease and an inactive and unfit way of life exists in every age group: children, adults, and the elderly. Researchers have examined the effect of activity in a number of studies. Recent meta-analysis, describing the beneficial effects of PA, provide a high level of evidence regarding its impact on overall mortality (Kelly et al., 2014; Lollgen, 2009), cardiovascular disease-related mortality, or cancer-relate mortality (Je et al. 2013; Fong et al., 2012; Steffens 2016). For a recent example, in a population-based cohort study in the United Kingdom, those who were active at the start and had maintained activity levels had lower all-cause mortality risks (28% for medium level baseline activity and 33% for high baseline physical activity) (Mok et al., 2019). Of note, there were benefits for increasing PA, no matter the baseline level, even for those in the lowest activity level group. Lower mortality was found from all causes, cardiovascular disease, and cancer even when other lifestyle factors such as diet, body mass index, blood pressure, triglycerides, cholesterol, and medical history were considered (Mok et al., 2019). The researchers concluded that "*meeting and maintaining at least the minimum physical activity recommendations would potentially prevent 46% of deaths associated with physical inactivity*" (Mok et al., 2019).

Despite all this positive evidence, exercise is largely under-utilized in tackling chronic diseases compared to other strategies (Sallis, 2015). Furthermore, to date, in spite of this framework, no overall improvements in PA participation have been observed globally (Bull et al., 2020).

The last century has been the cradle of our societies' modernization and automation favouring the occurrence and development of sedentary opportunities and behaviours (Thivel et al., 2018). This sedentariness has lately been described as a major mortality risk factor (Rezende et al., 2016), independent of PA (Patel et al., 2010). Moreover, approximately 5.3 million of deaths are attributed to physical inactivity (Wen et al., 2012). For these reasons, many have suggested that physical inactivity is the major public health problem of our time (Blair et al., 2009). As reported in the recent Worldwide trends by the Lancet Global Health Journal: "*if current trends continue, the 2025 global physical activity target (a 10% relative reduction in insufficient physical activity) will not be met. Policies to increase population levels of physical activity need to be prioritised and scaled up urgently*" (Guthold et al., 2018).

In connection to that, in 2018, the World Health Assembly (WHA) approved a new *Global Action Plan on Physical Activity (GAPPA) 2018–2030* and adopted a new voluntary global target to reduce global levels of physical inactivity in adults and adolescents by 15% by 2030 (WHO, 2018). The World Health Organization recommends all countries establish national guidelines and set physical activity targets. Nevertheless, there is still an urgent need to increase priority and investment directed towards services to promote PA, given that the most recent global estimates show that one in four (27.5%) adults and more than three-quarters (81%) of adolescents do not meet the recommendations for aerobic exercise, as outlined in the 2010 Global Recommendations on Physical Activity for Health (WHO, 2010; Guthold et al., 2018; Guthold et al., 2020). Lack of PA is a major public health problem, yet the population in modern society is successively becoming more sedentary (Owen et al., 2020). Moreover, no overall improvement in global levels of participation over the last two decades and substantial gender differences has been detected (Guthold et al., 2018; Guthold et al., 2020). The new WHO 2020 Guidelines on Physical Activity and Sedentary Behaviour, an update of those of 2010, provide evidence-based public health recommendations on PA and sedentary behaviour for all-age group individuals, regarding the amount and types of physical activity through which significant health benefits can be achieved and health risks mitigated (WHO, 2020). In addition to that, it is important to take into account the definitions stated in the aforementioned new Guidelines, showed in Table 3 (Bull et al., 2020).

Table 3. Glossary of terms

Term	Definition
Aerobic physical activity	Activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity—also called endurance activity—improves cardiorespiratory fitness. Examples include walking, running, swimming and bicycling.
Balance training	Static and dynamic exercises that are designed to improve an individual's ability to withstand challenges from postural sway or destabilising stimuli caused by self-motion, the environment or other objects.
Bone-strengthening activity	Physical activity primarily designed to increase the strength of specific sites in bones that make up the skeletal system. Bone-strengthening activities produce an impact or tension force on the bones that promotes bone growth and strength. Examples include any type of jumps, running and lifting weights.
Disability	From the International Classification of Functioning, Disability and Health, an umbrella term for impairments, activity limitations and participation restrictions, denoting the negative aspects of the interaction between an individual (with a health condition) and that individual's contextual factors (environmental and personal factors).
Domains of physical activity	Physical activities can be undertaken in various domains, including one of more of the following: leisure, occupation, education, home and/or transport.
Household domain physical activity	Physical activity undertaken in the home for domestic duties (such as cleaning, caring for children, gardening, etc).
Leisure-domain physical activity	Physical activity performed by an individual that is not required as an essential activity of daily living and is performed at the discretion of the individual. Examples include sports participation, exercise conditioning or training and recreational activities such as going for a walk, dancing and gardening.
Light-intensity physical activity (LPA)	On an absolute scale, light intensity refers to physical activity that is performed between 1.5 and 3 METs. On a scale relative to an individual's personal capacity, light-intensity physical activity is usually a 2–4 on a rating scale of perceived exertion scale of 0–10. Examples include slow walking, bathing or other incidental activities that do not result in a substantial increase in heart rate or breathing rate.
Metabolic equivalent of task (MET)	The metabolic equivalent of task, or simply metabolic equivalent, is a physiological measure expressing the intensity of physical activities. One MET is the energy equivalent expended by an individual while seated at rest, usually expressed as mLO^2/kg/min.
Moderate-intensity physical activity (MPA)	On an absolute scale, moderate-intensity refers to the physical activity that is performed between 3 and <6 times the intensity of rest (METs). On a scale relative to an individual's personal capacity, MPA is usually a 5 or 6 on a

	rating scale of perceived exertion scale of 0–10.
Moderate-to-vigorous intensity physical activity (MVPA)	On an absolute scale, MVPA refers to the physical activity that is performed at >3 METs (ie, >3 times the intensity of rest). On a scale relative to an individual's personal capacity, MPA is usually a 5 or above on a scale of 0–10.
Multicomponent physical activity	Multicomponent physical activity are activities that can be done at home or in a structured group or class setting and combine all types of exercise (aerobic, muscle strengthening and balance training) into a session, and this has been shown to be effective. An example of a multicomponent physical activity programme could include walking (aerobic activity), lifting weights (muscle strengthening) and could incorporate balance training. Examples of balance training can include walking backwards or sideways or standing on one foot while doing an upper body muscle- strengthening activity, such as bicep curls. Dancing also combines aerobic and balance components.
Occupation domain physical activity	See work domain physical activity.
Physical activity (PA)	Any bodily movement produced by skeletal muscles that requires energy expenditure.
Physical inactivity	An insufficient physical activity level to meet present physical activity recommendations.
Recreational screen time	Time spent watching screens (television (TV), computer, mobile devices) for purposes other than those related to school or work.
Sedentary screen time	Time spent watching screen-based entertainment while sedentary, either sitting, reclining or lying. Does not include active screen-based games where physical activity or movement is required.
Sedentary behaviour	Any waking behaviour characterised by an energy expenditure of 1.5 METs or lower while sitting, reclining or lying. Most desk-based office work, driving a car and watching television are examples of sedentary behaviours; these can also apply to those unable to stand, such as wheelchair users. The guidelines operationalise the definition of sedentary behaviour to include self-reported low movement sitting (leisure time, occupational and total), TV viewing or screen time and low levels of movement measured by devices that assess movement or posture.
Transport domain physical activity	Physical activity performed for the purpose of getting to and from places, and refers to walking, cycling and wheeling (ie, the use of non-motorised means of locomotion with wheels, such as scooters, roller-blades, manual wheelchair, etc). In some contexts, operation of a boat for transport could also be considered transport-related physical activity.
Vigorous-intensity physical activity (VPA)	On an absolute scale, vigorous intensity refers to physical activity that is performed at 6.0 or more METs. On a scale relative to an individual's personal capacity, VPA is usually a 7 or 8 on a rating scale of perceived exertion scale of 0–10.

Work domain physical activity	Physical activity undertaken during paid or voluntary work.

Note: From *World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Bull et al. 2020*

To sum up, low physical activity levels result in harmful and even detrimental consequences. Additional problems arise with a physically inactive lifestyle: diminished self-concept, greater dependence on others for daily living, reduced opportunity and ability for normal social interactions, and overall diminished quality of life (Dustine et al., 2000). Conversely, the choice of being active is not perceived only as healthy but also as convenient, enjoyable, safe, affordable, and valued (Hallal et al., 2012). Indeed, PA plays a fundamental role in many health outcomes, including the risk for all-cause and cause-specific mortality such as coronary heart disease, stroke, cancer at multiple sites, type 2 diabetes, obesity, hypertension, and osteoporosis. Furthermore, it improves physical fitness, such as aerobic capacity, muscle strength and endurance; functional capacity, or the ability to engage in activities needed for daily living and brain health, proving to be useful in conditions that affect cognition, such as depression, anxiety and Alzheimer’s disease (U.S. Department of Health and Human Services, 2018; WHO, 2020). Moreover, PA and exercise improve the immune system enabling the body to fight infectious diseases resulting in less overall susceptibility to sicknesses (Simpson et al., 2015). Finally, additional health benefits exist for preventing disease complications and improved quality of life.

1.2 Quality of Life

In recent years, particular attention has been placed to health in terms of quality of life. Nowadays, despite the increased longevity and the development of sophisticated health care technologies and treatments, QoL is damaged given the growing prevalence of chronic disease that can negatively compromise the lives of people affected. It is well known that chronic diseases are slow in progression, long in duration, and they require medical treatment. Consequently, not only do they damage purely biological and functional aspects of the organism, they are also a major contributor to healthcare costs (Megari, 2013). Most importantly, the majority of chronic diseases hold the potential to worsen the overall health of patients by limiting their capacity to live well, affecting functional, social, emotional, relational and working status (Devins et al., 1983).

In connection to this, the World Health Organization (WHO) defines health as *"not merely the absence of disease or infirmity, but a state of complete psychical, mental and social well being"* (WHO, 1958). Quality of Life definition is even more complex. According to WHO, QoL is defined as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (WHO, 1996). WHO stated that QoL is the "*feeling of overall life satisfaction, as determined by the mentally alert individual whose life is being evaluated"* (Meeberg, 1993). This estimate is subjective, and encloses all domains of life, including elements of a biopsychosocialspiritual model (Hiatt, 1986). In essence, the concept of QoL refers to the physical, psychological and social consequences of a disease.

One major challenge in this concern is related to the comparison of professional and patient perspectives on patient QoL. As reviewed by Sprangers and Aaronson (1992), professionals are poor judges of patient QoL. Moreover, professionals consistently rate patient QoL as poorer than patients do. For these reasons, it is necessary to take into consideration QoL assessment as it has become an important goal of treatment and marker of success in health care interventions in chronic diseases generally. In many disorders, health interventions will have little impact on mortality statistics but great potential for reducing disability and increasing QoL (McGee, 2001).

In the context of chronic diseases research, to measure “quantitatively" the "qualitative" aspects of life, it is necessary to take into consideration only the aspects of life that are health-related, therefore pertinent to his mission and modifiable by his interventions. To date, health-related quality of life, technically defined as health-related quality of life (HRQOL), is studied as a primary or secondary outcome as it is an important measure to evaluate the impact of a disease and the effects of medical intervention, thus, an improvement in HRQOL is considered to be an essential primary outcome and determinant of therapeutic benefit (Staquet et al., 1998). In addition, information on the impact of chronic diseases on HRQOL can make health services more patient-centred providing information about patient’s voice. Considering that the number of people with chronic diseases is increasing, it is necessary for them to improve their HRQOL. The goal can be achieved through intervention specifically designed by researchers with the aim of strengthen public health actions to manage chronic disease (Devins et al., 1983). They may include different programs involving exercise programs, relaxation training, health education, stress and self-management (Molzahn, 2006; van Elderen, 1995).

To sum up, QoL is inherently a dynamic, multilevel and complex concept, reflecting objective, subjective, macro-societal and micro-individual, positive and negative influences which interact (Lawton et al., 1991). On the other hand, HRQOL is a multidimensional construct encompassing physical, psychological, and social functioning domain that are affected by one's disease and/or treatment (Sprangers, 2002). Finally, integrated patient treatment should include a lot of specialties in order to achieve the enhancement of HRQOL in patients with chronic disease.

1.3 Quality of life in relation to osteoporosis and vertebral fractures

As already stated above, with population aging with an increased life expectancy, people are now living longer and are becoming increasingly susceptible to non-communicable diseases, in particular musculoskeletal disorders (Hoy et al., 2010). Patients with musculoskeletal disorders experience loss of mobility, of independence and higher mortality rates. As a consequence, all musculoskeletal disorders have a significant impact on patients' health-related quality of life (Xie et al., 2016; Abimanyi-Ochom et al., 2015; Tarride et al., 2016; Al-Sari et al., 2016). By measuring QoL, clinical evolution and functional changes can be predicted, as well as understanding the conditions that will lead to developing better osteoporosis treatments, thereby improving patient health, reversing bone loss and reducing the risk of fractures (Madureira et al., 2012). Therefore, improvement of QoL should be one of the priorities of any intervention to prevent and treat musculoskeletal disorders in the ageing population (Beaudart et al., 2018). Osteoporosis is the most prevalent metabolic bone disease in older people and has been shown to have an adverse effect on QoL as well as physical health in women (Park, 2018).

In people 65 years and older, the increase in incidence of osteoporotic fractures is accompanied by grim effects on disability and mortality. Consistent with this, an increasing economic and societal burden in the context of population aging and increased life expectancy, inevitably occurs. Worse still almost all patients remain undiagnosed and untreated, especially high-risk patients (Alejandro et al., 2018).

For these reasons, measuring bone density and investigating the effect of interventions aimed at improving it with different modalities, should be part of the regular risk evaluation for prevention and treatment of osteoporosis and related fractures. However, there is still limited information in this regard, especially in terms of fracture incident proportions in postmenopausal women (Cranney et al., 2007, Cipriani et al., 2018).

The main consequences are hip and vertebral fractures, which can lead to the greatest activities of daily living limitation, by causing pain, physical function and mobility reduction, thus adversely affect QoL. In addition, low mood, depression and social isolation can often result. As in other important chronic conditions, assessing health-related quality of life as an outcome measure is becoming increasingly important in health services research and in clinical trials (Morris et al., 2001). Nowadays it is widely known that PA can improve the overall QoL and, among women with osteoporosis, it may contribute also to increasing self-esteem and social life (Koevska et al., 2019). Regarding the effects of physical function on QoL in patients with vertebral fractures, in spite of the limited evidence highlighted by Gibbs et al., some preliminary findings indicate a positive relation (Gibbs et al., 2019).

A recent study by Stanghelle et al., 2019, aimed to examine the independent associations between HRQOL, physical function and pain in older women with OP and vertebral fracture, showed that pain and walking speed were, independently of one another, associated with HRQOL. These findings can inform clinicians and health managers about the importance of pain management and exercise interventions in health care for this group. The authors concluded that future research should address interventions targeting both physical function and pain with HRQOL as an outcome (Stanghelle et al., 2019).

1.4 Adapted Physical Activity

Adapted physical activity (APA), is defined by the International Federation of Adapted Physical Activity (IFAPA), as a "*professional branch of kinesiology / physical education / sport & human movement sciences, which is directed toward persons who require adaptation for participation in the context of PA".* From a sport science perspective, "*Adapted physical activity science is research, theory and practice directed toward persons of all ages underserved by the general sport sciences, disadvantaged in resources, or lacking power to access equal PA opportunities and rights*". APA services and supports are provided in all kinds of settings. Thus, research, theory and practice relate to the needs and rights in inclusive as well as separate APA programs (Sherrill et al., 2008).

In Italy, the concept of APA emerged starting from the 2000s, in order to promote physical activity and improve health for people with chronic conditions. These kinds of initiatives were in response to the Italian health scenario, which has seen an increase in chronic condition patients due to the progressive increase in the aging of the population. Italy recognizes the situation as a health emergency and acknowledges that exercise is a fundamental prevention tool for these pathologies. Starting in Tuscany, the APA trend has now spread to other regions. APA, understood in this way, includes exercise programs, carried out in groups, specifically designed for subjects suffering from chronic diseases already stabilized, aimed at lifestyle modification, tertiary prevention of disability, maintenance of residual motor activities and favouring social integration. It is important to stress that APA differs from rehabilitation, because it is a community based program not provided by health care services aimed at patients suffering from stabilized diseases (Weinrich et al., 2014). APA is a tool that allows the maintenance of recovered motor activities following rehabilitation. The spread of APA programs has led to the request for trainers adequately trained for this role. In fact, a key role in establishing and maintaining the success of exercise is that of the trainers that manage APA sessions.

Key facts about Adapted Physical Activity in Italy:

- APA is based on standardised exercise programs designed for people with chronic diseases (e.g. low-back pain, Parkinson’s disease, osteoarthritis);
- APA can also be function-oriented instead of disease-oriented (classes are homogeneous for functional capacity but not for diagnosis);
- APA are middle-low impact programs, adapted to the functional capacity of the participants and aimed at improving postural alignment, endurance, muscle strength and relaxation, motor coordination, and ergonomic education;
- APA is promoted but not provided by the Regional Health Services (participants pay a small fee).

1.5 The role of the trainer

In the world of healthcare, it has been understood that a patient-centered communication approach is a powerful tool in the care system. By now the only technical-scientific skills are not enough, the service to the person requires particular attention also to the interpersonal dimension. It has been understood that the patient, or the person in general, is the "best expert of his own illness, or of his own body" so must be listened to, consulted and must become, thanks to us who interact with him, aware and therefore protagonist. In fact, the QoL of people with chronic diseases can also be improved through good communication during the course of activities, under the supervision of the trainer/educator who accompanies the person in achieving greater awareness of his body, greater safety during the execution of exercises, and re-acquisition of autonomy in daily activities. In this regard, the "communicative relational skills" such as active listening and empathy are essential in learning to understand each other and understand their feelings and fears by establishing a relationship of trust and reliability. Active listening is different from hearing: the latter occurs through the auditory system whereas listening is a psychological aspect that requires a particular capacity for understanding. Empathy, on the other hand, what is meant is the ability to empathize with the condition of another person (to put oneself in the other's shoes) and to feel oneself in the situation of the user and therefore to be able to better assist and support. Emotional intelligence, as mentioned above, also includes skills such as: memorization of case histories of patients and their names; monitoring of feedback during the execution of interventions; transmitting and sharing useful skills and tips to achieve awareness of the body first and autonomy afterwards (Goleman, 2011).

For this purpose, the key role is held by the trainers of exercise. Their function is so important especially when dealing with people suffering from chronic condition. As they do not only occupy the role of exercise experts for chronic disease but also an educational, relational and support role. In fact, in addition to the dosage of APA there are other aspects to which to pay attention as the relational and communicative aspects. From a practical point of view, the trainer seeks to manage an APA lesson according to the principles described above. During the initial sessions, the trainers should propose precautions to be taken in everyday life (lie down and get up from the ground and from the bed, get up / lie down in bed, tie the shoes, collect objects from the ground). The trainers specified and controlled, the right posture, breathing and activation of the core, for each the exercise. Moreover, during the administration program, the following principles were envisaged: keep individual case histories in mind, trying to make persons comfortable through active listening, by announcing the program of each lesson and explaining the objectives of the exercises of every phase. Once you have identified the general level of fitness, aim every time to standardize the motor learning background. It is essential to perform the exercises by placing the emphasis on the knowledge of your body and the answers gradually obtained during the movement. In fact, through feedback it is possible to educate people to self-correction. All this is necessary to achieve motor autonomy: to know each other, to acquire and to correct oneself. As the motor task becomes more and more complex, it is therefore necessary to make people aware that they are working in safety by continuously monitoring their responses. This will then allow the patient, to rely on and establish a relationship of trust that goes to mitigate the fears and hesitations that often affect the benefit of the activity. During the cool down phase, it is important to maintain the education of body awareness, also collecting the final sensations on the activities carried out, in order to reacquire autonomy and active self-management. After all, the protocol foresees 3 stages of progression in relation to the improvement and evolution of the abilities achieved by the individual subjects.

Trainers are the figure that can make the difference as they have the task of caring for people with chronic conditions, making them feel safe and at ease, understanding them empathically, transmitting the fundamental principles of the exercise so as to make them autonomous. Their educational task is fundamental in the post-acute maintenance phase, as they constitute the last link in the care system that can lead to a change in lifestyle. Furthermore, the success of the exercise program also depends on how the gym is managed and conducted: a positive environment, in which people feel at the centre of, can make the difference.

2. Osteoporosis

"Our skeleton is formed before we are born, supports us throughout our lives, and can remain long after we die. Regardless of age, gender, race, nationality, or belief set, we all have one. Yet this essential organ is so often taken for granted".

World Osteoporosis Day Report 2015 (Cooper et al., 2015)

2.1 Introduction

Among the chronic diseases, osteoporosis is called the "silent" one. OP, literally porous bone, is a disease in which the density and quality of bone is reduced. As bones become more porous and fragile, the risk of fracture rises. Bone loss resulting in bone fragility was thought to occur through distinct mechanisms leading to primary and secondary osteoporosis (Bilezikian et al., 2018). Primary OP can be of two major types: postmenopausal osteoporosis and age-related or senile osteoporosis (Eastell et al., 1987). On the other side, secondary OP is caused by a number of disorders and drugs (Rossini et al., 2016). Independent of age or estrogen deficiency, secondary causes of OP are very common and represent the collection of heterogeneous underlying diseases and medications that may contribute to bone loss and increase bone fragility particularly in premenopausal women and in men with OP. However, they have also an impact in accelerating bone loss in postmenopausal and age-related osteoporosis. Fortunately, some author stated that a number of these secondary causes may also be treatable and thus reversible (Painter et al., 2006; Mirza et al., 2015).

Bone loss is an inevitable consequence of aging in both women and men (Orwoll et al., 2013). Despite the increase in knowledge due to the public health burden caused by OP, the disease is not frequently detected or treated in men. Moreover, guidelines for the evaluation of osteoporosis in men are not well validated (Watts et al., 2012). However, recommendations have recently emerged and studies of OP in men has revealed male–female differences that have contributed to better understand bone biology in general (Adler, 2018). As in women, aging is associated with large changes in bone mass and architecture in men though, the magnitude of these changes is less than those in women (Seeman, 2002). In general, the pattern of age-related bone loss is similar in both genders, but in men the rate of loss is slower and obviously, there is no accelerated phase of bone loss associated with the menopause.

2.2 Bone biology

Bone tissue is a dynamic structure, which in the course of life undergoes constant modifications, collectively called "bone remodelling". Fundamental characteristics of the bone are strength and density, essential to provide support for the body and protection of vital organs; despite this, it also has a certain elasticity, able to allow the body to respond to trauma and movement without incurring injuries. Bones act also as a storage area for minerals, indeed it is an important reserve of minerals and ions, such as Calcium, Sodium, Magnesium, Potassium, necessary for tissue homeostasis; ultimately, it is the site of hematopoiesis, hosting, as far as the long bones are concerned, the bone marrow. It is a richly vascularized tissue and receives approximately 10% of cardiac output (Bilezikian et al., 2018). Our bones consist of two types of tissue: cortical bone the hard-outer layer, also known as compact bone due to its strong and dense nature and cancellous bone or trabecular bone, the spongy inner network of trabeculae, lighter and more flexible than the first one. In addition to osteoid (the unmineralized, organic portion of the bone matrix which forms prior to the maturation of bone tissue) and inorganic mineral salts deposited within the matrix, cells are present. They are responsible for both phases of bone remodelling process: formation (osteoblasts and osteocytes) and resorption (osteoclasts) (IOF, 2017). The osteoblasts derived from mesenchymal stem cells and are responsible for bone matrix synthesis and its subsequent mineralization. The osteocytes are osteoblasts that become incorporated within the newly formed osteoid, which eventually becomes calcified bone. Situated deep in the bone matrix, they are thought to be ideally situated to respond to changes in physical forces upon the bone and to transduce messages to cells on the bone surface, directing them to initiate resorption or formation responses. Finally, the osteoclasts which are large multinucleated cells, like macrophages, derived from the hematopoietic lineage. Their function in the resorption of mineralized tissue begins with the secretion of bone-resorbing enzymes which digest bone matrix.

The structural integrity of bone is maintained throughout life, so that most of the adult skeleton is replaced about every 10 years, by the process of bone remodelling, illustrated in Figure 1.

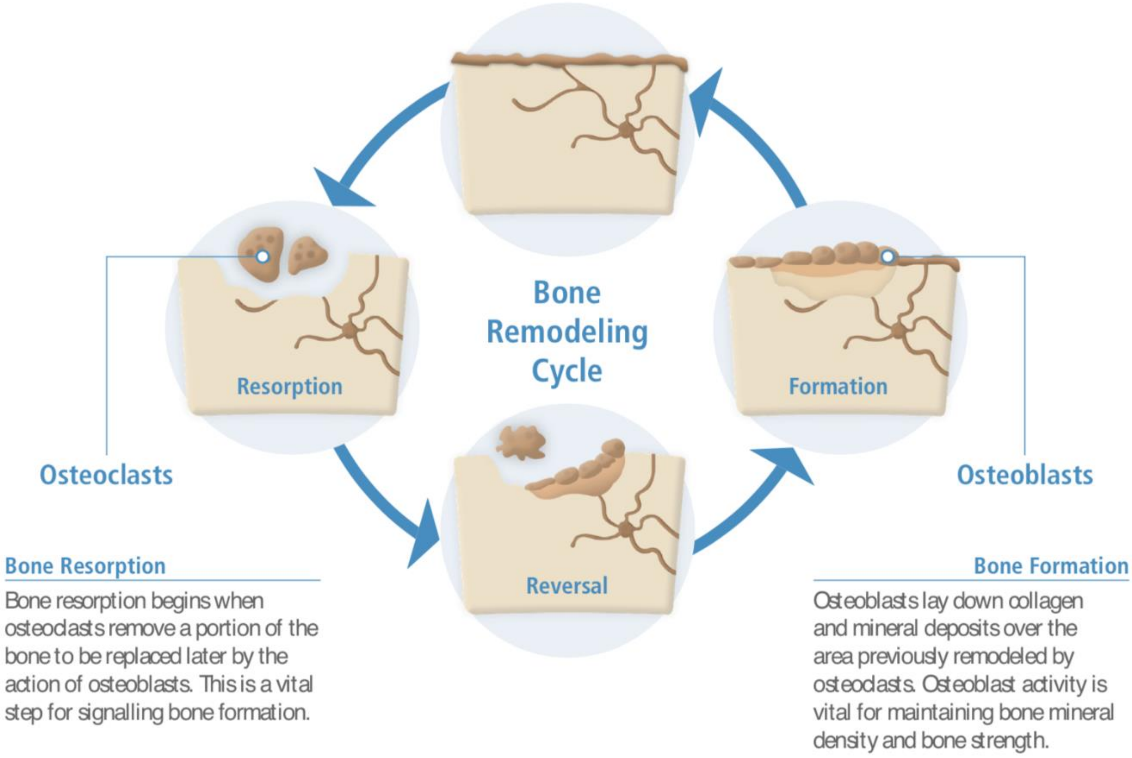


Figure 1. Bone renewal through the bone remodelling cycle (From IOF Compendium, 2019)

As already stated above, our skeleton is a considerably active living tissue composed of different types of cells, blood vessels, proteins and minerals. The size and the amount of bone within our skeleton, changes significantly throughout life. Indeed, at birth, our skeleton is composed of 300 soft bones which are transformed during childhood and adolescence into hard bones, whereas, given that some bones fuse during the developmental process, the adult skeleton has 206 bones. Around mid-twenties, males and females have achieved the peak bone mass after which a gradual decline into old age occurs in men, while in women occurs a plateau followed by an accelerated period of bone loss for several years after the menopause (Figure 2).

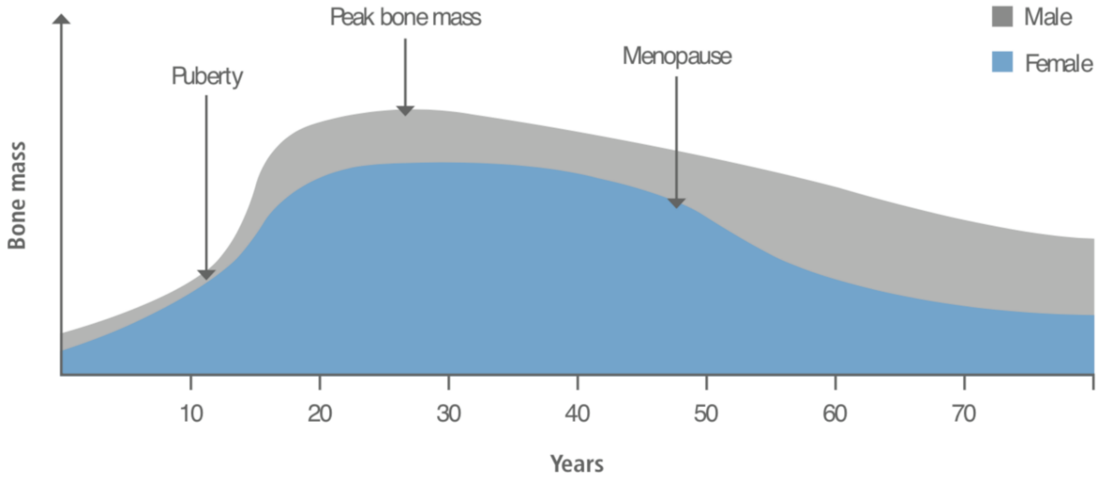


Figure 2. Bone mass throughout the life cycle (From IOF Compendium, 2019)

According to Cooper et al., the main objectives for good bone health at the various stages of life are (Cooper et al., 2015):

- Children and adolescents: Achieve genetic potential for peak bone mass;
- Adults: Avoid premature bone loss and maintain a healthy skeleton;
- Seniors: Prevent and treat osteoporosis.

2.3 Epidemiology

As already mentioned the process of bone loss occurs silently and progressively. Often there are no symptoms until the first fracture happens (IOF, 2019). Osteoporosis is a very common condition. The number of individuals aged ≥50 years at high risk of osteoporotic fracture, worldwide in 2010, was estimated at 158 million and it is expected to double over the next 40 year (Odèn et al., 2015). It is estimated that 75 million people in Europe, USA and Japan are affected by OP (Kanis, 2007). Among the population aged over 50 years, one out of three women and one in five men will experience a fragility fracture which impose a substantial burden on individuals who suffer them, their careers and family members. Moreover, a correlation subsists between the number of fractures an individual suffers and decline in physical function and health-related quality of life (HRQOL) (Papaioannou et al., 2009; Borgstrom et al., 2013). Kerr et al., stated a fracture event is followed by a cycle of impairment, as illustrated in Figure 3 (Kerr et al., 2017).

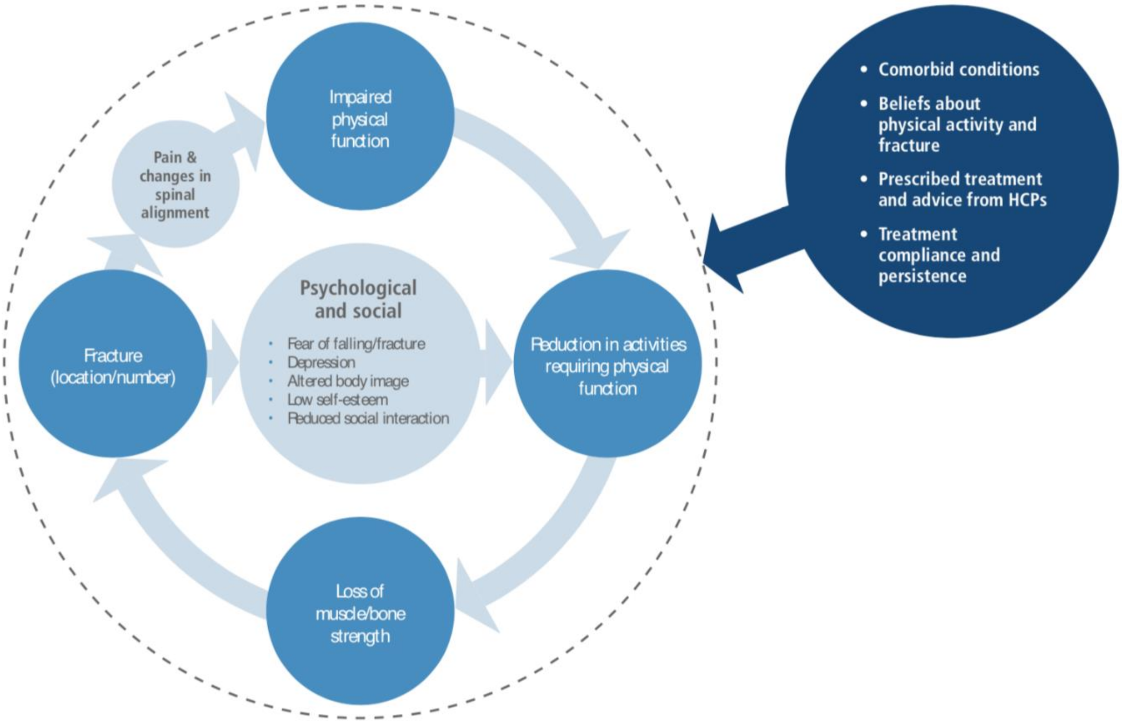


Figure 3. The cycle of impairments and fracture in osteoporosis (From Kerr et al., 2017)

Worldwide, OP is estimated to affect 200 million women - approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-thirds of women aged 90 (Kanis, 2007). In Italy, according to Cipriani et al., more than 50% of postmenopausal women aged 50 and older, has osteoporosis (Cipriani et al., 2018).

The International Osteoporosis Foundation (IOF) reports that at the turn of the century, 9 million fragility fractures occurred annually. This included 1.6 million hip fractures which impose a devastating burden on sufferers and their families, and all too often result in premature death. The 1.4 million individuals who sustained vertebral fractures endure back pain, loss of height and many other adverse effects on the quality of their lives. In addition, the cost that OP imposes on healthcare budgets is staggering. In 2010, European Union countries spent Euro 37 billion (US$40 billion), while in 2015 the United States spent US$20 billion (IOF, 2019). Table 4 shows epidemiological key statistics for six European countries (IOF, 2018).

Table 4. OP epidemiology: facts and statistics for six European countries

	EU6	France	Germany	Italy	Spain	Sweden	UK
Estimated number of individuals aged 50+ with osteoporosis in 2015	20 million	3.8 million	5.3 million	4 million	2.8 million	500 000	3.5 million
Prevalence of osteoporosis among men (♂) and women (♀) aged 50+ in 2015	N.A.	♂6.9% ♀22.7%	♂6.7% ♀22.5%	♂7.0% ♀23.1%	♂6.8% ♀22.5%	♂6.9% ♀22.5%	♂6.8% ♀21.8%
Estimated lifetime risk of hip fracture from men (♂) and women (♀) aged 50	♂ 6.1 - 13.7% ♀9.8 - 22.8%	♂6.0% ♀11.0%	♂9.8% ♀17.7%	♂7.9% ♀16.7%	♂9.0% ♀10.0%	♂13.7% ♀22.8%	♂8.3% ♀17.2%
Incidence of fragility fractures per year in 2017	2.7 million	382 000	765 000	563 000	330 000	120 000	520 000
Estimated increase in fragility fractures incidence 2017 - 2030	+23.0%	+24.4%	+18.5%	+22.4%	+28.8%	+26.6%	+26.2%
Fracture-related costs in 2017 (€)	37.5 billion	5.4 billion	11.3 billion	9.4 billion	4.2 billion	2 billion	5.3 billion
Estimated cost increase 2017 - 2030	+27.0%	+26.0%	+23.3%	+26.2%	+30.6%	+29.4%	+30.2%
Sick days taken by working individuals due to fragility fractures	7.6 million	1.5 million	1.4 million	717 000	355 000	1.1 million	2.6 million
Hours of care after a hip fracture, per 1000 individuals, per year	370 h	138 h	N.A.	882 h	756 h	191 h	248 h
Treatment gap (women who do not receive treatment after a fracture)	60 - 85%	85%	60%	77%	72%	83%	49%
Fracture liaison services (FLS) improves outcomes	+24% BMD testing -5% re-fracture rate		+22% treatment adherence -3% mortality			+20% treatment initiation	
N.A. = not available							

Note: From *International Osteoporosis Foundation: Broken bones, broken lives: a roadmap to solve the fragility fracture crisis in Europe* 2018

Key points about Osteoporosis in Italy (From Marcellusi et al., 2020)

- Overall, the economic burden associated to the OP patients in Italy was equal to €2.2 billion from the NHS and social security system perspective;
- Approximately 80% (€1.8 billion) of the total economic burden was associated to hospitalisation costs (63% related to hospitalisations due to fractures, 37% to hospitalisations due to other causes), 16% (€351 million) to pharmacological treatments cost, 3% (€71 million) to ambulatory visits and 1% (€13 million) to social security cost;
- The average annual hospitalisation cost per patient with severe osteoporosis (subjects aged ≥ 45 years with OP in primary or secondary diagnosis and with a fracture, the subjects aged ≥ 45 years with two fractures and those aged ≥ 45 years with three or more fractures.) was €12,336 (+ 44% if compared to non severe patients €8591).

Being a multifactorial disease, it is influenced by many factors which determine the individual's propensity to develop osteoporosis and suffer the fragility fractures it causes. Table 5 shows the main risk factors for OP and fracture (Rossini et al., 2016; IOF, 2017). Some of these factors are non-modifiable, while others can be avoided or ameliorated. From the perspective of the patient or their physician, as in all things, knowledge is power (IOF, 2018).

Table 5. Risk factors for osteoporosis

Fixed risk factors
• Age
• Female gender
• Ethnicity
• Family history of osteoporosis
• Early menopause (before the age of 45 years)
• Oestrogen deficiency and amenorrhea
• Height loss
• Prior fragility fracture (particularly spine, including morphometric fractures, wrist, hip and humerus)
Modifiable risk factors
• Cigarette smoking (current)
• Alcohol intake (3 or more units per day)
• Vitamin D deficiency
• Low physical activity
• Prolonged immobility
• Low dietary calcium intake
• Eating disorders
• Osteoporosis-associated diseased
• Low body mass index
• Frequent falls

Note: Adapted from *International Osteoporosis Foundation: Broken bones, broken lives: a roadmap to solve the fragility fracture crisis in Europe.* 2018 and *Guidelines for the diagnosis, prevention and management of osteoporosis. Rossini et al. 2016*

2.4 Diagnosis

The objectives of bone mineral measurements are to provide diagnostic criteria, prognostic information on the probability of future fractures, and a baseline on which to monitor the natural history of the treated or untreated patient (Kanis et al., 2019). Bone mineral density (BMD) is the amount of bone mass per unit volume (volumetric density), or per unit area (areal density), and both can be measured in vivo by densitometric techniques. A wide variety of techniques is available to assess bone mineral (John Wiley & Sons, 2013). The most widely used are based on X-ray absorptiometry in bone, particularly dual energy X-ray absorptiometry (DXA). Other techniques include quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the appendicular skeleton and to the spine, peripheral DXA, digital X-ray radiogrammetry, radiographic absorptiometry and other radiographic techniques. DXA is the most widely used bone densitometric technique. It is versatile in the sense that it can be used to assess bone mineral density/bone mineral content of the whole skeleton as well as specific sites, including those most vulnerable to fracture.

In 1994, the World Health Organization (WHO) established four general operational categories relating to BMD in postmenopausal women, principally for epidemiological classification, but which have become regarded as clinical diagnostic categories for OP summarized in Table 6 (WHO, 1994):

- Normal: A value for BMD within 1 standard deviation (SD) of the young adult reference mean, subsequently referred to as a T-score < -1;
- Low bone mass (osteopenia): A value for BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value, subsequently referred to as a T-score in the range -1 to -2.5;

- Osteoporosis: A value for BMD 2.5 SD or more below the young adult mean, subsequently referred to as a T-score < -2.5;
- Severe osteoporosis (established OP): A value for BMD more than 2.5 SD below the young adult mean in the presence of one or more fragility fractures.

Table 6. Summary of Diagnostic criteria

Status	**Femoral neck BMD T-score (SD)**
Normal	-1 and above
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or lower
Severe Osteoporosis	-2.5 or lower and presence of at least one fragility fracture

Note: From *International Osteoporosis Foundation. 2018*

Regarding fracture risk assessment, it is recommended to combine BMD with clinical risk factors for fracture (e.g. previous fracture, chronic glucocorticoid therapy, advancing age) instead of using BMD or clinical risk factors alone (Kanis, 2007). For this reason, fracture risk assessment tools such as FRAX (Kanis et al., 2011) and the Garvan Fracture Risk Calculator (Garvan Institute, 2011), have been developed for use in clinical practice. These tools can provide helpful information for making clinical decisions and may be incorporated into treatment guidelines (Leslie et al., 2014). Considering that fracture risk approximately doubles for every SD decrease in BMD, and that vertebral fracture are the most common type of fragility fracture, with only about one-third being clinically recognized (Cooper et al., 1993), assessment is highly important (Marshall et al., 1996; Bilezikian et al., 2018).

2.5 Vertebral Fractures

Vertebral fracture is the most common and usually the first osteoporotic fracture to occur, being present in 15% of women aged 50 to 59 years, 15% of men aged 69 to 81 years, and 50% of women aged more than 85 years (Melton et al., 1993; Karlsson et al., 2016). Due to their increasing prevalence with age, and to the fact that they are often asymptomatic, under-diagnosed, and under-treated, accurate recognition of vertebral fracture is essential to clinical evaluation (Kendler et al., 2016). Moreover, proper identification of vertebral fracture is critically important also for research in that over- or under-reporting by an inexperienced reader can significantly skew research findings (Li et al., 2009). Despite the clear importance of vertebral fractures identification, they remain underdiagnosed in clinical practice (Delmas et al., 2005). This may depend on the fact the typical clinical symptoms of back pain and restricted movement are usually attributed to degenerative change (Cooper et al., 1992). Furthermore, many vertebral fractures evident on imaging are not reported by radiologists and clinicians (Lenchik et al., 2004). In addition, it is recommended to avoid ambiguous terminology (eg, “vertebral collapse,” “compressed vertebral body,” “loss of vertebral height,” “wedging of vertebral body,” “wedge deformity,” “biconcavity,” or “codfish deformity”), or used in conjunction with the term “vertebral fracture” (Bilezikian et al., 2018).

Over the age of 50 years, fracture incidences in women begins to climb steeply, so that rates become twice those in men. This peak was historically thought to be mainly caused by hip and distal forearm fracture, but as Table 7 shows (Svedbom et al., 2013), vertebral fracture, when ascertained from radiographs rather than clinical presentation, can be shown to make a significant contribution (Felsenberg et al., 2002).

Table 7. Impact of osteoporosis-related fractures across Europe (Bilezikian et al., 2018; Svedbom et al., 2013)

Lifetime risk (%)	Hip	Spine	Wrist
Women	23	29	21
Men	11	14	5
Cases/year	620,000	810,000	574,000
Hospitalization (%)	100	2-10	5
Relative survival	0.83	0.82	1.00
Costs: all sites combined Euro 39 billion			

Note: From *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolis. Bilezikian et al. 2018.*

Vertebral fracture risk is 20% in the year following incident vertebral fracture. However, this relative risk is fourfold greater in those with a severe, rather than a mild, fracture and threefold greater in those with multiple, rather than a single, vertebral fracture (Lindsay et al., 2001). Most importantly, vertebral fractures are also associated with reduced QoL, reduced self-esteem, and increased mortality, particularly from pulmonary disease and cancer (Lips et al., 2005). Early recognition of vertebral fracture and appropriate treatment of OP significantly reduces the occurrence of new vertebral and non-vertebral fractures (Ensrud et al., 2011; Kling et al., 2014).

2.6 Prevention

Bones are living tissue, and after birth, the skeleton continues to grow to the end of the teenage years, reaching a maximum strength and size (peak bone mass) in early adulthood, around the mid-20s. It is therefore never too early to invest in bone health. The prevention of OP beginning with optimal bone growth and development in youth, is fundamental (IOF, 2019). Genetic factors play a significant role in determining whether an individual is at an increased risk of OP. However, lifestyle factors such as diet and PA also influence bone development in youth and the rate of bone loss later in life. Giving that, throughout life the size of our skeleton and the amount of bone contained in it changes significantly, International Osteoporosis Foundation identifies the three key objectives for good bone health at various stages of life (IOF, 2015) summarized as follow:

- To achieve genetic potential for peak bone mass for children and adolescents through an adequate calcium intake, avoiding protein malnutrition and undernutrition; maintaining an adequate supply of vitamin D, participating in regular PA, averting the effects of second-hand smoking. The higher the peak bone mass, the lower the risk of OP. Indeed, it has been estimated that a 10% increase of peak bone mass in children reduces the risk of an osteoporotic fracture during adult life by 50% (Bonjour et al., 2009);
- To avoid premature bone loss and maintain a healthy skeleton for adults by adopting a healthy lifestyle including nutritional aspects as for children (adequate calcium and vitamin D intake), and participation in regular PA, avoiding smoke and alcohol;
- To prevent and treat OP for seniors, reducing the burden of consequences starting from ensuring an adequate nutritional intake, prevent falls and improve QoL.

In the broadest sense, the population can be subdivided into two distinct groups with respect to future fracture risk: the primary prevention population related to individuals without a history of fragility fracture and the secondary prevention addressed to individuals with a history of fragility fracture (IOF, 2019).

To date, the International Osteoporosis Foundation Compendium proposes 9 key priorities for the period 2020-2025 (From IOF, 2019):

Priority 1: Secondary fracture prevention

Policymakers, healthcare professional organisations and national OP societies must collaborate to provide Orthogeriatric Services and Fracture Liaison Services to all older people who suffer fragility fractures in their jurisdictions.

Priority 2: Osteoporosis induced by medicines

Where treatments are licensed to prevent OP induced by medicines, and guidelines have been published to inform best clinical practice, OP management must become a standard consideration for clinicians when prescribing medicines with bone-wasting side effects.

Priority 3: Primary fracture prevention

National osteoporosis societies to incorporate messaging regarding self-assessment of fracture risk with FRAX® into public awareness and education initiatives, as advocated in Priority 6. National OP societies to collaborate with healthcare professional organisations for primary care providers (PCPs) to jointly advocate for PCPs to routinely undertake fracture risk assessment when interacting with patients aged 50 years and over.

Priority 4: Nutrition and exercise

Specific initiatives encompassing nutrition and exercise are required for particular age groups:

Expectant mothers: National OP societies to collaborate with national obstetrics organisations to advise government on optimising bone health of mothers and infants.

Children and adolescents: National OP societies to collaborate with government Ministries of Education, national teachers' organisations, national nutrition foundations/ councils, national dietician/nutritionist organisations, government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to educate children and adolescents on achieving their genetic potential for peak bone mass.

Adults and seniors: National OP societies to collaborate with government Ministries for Seniors, national nutrition foundations/councils, national dietician/nutritionist organisations, non- governmental organisations concerned with seniors' welfare and government Ministries of Sport and Recreation, national sports councils and relevant private sector corporations and providers to inform adults on their nutritional and exercise needs to maintain a healthy skeleton, avoid premature bone loss and avoid malnutrition in the elderly.

Priority 5: Healthcare professional education

National OP societies and healthcare professional organisations to collaborate to develop and encourage widespread participation in national professional education programmes designed for 3 distinct audiences: Lead Clinicians in Osteoporosis, orthopaedic surgeons and primary care providers.

Priority 6: Public awareness and education

National OP societies, healthcare professional organisations, policymakers and regulators to collaborate to develop impactful public awareness campaigns which empower consumers to take ownership of their bone health.

Priority 7: Improving access and reimbursement for diagnosis and treatment

OP must be designated a national health priority in all countries, with commensurate human and financial resources to ensure that best practice is delivered for all individuals living with this condition. In countries where the current disease burden is not known, epidemiological studies must be commissioned as a matter of urgency.

Priority 8: Development of national hip fracture registries

In countries without an existing national hip fracture registry, national OP societies, national orthopaedic associations and national geriatric/internal medicine associations to collaborate to develop a business case for a registry and advocate to government for resources to support widespread participation.

Priority 9: Formation of national falls and fracture prevention alliances

In countries without an existing national alliance, national OP societies to initiate dialogue with other relevant non-governmental organisations, policymakers, healthcare professional organisations and private sector companies to propose formation of a national falls and fracture prevention alliance modelled on successful examples from elsewhere. Formation of a national alliance has the potential to facilitate delivery of Priorities 1-8 (IOF, 2019).

2.7 Management of Osteoporosis

Experts have recently highlighted "a crisis in the treatment of osteoporosis" as both prescription and adherence to pharmacotherapy regimes have decreased in recent years (Khosla et al., 2016). Similar trends have been observed for non-pharmacological treatment. Therefore, multicomponent interventions encompassing health education for both clinicians and patients may represent the key factor to improving prescription and compliance rates for OP management (McMillan et al., 2017).

The recent clinical guidelines for the prevention and treatment of OP stated that a global approach is needed in this scenario (Tarantino et al., 2017; Compston et al., 2017; Kanis et al., 2019). The idea is increasingly supported by clinical evidence, particularly for chronic conditions. Indeed, a patient-centered approach encompassing a partnership between health professionals and patients is fundamental to a successful disease's management (Kerr et al., 2017).

Crucially, health care systems should be structured to meet the needs of chronic disease patients in terms of their preferences, values, and expectations (Harkness et al., 2005; Davis et al., 2005). For those with chronic conditions, such as OP, it means giving them an opportunity to understand their condition and the skills needed to optimize the time they invest in maintaining good health. People with chronic diseases, including OP, require a global approach to achieve better care. The management of OP and fragility fractures, which are the most serious complications of the disease, must be multidisciplinary and comprehensive. The basic components of the comprehensive approach are nutrition, PA, behavioural interventions and/or pharmacological treatment in individuals with osteoporotic fractures or those at high risk for fractures according to the fracture liaison service strategy (Yates et al., 2015). This approach is useful at all disease stages, from primary prevention in childhood and adolescence through subsequent ages and stages (where the aim is to achieve and maintain optimal peak bone mass and strength), right up to the tertiary prevention of elderly subjects with fragility fractures in order to counteract functional and structural regression (grade A recommendation) (WHO global report).

2.8 Therapeutic strategy: pharmacological treatment

Pharmacological treatments are prescribed to decrease the risk of fragility fractures. Many drugs with different mechanisms of action have been approved for the prevention and treatment of OP, are effective and available worldwide. These medications must be used in conjunction with calcium and vitamin D supplements, recommended lifestyle changes, adequate nutrition and PA. Pharmacological treatments can be divided into two categories:

- Anti-resorptive agents, which include oestrogen, selective oestrogen receptor modulators (SERM), bisphosphonates and denosumab, reduce bone resorption (and subsequently bone formation), preserving BMD;
- Anabolic agents, which include teriparatide (PTH1-34), romosozumab and abaloparatide (34 amino acid synthetic analogue of parathyroid hormone-related protein (PTHrP) stimulate bone formation (and subsequently bone resorption), thereby increasing BMD.

According to the International Osteoporosis Foundation, the commonly available treatments are: Bisphosphonates, Denosumab, Anabolics, Hormone Replacement Therapy (HRT), Selective oestrogen Receptor Modulators (SERM). As a side note Calcitonin is not considered a first-line therapy as well no longer available in Europe, due to its limited anti-fracture efficacy relative to other available agents (Overman et al., 2013). Concerning Strontium Ranelate agent, it has modest evidence of efficacy but it is almost unavailable in Europe and USA (Marie, 2006; IOF, 2020).

To date, Bisphosphonates (BP) are considered first-line therapy for postmenopausal women with OP due to their favorable benefit to harm balance and low cost (Bilezikian et al., 2018). BP are synthetic compounds that have high affinity for calcium crystals, concentrate selectively in the skeleton, and decrease bone resorption. The first BP was synthesized in the 19th century but their relevance to medicine was recognized in the 1960s, and they were first administered to patients with OP in the early 1970s. Currently, alendronate, ibandronate, risedronate, and zoledronic acid are approved for the treatment of OP worldwide, while other BPs are also available in some countries (IOF, 2020).

Drugs are available for oral (daily, weekly, monthly dosing) or parenteral (subcutaneous, intravenous) administration, some with dosing intervals of 6 months or longer, which many patients find to be very convenient and which improve short-term persistence with therapy.

In the absence of contraindications, Denosumab (Prolia; Amgen, Inc., Thousand Oaks, CA, USA), a fully human monoclonal antibody that inhibits the receptor activator of RANKL, is considered a second-line therapy (after bisphosphonates) in most countries. Additionally, it has been approved in men for the treatment of bone loss with hormone ablation therapy for prostate cancer (Costa et al., 2015). Usually, Denosumab is administered by subcutaneous injection every six months. However, it is contraindicated in people with hypocalcemia, and sufficient calcium and vitamin D levels must be reached before starting on denosumab therapy. With BP and denosumab, protection from fractures persists as long as therapy is administered (IOF, 2020).

Teriparatide, recombinant 1-34 N-terminal fragment of human parathyroid hormone, is an effective stimulator of bone formation when administered intermittently. By activating bone remodelling, it stimulates the formation of new bone, particularly in the trabecular compartment where the structure and strength are substantially improved. In general, these drugs are quite well tolerated with few serious safety concerns. The combination of Teriparatide and Denosumab increases hip and spine BMD more than either drug alone and results in improved cortical micro-architecture and greater estimated bone strength at the distal radius and tibia. Furthermore, the initial use of an anabolic agent followed by an antiresorptive drug provides the largest net increases in bone mass of any sequential approach and this strategy should be strongly considered in patients with severe disease in whom the eventual use of anabolic agent is likely. Conversely, the specific transition from Denosumab to Teriparatide seems to be associated with highly accelerated bone turnover and rapid bone loss, thus should be avoided in patients with significant skeletal fragility (Finkelstein et al., 2010; Tsai et al., 2013).

Another anabolic agent is Romosozumab: a humanized monoclonal antibody against Sclerostin, which is a secreted protein by the osteocyte, as well as bone formation inhibitor. Romosozumab (210mg every month administered by subcutaneous injection) has been shown to increase bone formation and decrease bone resorption (Padhi et al., 2011). At year 1, it reduces the incidence of new vertebral fractures and clinical fractures by 73% and 36%, respectively (Cosman et al., 2016). Similar to Denosumab, Romosozumab effects are reversible when the treatment is stopped, hence the therapy will need to be administered in sequence with an anti-resorptive (IOF, 2020).

In postmenopausal women with OP, the primary outcome investigated in clinical trials is the reduction of fracture. Treatments have been shown to reduce the risk of hip fracture up to 40%, vertebral fractures by 30-70% and some compounds reduce the risk for non-vertebral fractures up to 30-40%. Table 8 shows, from randomized controlled trials, the anti-fracture efficacies of the most frequently used treatments approved for postmenopausal OP (Cramer et al., 2007; IOF, 2019)

Table 8. Anti-fracture efficacy of osteoporosis treatments (IOF, 2019)

	Effect on vertebral fracture	Effect on non-vertebral fracture	Effect on hip fracture
Alendronate	+	+	+
Risedronate	+	+	+
Ibandronate	+	-	-
Zoledronic acid	+	+	+
Hormon Replacement Therapy	+	+	+
Raloxifene / Bazedoxifene	+	-	-
Teriparatide	+	+	-
Abaloparatide	+	+	-
Denosumab	+	+	+
Romosozumab	+	+[1]	+[1]

+ significant reduction of fracture in randomized placebo-controlled clinical trials (RCTs) of variable duration (18 months to 6.8 years)
- not demonstrated in primary RCTs
+1 in sequence with alendronate vs alendronate alone
Note: results from subgroup and post-hoc analyses or meta-analyses have not been considered
Note: From *International Osteoporosis Foundation Compendium of Osteoporosis, Second Edition. 2019*

2.9 Non-pharmacological treatment: Physical Activity

Physical activity can improve bone health during childhood and adolescence, while in the adulthood attenuate bone loss, increase or preservation of muscle mass, strength, and power, and the reduced the risk of falls, all of which may reduce fracture risk. Therefore, exercise is believed to be the most fundamental non-pharmacological treatment for delaying the outbreak of osteoporosis and facilitating the healing of fall-related fractures (Agostini et al., 2018). Given the decreasing of physical activity practice among elderly, emphasis on exercise is crucial especially for people more prone to osteoporosis.

However, although PA contributes to osteogenesis as reviewed by Benedetti et al., not all exercise modalities are effective at improving all fracture risk factors (Benedetti et al., 2018).

Indeed, there are different types of exercise that lead to vitalization. Admittedly, for patients with spine disorders such as vertebral fractures, multicomponent exercises appear to be the most effective (Gibbs et al., 2019). More importantly, although exercise may prevent osteoporosis, safe exercise is crucial especially for individuals with fractures (Sinaki et al., 2012; Sinaki et al., 2013).

A fundamental principle in exercise physiology is specificity; physiological adaptations are closely coupled to the type, intensity, and volume of exercise, or, that exercise should be tailored to the desired outcome. To be most effective at reducing both fall and fracture risk, exercises' type and doses must be informed by high-quality evidence and most importantly, tailored to an individual's needs and therapeutic goals (Bilezikian et al., 2018). As stated in the new WHO Guidelines on Physical Activity and Sedentary Behaviour, there is high certainty evidence that higher levels of PA that combines balance, strength, gait, and functional training (e.g. multicomponent physical activity) are associated with a reduced rate of falls and risk of injury from falls in older adults. Furthermore, there is moderate certainty evidence that programmes involving multiple exercise types may have significant effects on bone health and OP prevention (WHO, 2020). Indeed, clinical practice guidelines recommend exercise as a strategy to manage osteoporosis and reduce the risk of fractures (Beck et al., 2017; Giangregorio et al., 2014). Based on the current evidence, exercise programs targeting OP, multiple fall and fracture risk factors in adults should be multimodal in design, including a combination of moderate to high-intensity progressive resistance training, weight-bearing impact, and functional balance and mobility training (Zhao et al., 2015). A summary of the key recommendations is presented in Table 9 (Bilezikian et al., 2018).

Table 9. Exercise prescription recommendations to the prevention and management of osteoporosis, falls and fractures

Type	**Frequency**	**Intensity**	**Dose**	**Exercises/Precautions**
Progressive resistance training	≥2 days per week	Start with slow and controlled movements Progress to 70–85% of 1-RM (5–7/8 on Borg 0–10-point RPE scale or hard/very hard) Consider progressing to high-velocity resistance and functional training for lower extremities to improve muscle power (light to moderate loads, 30–70% of 1-RM)	≥8 exercises 2–3 sets 8–12 repetitions 1–3-minute rest between sets	Exercises: squats, lunges, hip abduction/ adduction, leg press, thoracic/lumbar extension, plantar/dorsiflexion, abdominal/postural exercises, lateral pulldown/bent over row, wall/ counter/floor push up, triceps dips, and lateral shoulder raises Emphasize exercises performed in standing (weight bearing); clinical judgment is needed regarding the safety of lifting weights higher than shoulder height; use spine sparing strategies to avoid spine flexion or twisting
Weight-bearing impact exercise	4–7 times per week	Moderate to high impact activities (>2–4 BW), as tolerated Increase height of jumps, add weights/weighted vest, change direction of movements For sedentary or moderate/ high-risk individuals, start with low impact exercises (see precautions)	50–100 jumps per session (3–5 sets, 10–20 repetitions) 1–2-minute rest between sets For high-risk individuals, aim to progress to 50 repetitions or as part of short bouts (≥10minutes) of weight-bearing exercise	Multidirectional activities: jumping, bounding, skipping, hopping, bench stepping, and drop jumps It is advisable that moderate/high-risk individuals perform low impact only, or progress impact magnitude and direction with caution
Challenging balance/ mobility	Accumulate at least 2–3 hours per week of activity that	Must be challenging (close to limit of balance)	Incorporate into daily activities or combine with PRT or	Include static and dynamic movements: reduce base of support, shift weight to limits of stability (eg,

	includes challenging balance activities		impact exercise (eg, balance for 10–30 seconds while waiting for kettle to boil)	leaning/ reaching), perturb center of mass, stepping over obstacles, alter surface (foam mats), multisensory activities (eg, reduce vision), and dual tasking. Consider tai chi For individuals with impaired balance or high fracture risk, start with static and progress to dynamic balance exercises

** In accordance with most national physical activity guidelines, adults should accumulate ≥150 minutes per week of moderate to vigorous intensity physical activity. To realistically accomplish all of the above therapeutic goals, one could combine activities (eg, lunges as a leg-strengthening exercise that also challenges balance, and a step class that includes impact exercise and moderate/vigorous aerobic challenge and simultaneously challenges balance). BW=body weight; PRT=progressive resistance training; 1-RM=one repetition maximum; RPE=rating of perceived exertion.* *Note:* From *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolis. Bilezikian et al. 2018.*

To reach this conclusion, several studies have been conducted with the aim to investigate the timing and effect of exercise in increasing bone mass and preventing falls. Weight-bearing impact exercise programs that include moderate to high impact (more than two to three times body weight) and novel or diverse multidirectional activities have been shown to maintain or improve hip and spine BMD, although with modest gains (~1% to 3%), in premenopausal women, and to a lesser extent in postmenopausal women and older men (Taaffe et al., 2013). Nevertheless, questions still remain regarding the safety and efficiency of high, novel, or diverse impact loading for older or osteoporotic individuals given the mixed findings reported in the literature and the fact older people may experience pain from comorbidities such as osteoarthritis, which may influence long-term adherence. On the other side, progressive resistance training (PRT) is the most effective type of exercise to improve muscle mass, size, and strength, including in individuals who are frail or have a history of fracture (Borde et al., 2015; Stewart et al., 2014). Also resistance training is often prescribed to improve functional outcomes (eg, balance, gait, mobility) and prevent falls, but, as reviewed by others, there are mixed findings from RCTs in older adults (Orr et al., 2008; Sherrington et al., 2011). Currently, the most effective PRT programs are those that applied moderate to high loads (70% to 85% of maximal strength), incorporated the principle of progressive overload, were performed at least twice per week, and which specifically targeted muscles attached to or near the hip and spine (Beck et al., 2017; Giangregorio et al., 2013). However, there are heterogeneous findings with regard to the effects of PRT alone on hip and spine BMD in postmenopausal women and older men (Zhao et al., 2015). Hence, further research is needed.

Howe et al. in a Cochrane systematic review, suggested that combination exercise programs, including weight-bearing activities and progressive resistance training, have a statistically significant positive effect on bone density at the spine in postmenopausal women compared to individuals that perform their usual activities (Howe et al., 2011). Nevertheless, after two years Giangregorio et al. stated that there is no definitive evidence supporting the benefits of exercise in women with vertebral fragility fractures mainly due to the fact that findings were inconsistent and the quality of evidence was very low (Giangregorio et al., 2013). However, the National Osteoporosis Foundation (NOF) strongly endorses lifelong PA at all ages, stating that proper exercise, particularly regular weight-bearing and muscle-strengthening type, may improve physical performance/function, bone mass, muscle strength, and balance, and can reduce the risk of falling (Cosman et al., 2014). Moreover, exercise has a positive effect on bone health, especially during the late childhood and adolescence, which are critical periods for skeletal growth and development. In a recent systematic review, Weaver et al. found beneficial effects of PA, including dynamic resistance exercise and jumping performed at least 3 days per week, on both BMD and bone strength in youth (Weaver et al., 2016). Accordingly, a systematic review showed that, in older adults and elderly individuals, strength exercise is effective for improving or maintaining site-specific bone mass, and multicomponent exercise programs including resistance, aerobic, high-impact, and/or weight-bearing training may help to prevent age-related bone loss, especially in postmenopausal women (Gomez-Cabello et al., 2012). Zehnacker et al., in a systematic review, suggested that to achieve the best results of resistance exercise in postmenopausal women, high-loading, high-intensity training for three sessions per week and for two or three sets per session is needed (Zehnacker et al., 2007). Another recent systematic review showed that resistance training alone or in combination with impact-loading activities is more effective at preventing bone loss in middle-aged and older men (Bolam et al., 2013). All of the aforementioned systematic reviews reported that walking is not effective at preventing OP, despite being an affordable activity for most people and an exercise able to improve aerobic fitness, body composition, and cardiometabolic health (Ma et al., 2013). The issue is that it imparts relatively low-magnitude loads on bones that are unlikely to exceed the threshold to stimulate an adaptive skeletal response. Therefore, it only provides a modest increase in the mechanical loads applied to the skeleton. Thus, walking as a single intervention to prevent OP, falls, or fractures is not the best strategy (Bilezikian et al., 2018). Similarly, swimming and cycling have no effect on bone health, even though they incorporate forceful muscle contractions (Stewart et al., 2000; Taaffe et al., 1995). However, supervised home- and water-based exercises are viable options in case of severe impairments and activity limitations (Varaha et al., 2018). Concerning the effects of exercise on BMD, a randomized controlled trial by Marques et al. demonstrated that a specific exercise program including a combination of weight-bearing exercise with moderate/high intensity and slow progressive strength exercises could maintain and improve the hip and/or vertebral BMD as well as skeletal muscle mass and strength in postmenopausal women and in elderly people (Marques et al., 2011). Accordingly, Zhao et al. suggested that resistance training was helpful for maintaining femoral neck and lumbar spine BMD in postmenopausal women. However, a subgroup analysis showed that combined protocols integrating resistance training with high-impact or weight-bearing exercises enhanced hip and spine BMD, whereas resistance-alone protocols produced only nonsignificant preventive effects on postmenopausal bone loss (Zhao et al., 2015). In addition, Zhang et al. demonstrated that individuals receiving both pharmacological treatment (antiresorptive drugs) and exercise had higher lumbar spine BMD than individuals treated only with antiresorptive agents (Zhang et al., 2014). To sum up in this regard, research demonstrates that free-living PA and exercise are associated with both cross-sectional and prospective significant but modest improvements in BMD and, at the very least, appear to exert homeostatic influences on BMD during ageing (McMillan et al., 2017). Specifically, research appears to indicate that resistance training and weight-bearing activity may be most efficacious for maintaining and increasing BMD in older adults. However, the situation is not so clear. A recent systematic review and meta-analysis by Shojaa et al., with the aim to summarize the effect of exercise on BMD among post-menopausal women, included seventy-five studies investigating the BMD changes of the lumbar spine, femoral neck and total hip. The results were heterogeneous due to the large variation among the exercise protocols of the studies. The conclusion suggested by these findings was that the true effect of exercise on BMD is diluted by a considerable amount of studies with inadequate exercise protocols.

2.10 Physical Activity and vertebral fractures management

Currently there is little to no direct evidence that exercise can prevent fractures in people with established OP, nevertheless there is indirect evidence that exercise can influence fracture risk via outcomes along the causal pathway to fractures in older adults, including BMD, falls, and spinal alignment (Bilezikian et al., 2018). To date, few studies have investigated the efficacy of exercise on BMD in individuals with osteoporosis, vertebral fractures, or secondary OP, mostly due to the fact that individuals with OP are often on medications influencing bone metabolism. However, several trials over 12 to 18 months in older women or men with osteopenia and/or OP or falls risk factors have reported that supervised, multi- modal exercise programs incorporating moderate- to high-intensity PRT, impact, and balance exercise training can maintain or improve BMD and increase muscle mass, strength, and function (Bolton et al.; 2012; Gianoudis et al., 2014; Kukuljan et al., 2011; Watson et al., 2018). In light of the limited evidence, an international consensus process was conducted (termed Too Fit to Fracture) to develop exercise recommendations for individuals with OP or vertebral fractures (Giangregorio et al., 2014). The consensus was that, given the larger body of evidence examining the effects of exercise on bone health in postmenopausal women and older men, the effects of exercise on BMD in older adults is site- and exercise mode-specific, and should combine dynamic, weight-bearing, aerobic exercise with PRT and balance exercises. The recommendations also discouraged aerobic exercise to the exclusion of PRT and balance training. Individuals at high risk of fracture, such as those with vertebral fractures, should prefer form and alignment over intensity and moderate over vigorous aerobic exercise, when it comes to PRT. Admittedly, safety of moderate or high impact exercise in individuals with established OP is unknown. Moreover, whether individuals with established osteoporosis can improve BMD with exercise, is still unknown. For these reasons, the primary therapeutic goal should be to prevent bone loss.

What is more exercise decreases both pain and subsequent fracture risk in patients with vertebral fracture (Sinaki et al., 2002; Harrison et al., 1993; Sinaki, 2012; Sinaki et al., 1984). Indeed, for patients with chronic pain derived by vertebral fracture, physical therapy could be useful in order to improve general muscle strengthening, posture and balance, and strengthen quadriceps muscles. Taking into consideration the initial condition of the patient, they should be provided with exercise recommendations that includes weight-bearing aerobic activities, postural training, progressive resistance training, stretching, and balance training. Additionally, gait stabilization and fall prevention can greatly benefit patients. Last but not least an evaluation of the home environment for fall risk hazards is encouraged. Patients should be advised to avoid activities that may put them at risk for more vertebral fractures, which include forward bending, exercising with trunk in flexion, twisting, sudden, abrupt movements, jumping, and jarring movements, high-intensity exercise, and heavy weight-lifting (Sinaki et al., 2013).

To sum up, exercise is the only strategy that has the potential to improve all modifiable fracture risk parameters (fall risk, fall impact, bone strength), if it is tailored to each individual's needs and the right type and dose is prescribed. For the prevention of OP and falls in community-dwelling healthy adults, multimodal programs including targeted progressive resistance training, weight-bearing impact activities, and challenging balance and mobility training are most effective for improving hip and spine BMD, and muscle mass, strength, power, and function. Regular walking has modest or no effect on bone or muscle mass or function, and the evidence for whole body vibration is inconclusive. For people with a previous low trauma fragility fracture, or who are deconditioned, have comorbid conditions, kyphosis, poor posture, poor trunk muscle control/strength, and/or impaired mobility, a multimodal program is also recommended but with a focus on challenging balance and mobility training, trunk postural exercises, and spine sparing strategies in addition to progressive resistance training and weight-bearing (low impact) aerobic physical activity. For these individuals and those with OP, supervision and coaching on good alignment and correct technique is particularly important when initiating and/or progressing an exercise program (Bilezikian et al., 2018).

3. Justification and aims

Physical activity interventions are recommended in the prevention and treatment of osteoporosis, additionally to decrease the risk of future bone fractures by increasing bone mineral density during all stages of life (Xu et al., 2016; Daly, 2017). However:

- Evidence based clinical practice guidelines for exercise prescription adapted to individuals with vertebral fractures are lacking and no definitive conclusion can be made relatively to the effect of exercise programme on Quality of Life and Pain management in people with OP and vertebral fractures (Gibbs et al., 2019);
- Few studies have been investigating the hypothetical different effects of exercise programme, taking into consideration the setting in which it is being administered (Bragonzoni et al., 2020);
- It still remains unclear how the biomarkers analysis in people with OP could be useful to detect the effects of physical activity intervention in the context of an integrated therapeutic strategy aimed to promote bone anabolism (Brown et al., 2009).

For these reasons, the present thesis aims to increase the knowledge on the type of exercise and training tailored for people with OP with and without vertebral fractures and its relative effects on quality of life, physical fitness and fear of falling. Moreover, effects of exercise on BMD and on bone biomarkers are investigated to deepen the topic.

A multi-method approach has been used to provide insight on the topic that just arose.

The subsequent three chapters are based on the following peer-reviewed articles:

- Study I: Marini S., Barone G., Masini A., Dallolio L., Bragonzoni L., Longobucco Y., Dallolio L. **The Effect of Physical Activity on Bone**

Biomarkers in People With Osteoporosis: A Systematic Review. Front. Endocrinol. 2020; 11:585689. doi: 10.3389/fendo.2020.585689;

- Study II: Marini S, Leoni E, Raggi A, Sanna T, Malavolta N, Angela B, Maietta Latessa P, Dallolio L. **Proposal of an Adapted Physical Activity exercise protocol for women with osteoporosis-related vertebral fractures: a pilot study to evaluate feasibility, safety and effectiveness.** Int J Environ Res Public Health. 2019; 16(14) 2562. doi: 10.3390/ijerph16142562;
- Study III: Bragonzoni L, Barone G, Benvenuti F, Canal V, Ripamonti C, Marini S, Dallolio L. **A Randomized Clinical Trial to Evaluate the Efficacy and Safety of the ACTLIFE Exercise Program for Women with Post-menopausal Osteoporosis: Study Protocol.** Int J Environ Res Public Health. 2020; 17(3) 6123. doi: 10.3390/ijerph17030809.

The candidate's contribution for each study is summarized as following:

- Study I: Conceptualization and systematic review design; abstract and papers independent revision; acquisition, analysis and interpretation of the data; writing of the original draft;
- Study II: Methodology and formal analysis; investigation and data curation; writing of the original draft;
- Study III: Contribution to the study design; writing of the original draft.

4. Study I

The Effect of Physical Activity on Bone Biomarkers in People with Osteoporosis: A Systematic Review

4.1 Introduction

Bone is hard tissue that is in a constant state of flux, being built up by bone-forming cells called osteoblasts while also being broken down or resorbed by cells known as osteoclasts (WHO, 2003). The assessment of bone quality can involve several parameters, including the extent of mineralization, the number and distribution of micro fractures, the rate of osteocyte apoptosis, and changes in the collagenous bone matrix. The status of bone mass is usually measured using a densitometry method (Leeming et al., 2009). However, it is more difficult to accurately examine bone structure and strength in live tissue only by Dual X-ray Absorptiometry (DXA) (Seibel et al., 2005). Some blood and urinary molecules have been identified as biomarkers to detect the dynamics of bone turn-over (Kuo et al., 2017). They are ideal tools to evaluate the actual metabolic status of the bone, as well as a well-established result of abnormal metabolism (Banfi et al., 2010). Table 1 shows the most reviewed bone biomarkers to assess the different phases of bone metabolism process (Kuo et al., 2017; Vasikaran et al., 2011; Nagy et al., 2020; Park et al., 2018; Liu et al., 2019; Glendenning et al., 2019; Drake et al., 2017).

Table 1. Summary of bone turnover biomarkers currently available and their characteristics

Biomarkers	Assay method	Characteristics	Reference
Bone formation markers			
Alkaline phosphatase (ALP)	Serum Standard Auto-analyzer technique	Widely used but non-specific for bone turnover	Vasikaran,2011; Kuo,2017
Bone alkaline phosphatase (BALP)	Serum EIA-CLEIA	Applied for the monitoring of osteoporosis.	Kuo,2017; Nagy,2020; Park,2018
Osteocalcin (OC)	Serum IRMA-ECLIA	No significant utility for the assessment of osteoporosis. Promising for the investigation of osteoporosis therapy efficacy	Liu,2019; Kuo,2017; Nagy,2020
Procollagen type 1 C-terminal propeptide (P1CP)	Serum Radioimmunoassay	Limited study in literature. Promising for the investigation of bone formation	Kuo,2017; Nagy,2020
Procollagen type 1 N-terminal propeptide (P1NP)	Serum RIA-ECLIA	The most sensitive marker to measure the bone formation rate the most accepted marker for monitoring drug therapy.	Kuo,2017; Glendenning,2018; Nagy,2020
Bone resorption markers			
Amino-terminal crosslinked telopeptide of type 1 collagen (NTX-1)	Urine EIA-CLEIA	Stable and not affected by food intake. Promising marker for osteoporosis management	Kuo,2017; Nagy,2020
Bone sialoprotein (BSP)	Serum immunoassay	Potential biomarker for osteoporosis assessment	Kuo,2017
Carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX-1)	Serum/plasma/urine EIA-CLEIA	Specific and sensitive biomarker for osteoporosis management. Useful marker for monitoring drug therapy	Kuo,2017; Glendenning,2018; Nagy,2020
Cathepsin K (CTSK)	Serum ELISA	Potential marker for monitoring drug therapy	Kuo,2017; Drake,2017
Deoxypyridinoline (DPD)	Urine HPLC-EIA-CLEIA	Not very sensitive for osteoporosis management	Kuo,2017; Nagy,2020
Hydroxylysine (HYL)	Urine HPLC	Limited application due to the lack of a simple routine method	Kuo,2017

Hydroxyproline (HYP)	Urine Spectrophotometric technique	Not very sensitive for osteoporosis management, it has been replaced by more specific markers	Kuo,2017
Osteopontin (OP)	Plasma ELISA	Promising biomarker to monitor the parathyroid hormone treatment in menopausal osteoporosis	Kuo,2017; Glendenning ,2018; Nagy,2020
Pyridinoline (PYD)	Urine HPLC	Non-specific for diagnosis and treatment of osteoporosis	Kuo,2017; Nagy,2020
Tartrate-resistant acid phosphatase 5b (TRAP 5b)	Serum/plasma EIA	Good specificity and high sensitivity for monitoring drug therapy	Kuo,2017; Nagy,2020
Regulators of bone turnover			
Dickkopf-1 (DDK-1)	Serum ELISA	Insufficient clinical data for osteoporosis management	Kuo,2017; Nagy,2020
Osteoprotegerin (OPG),	Serum ELISA	Insufficient data for clinical management of osteoporosis	Kuo,2017
Receptor activator of NF-kB ligand (RANKL)	Serum ELISA	Insufficient data for diagnosis and treatment of osteoporosis	Kuo,2017
Sclerostin	Serum ELISA	Insufficient clinical data for osteoporosis assessment	Kuo,2017; Nagy,2020

The negative balance of bone turnover, due to the absolute (increase in osteoclastic function) or relative (inadequacy of osteoblastic function) prevalence, represents a health problem. The most common cause of this process is aging, but it can also result from other conditions such as immobilization, cortisone therapy, or estrogen deficiency. The most common metabolic bone disease is osteoporosis, which is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures (Prentice, 1997). Currently, it has been estimated that more than 200 million people are suffering from OP, and this number is increasing due to the aging population and the change in lifestyles. According to recent statistics from the International Osteoporosis Foundation, OP affects one in three women and one in five men over the age of 50 years worldwide (IOF, 2018). Estrogen deficiency is the main etiopathogenic factor in postmenopausal OP. Indeed, throughout the menopausal transition, serum estradiol and estrone levels decrease, with an increase in bone resorption leading to OP (Lupsa et al., 2015; Consensus Development Conference, 1993).

Nowadays, osteoporosis is a major public health concern worldwide due to its healthcare cost and requires a multi-modal care approach including both pharmacological and PA interventions (Kendler et al., 2016). In Europe, the most commonly administered agents involved in OP drug therapy are raloxifene, BP, agents derived from parathyroid hormone, and denosumab (Kanis et al., 2019; Choi et al., 2013). The guidelines for the prevention and treatment of OP recommend regular physical exercise. A low level of PA represents an important risk factor for OP due to the reduced mechanical stimulation of osteoblasts. For these reasons, PA should be part of the comprehensive management of osteoporotic patients since it can reduce disability, improve physical function, lower the risk of subsequent falls, and act on bone structure (Cosman et al., 2014; Howe et al., 2011).

It is likely that PA induces an anabolic or homeostatic effect on bone *via* mechanotransduction (McMillan et al., 2017). Although the mechanism underlying the effects of exercise on bone remodeling is not yet fully understood, some hypotheses seem more probable. One is the piezoelectric effect: when the mechanical impulse transmitted to the bone is converted by hydroxyapatite crystals into an electrical impulse that leads to greater bone mineralization. Another is the vascular effect: when the increase in muscle activity leads to a positive variation in the bone blood flow, improving the local metabolism (Tong et al., 2019). In particular, exercise carried out under conditions of weight-bearing determines the most significant benefits, as the mechanical stress is more intense. Also, the bone response to exercise is greater in districts where more mechanical stress is exerted. Furthermore, aerobic exercise seems to be particularly effective in the enzymatic activation of the osteoblasts (Benedetti et al., 2018).

Nowadays bone metabolic biomarkers have become useful clinical parameters in the management of osteoporosis and their use continues to expand (Nishizawa et al., 2013), as the possible variation in their concentrations may indicate an anabolism status or a bone catabolism (Vincent et al., 2002). The monitoring of bone turnover biomarkers could be a useful assessment tool to understand the physiological mechanism deriving from the osteogenic effect of PA (Cadore et al., 2005) and to assess the impact of exercise on osteoporotic bone (Maimoun et al., 2011; Moher et al., 2009). This highlights the need for an investigation of the influence of exercise on biomarkers linked to bone turnover in the osteoporotic population. In this scenario, the purpose of the present systematic review was to evaluate and critically analyze, for the first time, the available evidence on the effects of PA interventions on bone biomarkers in people with OP.

4.2 Methods

4.2.1 Search Strategy and Data Sources

We conducted this current Systematic Review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). Beforehand, we registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO).

The following PICO (Patients, Interventions, Comparators and Outcomes) question was developed, addressing the primary search objective, through the following search terms:

(P) Osteoporotic people, aged 45–80+; (I) Physical activity; (C) Standard care or no exercise treatment; (O) The effect of physical activity interventions on bone biomarkers. We searched electronic databases, with a 10-year time limit on the publication date because we were interested in recent pharmacologic treatments and approaches. The primary search was performed on 20 October 2019 and was updated on 14 May 2020. In all data bases we applied the following criteria to define the research: we included only Clinical Trial, Clinical Study, Comparative Study, Observational Study, Randomized Controlled Trial with Full text available, published in the last 10 years; with Human subjects. We defined a range of population aged 80 and over: 80+ years, Middle Aged + Aged: 45+ years, Middle Aged: 45–64 years, Aged: 65+ years.

The databases searched were: MEDLINE (PubMed); Embase (Ovid); Cochrane Central Register of Controlled Trials (Central); CINAHL (EBSCO); TRIP Medical. The search terms were adapted when necessary to fit the specific search requirements of each database.

Search strategies (strings adapted to the different databases) used the following Boolean expression: keywords and terms: “(((((((((((((((((((((Osteoporoses) OR Osteoporosis, Post-Traumatic) OR Osteoporosis, Post Traumatic) OR Post-Traumatic Osteoporoses) OR Post-Traumatic Osteoporosis) OR Osteoporosis, Senile) OR Osteoporoses, Senile) OR Senile Osteoporoses) OR Osteoporosis, Involutional) OR Senile Osteoporosis) OR Osteoporosis, Age-Related) OR Osteoporosis, Age Related) OR Bone Loss, Age-Related) OR Age-Related Bone Loss) OR Age-Related Bone Losses) OR Bone Loss, Age Related) OR Bone Losses, Age-Related) OR Age-Related Osteoporosis) OR Age Related Osteoporosis) OR Age-Related Osteoporoses) OR Osteoporoses, Age-Related) AND (((((((((((((((((((((((((Exercises) OR Physical Activity) OR Activities, Physical) OR Activity, Physical) OR Physical Activities) OR Exercise, Physical) OR Exercises, Physical) OR Physical Exercise) OR Physical Exercises) OR Acute Exercise) OR Acute Exercises) OR Exercise, Acute) OR Exercises, Acute) OR Exercise, Isometric) OR Exercises, Isometric) OR Isometric Exercises) OR Isometric Exercise) OR Exercise, Aerobic) OR Aerobic Exercise) OR Aerobic Exercises) OR Exercises, Aerobic) OR Exercise Training) OR Exercise Trainings) OR Training, Exercise) OR Trainings, Exercise) AND ((((((((((((((((((Bones and Bone Tissue) OR Bones and Bone) OR Bone Tissue) OR Bone Tissues) OR Tissue, Bone) OR Tissues, Bone) OR Bony Apophyses) OR Apophyses, Bony) OR Bony Apophysis) OR Apophysis, Bony) OR Condyle) OR Condyles) OR Bones) OR Bone) OR Bone Biomarker) OR Bone Biomarkers) OR Biomarker, Bone) OR Biomarkers, Bone)". After exporting articles, duplicates were removed. Moreover, we conducted a gray literature search of other papers and hand searches of key conference proceedings, journals, professional organizations' websites and guideline clearing houses. In accordance with the snowball technique, we examined references cited in the primary papers to identify additional papers.

Inclusion and Exclusion Criteria

Inclusion criteria:

1. Articles written in English;
2. Population with a diagnosis of osteoporosis (T score ≤ -2.5);
3. Physical activity intervention;
4. Bone Biomarker evaluation, bone biomarkers measured at least one time during the study;
5. Additional physical performance measured outcomes, or other indices of physical performance described in each study for example walking, balance, dexterity;
6. All the additional outcomes measured at least one time during the study;

7. Original primary data.

Exclusion criteria:

1. Articles not pertinent for the research topic;
2. Population with osteopenia, absence of osteoporosis diagnosis, different diseases;
3. Absence of physical activity intervention, physiotherapy, reported physical activity, other therapy;
4. Study protocol or other papers without original data.

Data Extraction and Quality Assessment

Four independent and blind investigators (SM, AM, GB, YL) screened and checked all the titles and abstracts retrieved in order to select pertinent items and to extract data following the inclusion criteria, using a pre-tested data extraction form. In case of doubts about the pertinence, the investigators assessed the eligibility of the study by reading the full text of the article.

The studies thus selected were independently and blindly assessed for the risk of bias by three researchers (SM, AM, GB), using the "Cochrane risk-of-bias tool for randomized trials" (Sterne et al., 2019). Any disagreement between the quality scores separately assigned by the blind reviewers was resolved through discussion and, if necessary, a fourth blind reviewer (YL) was involved as tiebreaker. The evaluation of risk of bias was made on the basis of the primary outcome of our interest, namely bone turnover biomarkers. This methodological choice was supported by the PRISMA guidelines (Moher et al., 2009).

The Cochrane risk-of-bias tool for randomized trials analyses seven bias categories for studies classified as a randomized controlled trial (RCT): (1) random sequence generation and (2) allocation concealment (concerning bias of selection and allocation),

(3) selective reporting for reporting bias, (4) blinding of participants and personnel (performance bias due to knowledge of the allocated intervention), (5) blinding of outcome assessment for detection bias, (6) incomplete outcomes data for bias in attrition, and another domain (7) called “other bias” based on the probable bias not covered in the other categories. Each category results in a value of high, low or unclear (when the authors did not provide enough evidence about the bias category) risk of bias. According to the Cochrane RoB Tool we converted the score to AHRQ (Agency for Healthcare Research and Quality) standards (Good, Fair and Poor). The threshold to provide the final score are the following: Good quality correspond to all criteria met (*i.e.* low risk of bias for each domain); Fair quality, only one criterion not met (*i.e.* high risk of bias for one domain) or two criteria unclear; Poor quality two or more criteria listed as high or unclear risk of bias.

The investigators extracted data independently, following the standardized norms for literature collection. We conducted a descriptive analysis of the studies by searching and extracting the following information from the articles: name of the first author, publication year, country, study design, population study with ages and number of experimental (EG) and control (CG) groups, sample size, type intensity and frequency of intervention, primary and secondary outcomes, results stratifying the studies for the different outcomes. Results were tabulated as mean ± SD where possible.

Any disagreement was resolved by consensus (LD, LB, FM). The study authors or investigators were contacted when additional information was necessary (Greenhalgh et al., 2005).

4.3 Results

4.3.1 Study Selection and Characteristics

As shown in Figure 1, a total of 992 articles were identified in the databases browsed and through hand search. Papers were published from 2012 to 2018; 374 studies were excluded because duplicated, 482 studies were excluded following abstract and/or title review. After this step, we judged 136 records as pertinent, 133 of which were subsequently excluded after a detailed full-text reading. The main causes of exclusion were related to the non-relevance and coherence with the aim of this study: the effects of PA interventions on bone biomarkers in people with OP. Furthermore, the majority of the articles were excluded due to the samples that did not match our inclusion criteria (people with osteopenia and not osteoporosis). As a result, only three papers (Arazi et al., 2018; Roghani et al., 2013; El-Mekawy et al., 2012) were finally included in the systematic review, fully meeting the eligibility criteria (Figure 1).

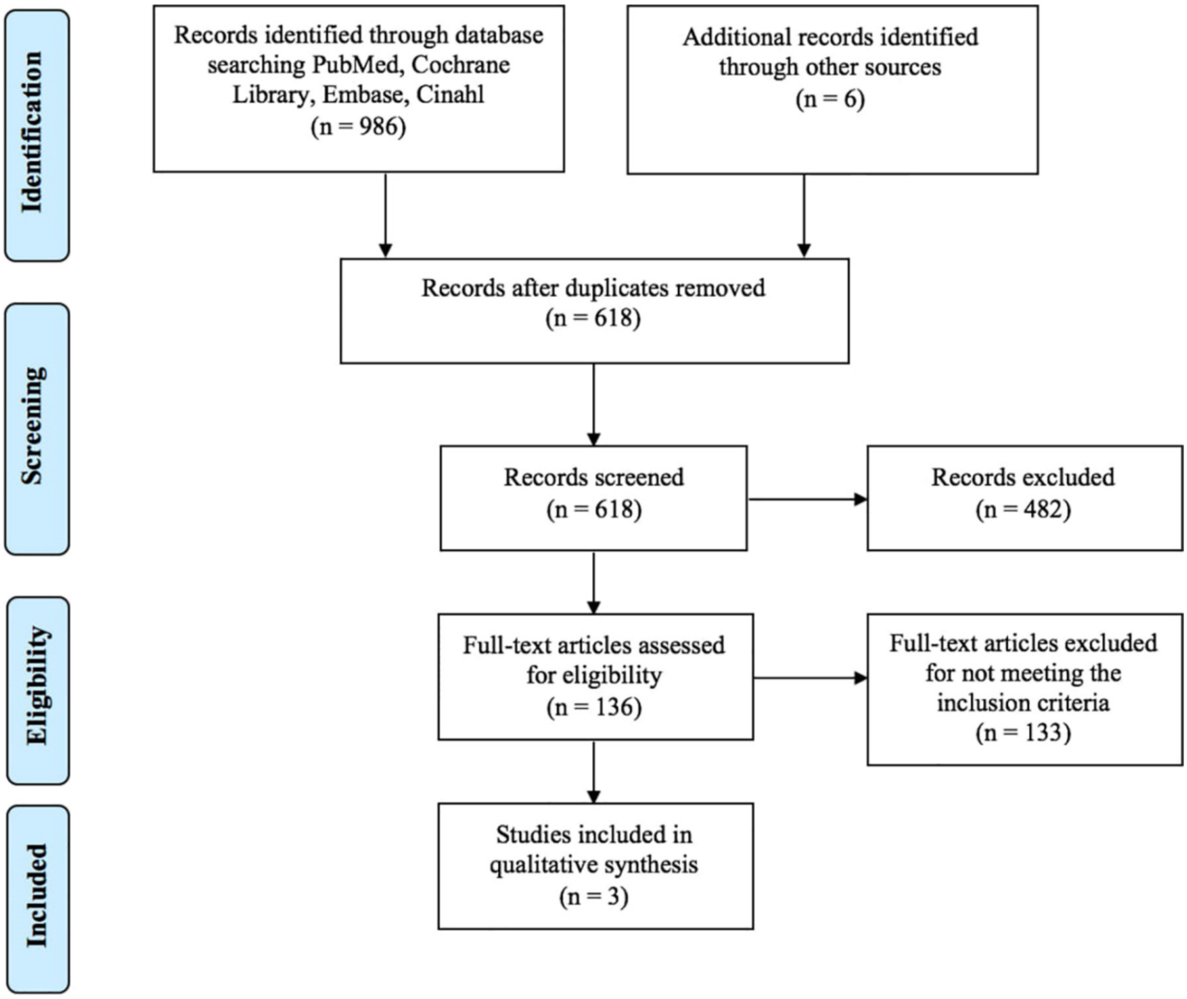


Figure 1. PRISMA diagram of the study selection

4.3.2. Risk of Bias

Following the descriptive analysis, we assessed the quality of each RCT study.

In accordance with the Cochrane risk-of-bias tool for randomized trials we assessed the quality based on biomarkers outcome (Figure 2). The three RCTs do not explain in detail the randomization methods or allocation of participants (items #1 and #2), and none of them had a research protocol registered; due to this, the selective reporting was assessed as unclear (item#3).

There was no blinding of participants (item #4), but the review authors judge that the biomarker outcome is not likely to be influenced by lack of blinding of participants. Regarding the blinding of outcome assessment (item #5) Roghani et al. was the only one that described and used techniques and methods that ensure the sensitivity of outcome assessment (Roghani et al., 2013); the studies by Arazi et al. (Arazi e al., 2018) and El-Mekawy et al. (El-Mekawy et al., 2012) were not clear in describing the methodology used to guarantee no risk of bias of outcome assessors. Overall, each RCT had one or more criteria unclear. For these reasons, the risk of bias was scored as "Poor quality".

Studies	Random sequence	Allocation concealment	Selective reporting	Other bias	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Quality
Arazi et al. 2018 (27)	yellow	yellow	yellow	yellow	green	yellow	green	Poor
El-Mekawy et al. 2012 (28)	yellow	yellow	yellow	yellow	green	yellow	green	Poor
Roghani et al. 2013 (26)	yellow	yellow	yellow	green	green	green	green	Poor

green: criterion met, yellow: criterion unclear, red: criterion not met

Figure 2. Risk of bias evaluation

4.3.3 Data Extraction

According to our aim focused on assessing the effects of PA on biomarkers, we extracted the data considering the bone biomarkers analysis and other hematological parameters as primary outcome; bone mineral density (BMD) assessment and physical performance tests as secondary outcome. Table 2 shows the main characteristics and results of the included studies evaluating the effects of PA interventions on bone biomarkers, in people with OP. The geographic origin of the studies was: Iran (n = 2, 66%) and Egypt. Study characteristics were heterogeneous. The sample size varied from 26 to 60 people. Ages ranged from 30–45 to 60–65 years. Concerning the subject's inclusion/exclusion criteria, in both Roghani et al. and El-Mekawy et al. studies, subjects were excluded if they were taking any drugs that affected bone metabolism or were receiving hormone replacement therapy. In Arazi et al. an inclusion criterion was not using low-fat dairy (milk, yogurt, cheese) as a source of vitamin D. The duration of the intervention varied from 6–10 weeks to 6 months with a common frequency of three times a week. The type of exercise training was, in all three studies (Cadore et al., 2005; Brown et al., 2009; Maimoun et al., 2011), aerobic such as walking on a treadmill or resistance weighted exercise, administered in more than one group. In both Roghani et al. and Arazi et al. were enrolled other experimental groups performing weighted aerobic exercise and aerobic-resistance training, respectively, while only the study by El-Mekawy included an outdoor walking intervention. The El-Mekawy et al. study did not have a control group, while the other two envisaged a standard care control group. In Arazi et al. two intervention groups (concurrent training and milk; only milk supplementation) received a supplementation of 500 ml daily milk for ten weeks.

Table 2. Studies included in the review

Study	Study design	Sample	Intervention	Outcomes	Results	Quality (RoB Tool)
Arazi et al., 2018 Rasht, Iran	RCT	N:40 age:30-45 EG-training:10 EG-training +milk:10 EG-milk:10 CG:10	**Duration:** 10 weeks **Type of intervention:** EG-training: aerobic exercises 10 weeks x 3 sessions/week, 90-110 min x session; EG-training+milk: aerobic exercises 10 weeks x 3 sessions/week, 90-110 min x session +500 ml daily milk for 10 weeks immediately (250 ml) and 1 hour after training (250 ml). EG-milk: 500 ml daily milk for 10 weeks, milk immediately (250 ml) and one 1 hour after training (250 ml), CG: standard care.	**Primary outcome**: ALP and 25OHD **Secondary outcome**: BMD hip values (right and left) and BMD lumbar spine (L2-L4)	**Primary outcome results** **Statistically significant improvement in ALP:** EG-training+milk p<0.001; EG-training p<0.001; EG-milk p=0.01. **Statistically significant improvement in 25OHD:** EG-training+milk p<0.001; EG-training p<0.001; EG-milk p=0.03. **Secondary outcome results** **Statistically significant improvement in BMD hip** EG-training+milk: right hip: p<0.001; left hip: p<0.001; EG-training: right hip: p=0.01; left hip: p<0.001; EG-milk: right hip: p=0.15; left hip: p=0.09. **Statistically significant improvement in BMD lumbar spine** EG-training+milk p=0.02; EG-training p<0.001; EG-milk p=0.10.	**Poor**
El-Mekawy et al., 2012 Cairo, Egypt	RCT	N: 60 women age:59.03±2.67 EG-A:20 EG-B:20 EG-C:20	**Duration:** 6 months **Frequency:** 3 times a week **Type of intervention:** EG-A: walk daily in the morning in fresh air, 30 min. EG-B: aerobic exercise training for hip and lumbar spine. Sustained muscle contraction for each specific exercise was maintained for 5 seconds	**Primary outcome**: ALP and calcium (Ca) **Secondary outcome**: Response of BMD neck and BMD	**Primary outcome results** **Pre-post change in ALP**: EG-A= pre: 175.68±33.48 vs post: 173.00±32.95, change pre:1.53%, p value<0.91; EG-B= pre: 157.00±35.23 vs post: 154.44±35.92, change:1.63%, p value<0.33; EG-C= pre: 153.48±36.44 vs post: 150.96±35.92, change:1.64%, p value<0.05. **Pre-post change in Ca**: EG-A= pre: 8.48±0.31 vs post: 8.66±0.3, change: 2.12%, p-value<0.81; EG-B= pre: 8.45±0.36 vs post: 8.66±0.37, change: 2.49%, p value<0.44; EG-C= pre: 8.48±0.34 vs post: 8.73 ±0.37, change: 2.95%, p-value<0.66. **Secondary outcome results**	**Poor**

			followed by 10 seconds of relaxation. EG-C: treadmill program for 30 min consisted of 5 min warm up which involved walking with no resistance and no inclination at the walk way of the treadmill followed by 20 min of walking with 15º inclination at the walk way of the treadmill at 60-75% of the training heart rate and ended by 5 min cool down.	lumbar spine to exercise	**Pre-post change in BMD neck**: EG-A= pre: -2.97± 0.64 vs post: -2.66 ±0.59, change:10.44%, p value<0.05; EG-B= pre: -2.87±0.67 vs post: -2.55±0.65, change: 11.15%, p-value<0.004; EG-C= pre:2.71±0.30 vs post: -2.38±0.32, change: 12.18%, p value<0.002. **Pre-post change in BMD lumbar spine**: EG-A= pre: -3.59±0.90 vs post: -3.26±0.88, change: 9.19%, p-value<0.01; EG-B= pre: -3.64±0.65 vs post: -3.29±0.74, change: 9.62%, p value<0.002; EG-C= pre: -3.44±0.83 vs post: -3.08±0.79, change: 10.47%, p-value<0.001.	
Roghani et al., 2013 Thran, Iran	RCT	N:27 age:45-65 CG:9 EG-aerobic:9 EG-weight:9	**Duration:** 6 weeks, 18 sessions **Frequency:** 3 times a week, 30 min each session **Type of intervention:** EG-Aerobic: treadmill submaximal, increasing the intensity every 2 weeks; EG-Weighted: Aerobic + wearing a vest 4–8 % of body weight; CG: usual care	**Primary outcome**: (tALP), BALP, and NTX levels, calcium (Ca), phosphorus (P).	**Primary outcome results** **Pre-Post change in tALP (U/L)**: EG-Aerobic= pre: 218.00±68.32 vs post: 226.12±72.11, change: +8.12, NS; EG-Weighted= pre: 222.44±60.96 vs post: 221.55±80.04, change: -0.89, NS; CG= pre: 181.50±83.36 vs post:186.70 ±80.04, change: +5.2, NS. **Pre-Post change in BALP (U/L)**: EG-Aerobic= pre: 156.12±38.08 vs post: 173.37±51.20, change: +10.25%, p=0.03; EG-Weighted= pre: 154.22±33.73 vs post: 166.44±43.92, change: +7.31%, p=0.05; CG= pre: 139.70±59.55 vs post: 136.60±57.37, change: -1.93%. **Pre-Post change in NTX (nM)**: EG-Aerobic= pre: 20.80±2.37 vs post:19.51±1.88, change: -5.99%, p=0.001; EG-Weighted= pre: 21.10±2.33vs post: 19.72±1.91, change: -6.34%, p=0.002; CG= pre: 21.08±2.32 vs post:21.20±2.38, change: +0.60%, p=0.6. **Pre-Post change in P(mg/dL):** EG-Aerobic= pre: 3.86±0.40 vs post: 3.84±0.3, change: -0.02, NS; EG-Weighted= pre: 3.33±0.43 vs post: 3.53±0.26, change: +0.2, NS; CG= pre: 3.79±0.42 vs post: 3.83±0.66, change: +0.4, NS.	**Poor**

		Secondary outcome: Balance: near tandem stand (NTS) and star-excursion (SE) test	**Pre-Post change in Ca (mg/dL)**: EG-Aerobic=pre: 9.10±0.11 vs post: 9.16±0.25, change: +0.06, NS; EG-Weighted= pre: 8.91±0.16 vs post: 9.23 ± 0.23, change: +0.32, p-value< 0.07; CG= pre: 9.06±0.38 vs post: 9.07 ± 0.20, change: +0.01, NS. **Secondary Outcome Results** **Pre-post change in SE test (cm):** EG-Aerobic= +10.72%, p-value<0.05; EG-Weighted= +13.43%, p-value<0.05; CG= -10.43%, p-value<0.05. **Pre-post change in Near Tandem Stand (NTS) test (s)** EG-Aerobic= +49.68 %, EG-Weighted= +104.66%, CG= -28.96%.

In the study by Arazi et al. the aim was to investigate the effects of concurrent training and milk, only training and daily milk consumption, on bone biomarkers and BMD. The exercise protocol for the concurrent training was performed by groups in 10 weeks, with three sessions of 90–110 min each week. Aerobic training included three sets of 5 min, running with 55–75% of heart rate maximum (HRmax) of the target and exercise intensity gradually increased for 5% HRmax and 3–5 min every two weeks (rest period of approximately 3 min between each set). Resistance training involved performing two sets of bench press, leg extension, wide grip pull-down, and leg curls, which were circular with 10 RM, and training intensity was gradually increased every two weeks for new 10 RM. At the end of 10 weeks, Arazi et al. reported a significant improvement in blood levels of 25-hydroxyvitamin D (25OHD) and ALP in all the experimental groups (concurrent training-milk, training group, milk group) compared to the control group (standard care), with a higher increase in the concurrent training-milk group ($p < 0.05$).

The study by El-Mekawy et al. conducted to determine the ideal type of exercise for the treatment of osteoporosis, foresaw three types of exercise (brisk walking in fresh air, specific exercise program for hip and lumbar spine, and weight-bearing exercise program on treadmill). The results obtained after 6 months showed a significant increase in all the primary and secondary tested parameters (pre-post change in ALP, BMD neck and BMD lumbar spine) in the three exercise groups.

Roghani et al. evaluated the effect of submaximal aerobic exercise with and without external loading, in three groups: aerobic group, weighted-vest group and control group. The exercise program performed by both the aerobic and weighted-vest group, consisted of 18 sessions of submaximal aerobic walking exercise on a treadmill three times a week, every other day, with each session lasting 30 min. The intensity of the exercise was increased gradually during the 6 weeks; specifically, 50% heart rate reserve (HRR) during the first 2 weeks, 55% HRR during the second 2 weeks, and 60% HRR during the last 2 weeks. Heart rate, blood pressure, and electrocardiogram (ECG) were monitored throughout the course of the exercise program. In the weighted-vest group the initial inner weight of the vest was 4% of the individual's body weight and was gradually increased by 2% every 2 weeks based on the tolerance level of each subject. The control group was requested not to change their daily PA or dietary patterns during the 6 weeks. As a result, BALP and NTX decreased significantly in both exercise groups ($p < 0.05$). The changes in bone biomarker levels were significant between each exercise group compared to the control group, except for the ALP pre-post changes. Concerning the secondary outcome of balance assessed through the near tandem stand (NTS) and star-excursion (SE) test, the exercise groups increased significantly while the control group decreased ($p < 0.05$).

4.4 Discussion

The present systematic review evaluates the effects of PA on bone biomarkers in the osteoporotic population and provides an outlook of their application to set up exercise programs.

Most of the articles included in the preliminary full text analysis from the database research involved osteopenic people without osteoporosis, and they did not meet the established inclusion criteria. For this reason, our findings focused on data from only three studies (Arazi et al., 2018; El-Mekawy et al., 2012; Roghani et al., 2012). Regarding the bone biomarkers assessment, all the studies investigated the serum ALP. Roghani et al. and El-Mekawy et al. both included serum calcium as an additional parameter, while Arazi et al. analyzed the 25-hydroxyvitamin D (25OHD).

All three studies included in our review reported a significant improvement in terms of bone biomarkers value in osteoporotic people participating in exercise interventions. The best effect in bone turnover was obtained with two different PA interventions including both aerobic and weighted-vest aerobic training in the study by Roghani et al. In particular, the study showed that short term submaximal walking training wearing a weighted vest is effective for stimulating bone formation and decreasing bone resorption in postmenopausal women with OP.

According to more recent literature (Kuo et al., 2017; Nagy et al., 2020; Park et al., 2018) the most specific and sensitive biomarkers for osteoporosis management and the most accepted for monitoring drug therapy are CTX-1(bone resorption) and P1NP (bone formation). These two biomarkers were not investigated in any of the three studies analyzed. Roghani et al. evaluated BALP, a widely-used bone formation biomarker, and NTX, a promising marker of bone resorption. On the other hand, both El-Mekawy et al.

and Arazi et al. investigated ALP, a non-specific bone turnover marker, even though widely applied in clinical diagnosis. These data hamper a robust evaluation of the findings.

Regarding quality assessment, the studies analyzed present further limitations due to the low quality. All three RCTs were scored as “Poor quality” according to the Cochrane Tool for Quality Assessment. In all the included studies, it was not possible to understand the methodology used for randomization and allocation concealment. Moreover, the three studies did not register the study protocol. Only Roghani et al. described specific methods to guarantee the sensitivity of outcomes assessment. Despite these limitations, Roghani et al. could be considered the most appropriate study with a lesser number of risks of bias.

As already mentioned in the *Introduction* of this article, OP has been increasingly studied over the years as it is a skeletal disease leading to structural deterioration of bone tissue and especially when related fractures occur, it significantly interferes with the QoL (Karlsson et al., 2020). Besides, concern has grown to identify effective strategies for managing OP.

Evidence has consistently proven the importance of regular participation in specific exercise programs to prevent and minimize the osteoporotic bone deterioration and its consequences on health (Cosman et al., 2014; Choi et al., 2012; Todd et al., 2004). In this review BMD assessment and physical performance tests have been evaluated as secondary outcome. Roghani et al. showed that weighed-vest aerobic exercise is more effective for improving the balance of participants than simple aerobic training. The other two studies evaluated the effect of PA on BMD estimated with DXA. El-Mekawy et al. reported an increase in BMD at neck and lumbar spine with the highest score for the weight bearing exercise group, and the lowest recorded in the brisk walking group. Arazi et al. showed that the concurrent training-milk intervention significantly improved the BMD measured at lumbar spine and hips.

To date, no optimal exercise training for osteoporotic people has been established, but there is growing evidence supporting a multimodal approach that includes different types of exercise and training (Bonaiuti et al., 2002; Daly et al., 2019). Resistance training and weight-bearing impact exercises seem to be the most suitable and specific to reduce the risk of fracture, acting on the musculoskeletal system; however, the benefits depend on the frequency and intensity of training (Daly et al., 2019). Balance and mobility exercises are also widely used to increase functionality and reduce the risk of falls (Greenway et al., 2012). On the other hand, aerobic PA that does not include impact (*e.g.* cycling or swimming) has a weak effect on prevention related to bone loss, due to the low impact on the musculoskeletal apparatus, inadequate to gain a bone adaptation (Greenway et al., 2012). In spite of this, aerobic exercises have great benefits on the cardiovascular and metabolic apparatus and body composition of osteoporotic patients. In addition, exercise can help to achieve beneficial and significant effects on quality of life, balance, and functional mobility also in patients with osteoporosis-related vertebral fractures (Stanghelle et al., 2019; Marini et al., 2019). However, there is still no agreement on which type of exercise, in terms of intensity, frequency, duration, type and setting, is optimal and can affect bone metabolism in people with OP (Gibbs et al., 2019; Shojaa et al., 2020; Bragonzoni et al., 2020).

Biomarkers of bone metabolism, reflecting the cellular activity linked to the bone turnover process, could be a valid tool to assess the efficacy of PA and exercise programs in the osteoporotic population. Of note, some studies, which we excluded after our preliminary full-test analysis because they include non-osteoporotic study groups, monitored the benefits of physical activity on bone metabolism by the evaluation of

P1NP and CTX, the two biomarkers considered specific for bone turnover (Mafrini et al., 2019; Dionello et al., 2016). Interestingly, an improvement in bone metabolism was induced by different types of exercise, for example a football training intervention (Bowtell et al., 2016; Skoradal et al., 2018). Moreover, Moreira et al. found a positive effect of high-intensity aquatic exercise on P1NP and CTX among people with osteoporosis and osteopenia on P1NP and CTX (Moreira et al., 2013). On the other hand, Wochna et al. did not obtain effects on CTX in healthy post-menopausal women performing aqua fitness activities in deep water (Wochna et al., 2019).

On the whole, the available scientific evidence points to a gap of knowledge regarding the potential of PA to influence biomarkers and does not allow an unequivocal conclusion about exercise programs suitable for people with OP. Despite the limitations reported in terms of the small sample size of the studies included and their quality and design, to our knowledge this systematic review is the first that investigates the effects of PA on bone biomarkers in the osteoporotic population. Hopefully, our findings can serve to summarize the existing literature on this topic and highlight the need for additional studies in this field.

Further research is required with a special focus on osteoporotic people, investigating the most specific bone biomarkers (CTX, P1NP) and following the guidelines on quality evidence to adopt more rigorous methodologies. In the future, bone turnover biomarkers could prove highly promising in the design and evaluation of exercise programs for OP interventions.

4.5 Conclusion

For the understanding of the physical activity role in osteoporosis management, a desired goal is to correlate the effects of exercise on bone turn-over biomarkers. Despite our comprehensive literature search, the level of available evidence does not allow us to establish a clear conclusion since the limit number of the studies and their poor quality according to Risk of Bias tool.

Although the results should be interpreted with caution, the reported data indicate the beneficial effect of exercise especially weighted and aerobic, in terms of improving bone formation biomarkers such as ALP and BALP, and decreasing bone resorption biomarkers such as NTX in the osteoporotic population. These findings could pave the way for planning future research to better assess the effectiveness of PA on bone metabolism. Further study population, performed with rigorous methodology, is needed to identify the most useful exercise able to modulate bone turnover biomarkers in people with osteoporosis.

5. Study II

Proposal of an Adapted Physical Activity Exercise Protocol for Women with Osteoporosis-Related Vertebral Fractures: A Pilot Study to Evaluate Feasibility, Safety, and Effectiveness

5.1 Introduction

Osteoporosis and the associated fractures constitute a major public health concern. Physical activity is a part of the comprehensive management of osteoporotic patients. Nevertheless, a Cochrane Review argued that no definitive conclusions can be made regarding the benefits of exercise for individuals with vertebral fracture (Giangregorio et al., 2013). Furthermore, although most guidelines for prevention and treatment of OP recommend practicing physical activity regularly, it is unclear which exercise is optimal for these patients (Varahra et al., 2018).

Our aim was to draw up and test a standardized exercise program, in terms of frequency, duration, intensity, and type of exercises, targeted for women with osteoporotic vertebral fractures. Specifically, we evaluated an exercise program in accordance with the principles of Adapted Physical Activity (APA), based on group exercise protocols, designed for individuals with chronic conditions, aimed at correcting sedentary lifestyle and preventing or mitigating frailty and disability through “individualizing instruction, matching personal strengths and interests” (IFAPA, 2014; European Innovation Partnership, 2017). Applying a quasi-experimental study design, we carried out a pilot study with the aim of evaluating the feasibility and the safety of the proposed APA program and its positive effect on HRQOL and some other related conditions such as fear of falling, pain, and physical performance.

5.2 Materials and Methods

5.2.1 Study Design and Subjects

The pilot study design was a quasi-experimental controlled 6-month trial, with non-random assignment. The sample was recruited from the Rheumatology Section of the Internal Medicine Operational Unit at the Sant'Orsola Malpighi Hospital in Bologna, Emilia Romagna Region (Italy), during daily outpatient activity. Subjects eligible for the study were post-menopausal women living at home, ambulatory, aged 60–75 years, affected by overt osteoporosis, verified by dual energy X-ray absorptiometry, with one or more vertebral fractures verified by radiography. Table 1 shows the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	**Exclusion Criteria**
▪ Post-menopausal women; ▪ Between the ages of 60 and 75; ▪ Osteoporosis verified by dual energy X-ray absorptiometry; ▪ With or without pharmacological therapy for osteoporosis; ▪ One or more vertebral fractures verified by radiography.	▪ Moderate or severe respiratory failure; ▪ Recent pulmonary embolism; ▪ Endocarditis, myocarditis, or recent pericarditis; ▪ Advanced intermittent claudication (study of Fontaine ≥3); ▪ Myocardial infarction for at least three months, or unstable angina or stress angina; ▪ Heart failure > III NYHA Class; ▪ Severe arterial hypertension (systolic ≥180 mmHg or diastolic ≥110 mmHg); ▪ Abdominal aortic aneurysm on ultrasound (transverse caliber >3.5 cm);

Inclusion Criteria	**Exclusion Criteria**
	▪ Anomalies of the rhythm that can represent a contraindication to the performance of moderate intensity physical activity; ▪ Arthrosis or fractures with severe limb limitation; ▪ Paralysis or important neuromotor disorders; ▪ Body Mass Index ≤18 or ≥32 kg/m^2; ▪ Neoplastic disease or with poor prognosis; ▪ Pre-existence of physical exercise administered; ▪ Haemoglobin <11 g/dL; ▪ 16. Other diseases that may hinder or prevent moderate intensity physical activity.

Notes: NYHA = New York Heart Association

After inclusion, the participants were interviewed in order to assess the presence of risk factors for osteoporosis (age, Body Mass Index, familiarity, pharmacological treatments, early menopause, amenorrhea, anorexia nervosa, dietary deficiencies in vitamin D, smoking, alcohol, PA). In addition, patients were evaluated for the presence of other clinical comorbidities by the Cumulative Illness Rating Scale (≥) (Hudon et al., 2005), and the level of weekly physical activity by the PASE (Physical Activity Scale for the Elderly) questionnaire, which combines information on leisure, household, and work-related activity (Washburn et al., 1999).

Participants were assigned to the experimental group (APA group) or to the control group (CG). The random assignment of patients to the two groups was not possible, since many women refused to participate in the experimental group for practical reasons. The control group consisted of patients who self-excluded only for organizational reasons (difficulty in reaching the gym or in participating in activities at pre-established times, family commitments). We therefore preferred enrolment on a voluntary basis, thus giving all patients the opportunity to participate in a potentially effective and presumably welcome intervention.

The experimental group undertook a protocol of APA based on 1-h group sessions twice weekly, for 6 months. The subjects of the CG were asked to maintain their current lifestyle. At baseline and after 6 months' follow-up, both groups were tested for the HRQOL as primary outcome. Fear of falling, lumbar back pain intensity, and physical performance were evaluated as secondary outcomes, since these conditions have a considerable effect on psychological state, anxiety, and loss of security, contributing to the deterioration of the QoL (Park, 2018). In addition, the adherence to the program was calculated as the number of sessions performed compared to the sessions proposed, and cases of abandonment due to adverse events were noted to evaluate the safety of the exercise protocol.

The Local Ethics Committee approved the study (Independent Ethics Committee, Azienda Ospedaliera di Bologna, Policlinico S. Orsola-Malpighi, ref. 143/2014/U/Sper). Informed consent was obtained from all individual participants included in the study.

5.2.2 Intervention

Table 2 summarizes the exercise protocol undertaken by the APA group and Table S1 in the Appendix shows the protocol in details.

Table 2. Components of APA protocol.

Duration	Warm Up	Workout	Cool Down
	15 min	**35 min**	**10 min**
Aim	Cardio-respiratory conditioning, increase body temperature and metabolism, joint mobilization, upper and lower limb coordination, proprioception and postural education	Bodyweight exercises for muscular reinforcement and neuromuscular activation, increasing muscle strength and balance, without weights.	Stretching, breathing education, and muscle relaxation maintaining body awareness, collecting individual feedback on the session, in order to reacquire autonomy and active self-management
Type of exercise	Multi-articular exercises able to safely solicit all the main muscle groups; focus directed to joint mobilization, balance, and postural control during walking	Resistance exercise affecting all the main muscle groups was performed using isometric and dynamic bodyweight exercises.	Predominantly exercises in an upright and supine static position, able to stretch the main muscles, holding a stretch position for up to 30 s.
Trainer's role	▪ To specify and control the right posture, breathing, and activation of the core, for each exercise ▪ To administer only the exercises of the APA protocol without varying them and to respect the progression of workload that is established ▪ To ensure that the intensity of the exercise does not exceed what is indicated, adapting the rhythm to the individual capacity ▪ To keep individual case histories in mind, trying to make persons comfortable through active listening, by announcing the program of each session and explaining the objectives of the exercises of every phase ▪ After identifying the general level of fitness, to standardize the motor learning background, since it is essential to perform the exercises by placing emphasis on the knowledge of body and the responses gradually obtained ▪ As the motor task becomes more and more complex, to make people aware that they are working in safety by continuously monitoring their responses		

In each physical activity session, the program consisted of a 15 min warm-up (aerobic, balance, and mobility exercises), followed by a 35-min sequence of strength exercises without weights, and finally 10 min of cool-down. Each session was composed of about

20 exercises, specifically selected by the trainers, according to the aim of each session, from the total 45 exercises from which the APA protocol is made up, using a simple equipment (i.e., mats, sticks, sponge balls, elastic bands). Simple and safe exercises were chosen, with incremental phases of intensity, aimed at developing mobility and balance, improve the proprioception, maintain or increase strength in major muscle groups, and optimize postural alignment. In particular, any exercise comporting spinal flexion was avoided, since it is known that this kind of exercise could favor vertebral fractures (Moreira et al., 2014; Sinaki et al., 2010). The program was performed in adequately equipped gyms under the direct supervision of graduates in Sciences and Techniques of Preventive and Adapted Physical Activity (Master Degree) specifically trained for the purpose. The protocol was developed over a period of 6 months and included 3 stages of progressive intensity in relation to the improvement and evolution of the abilities achieved by the participants and their feedback. Starting from the initial number of repetitions established for each exercise, the number of repetitions was increased in series of 2/3 (for example: 8 initial repetitions were progressively increased to 10–12). Once the objective was reached, the number of series could be increased up to a maximum of 5. Generally, the rest time between series was 30 s, depending on people's needs. Exercise intensity progression was based on the repetition number combined with the rate of perceived exertion, as measured by Borg Category Ratio 10 (CR-10) scale (Borg, 1998). The trainers also played a counselling role, advising on the precautions to be taken in everyday life.

5.2.3 Assessments at Baseline and 6-Months Follow-Up

The measurements were collected by designated and appropriately trained and blinded assessors.

5.2.4 Health-Related Quality of Life (HRQOL)

HRQOL was evaluated by means of two questionnaires: A specific instrument for osteoporosis, named ECOS-16 (Assessment of health-related quality of life in OP), and a generic instrument named EuroQoL (EQ-5D-3L).

The ECOS-16 is a disease-specific and validated questionnaire to be used by patients with vertebral fractures attributed to OP (Badia et al., 2004; Badia et al., 2002). The items of the ECOS-16 are divided into four dimensions: Pain, physical function, fear of illness, and psychosocial functionality. It allows calculating a total score (from 16 to 80), a partial score for each of the four dimensions, and two partial total scores: The Physical Component Summary score (PCS: Mean of pain and physical function scores) and the Mental Component Summary score (MCS: Mean of psychosocial and fear of illness scores). Lower scores correspond to a better quality of life (Salaffi et al., 2007).

The 3-level version of EuroQoL (EQ-5D-3L) is a standardized questionnaire for the measurement of HRQOL and was introduced in 1990 by the EuroQoL Group (Rabin et al., 2001). It essentially consists of 2 parts: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system includes the following five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: No problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled "best imaginable health state" and "worst imaginable health state".

5.2.5 Fear of Falling

Fall Efficacy Scale-International (FES-I) questionnaire. The subjects are called to express their degree of concern about the possibility of falling during the execution of 16 activities of daily life. The FES-I uses a four-level Likert scale, each of which corresponds to a score ranging from 1 (not at all worried) to 4 (very worried). The individual scores are added together to calculate a total score from 16 to 64 (Dewan et al., 2014; Hauer et al., 2011; Tinetti et al., 1990).

5.2.6 Lumbar Back Pain

Visual Analogue Scale (VAS). The subjects are asked to express the intensity of the perceived lumbar pain in a one-dimensional scale, consisting of a straight line of 10 cm in length, whose ends correspond to two opposite conditions. One extreme indicates the absence of pain and corresponds to 0, the other extreme indicates the worst pain imaginable and corresponds to 10 (Scott et al., 1976; Huskisson et al., 1974).

5.2.7 Physical Performance

Tinetti Performance-Oriented Mobility Assessment tool (POMA)—better known as Tinetti’s Scale—to assess the motor performance aimed at balance and gait. It was developed by Tinetti in 1986 to identify subjects at high risk of falls and consists of two parts: Balance assessment (9 items) and gait evaluation (7 items) for a total of 16 items, corresponding to 16 movements that the subject is called to perform. The supervisor assigns to each item a score ranging from 0 to 2 on the basis of the ability to perform the required actions: 0 = maximum incapacity, 2 = maximum capacity. The scores for the two sections, balance (maximum 16) and gait (maximum 12), are first counted separately and then added together to get an overall score (maximum 28) (Tinetti, 1986).

Six Minute Walking Test (6-MWT) to assess the functional exercise capacity correlated to physical fitness (Demers et al., 2001; Macko et al., 2005). This test measures the distance (in meters) that a subject can quickly walk on a flat, hard surface in a period of 6 min. It is very easy to administer and allows measuring patients' residual functional capacity in a number of pathological conditions, including osteoporosis (Enright, 2003; Shipp et al., 2000). The 6-MWT was associated with the Borg CR-10 Scale of Perceived Exertion, which allows individuals to subjectively rate their level of exertion during exercise. After the 6-MWT, the subjects were invited to rate their perceived exertion (Borg, 1998) with a number from 0 (extremely easy) to 10 (extremely heavy).

Chair Sit-and-Reach to assess the lower body flexibility. This is a safe and socially acceptable test, alternative to traditional floor sit-and-reach test in older adults (Jones et al., 1998). The subject sits on the edge of the chair. One foot must remain flat on the floor, the other leg is extended forward with the knee straight, heel on the floor, and ankle bent at 90°. With one hand on top of the other and tips of the middle fingers flush, the subject is invited to slowly reach forward toward the toes by bending at the hip, keeping the back straight, head up, and the knee straight. The position must be maintained for 2 s. The distance is measured between the tips of the fingertips and the toe. The score is recorded to the nearest 1 cm as the distance reached, either a negative or positive score.

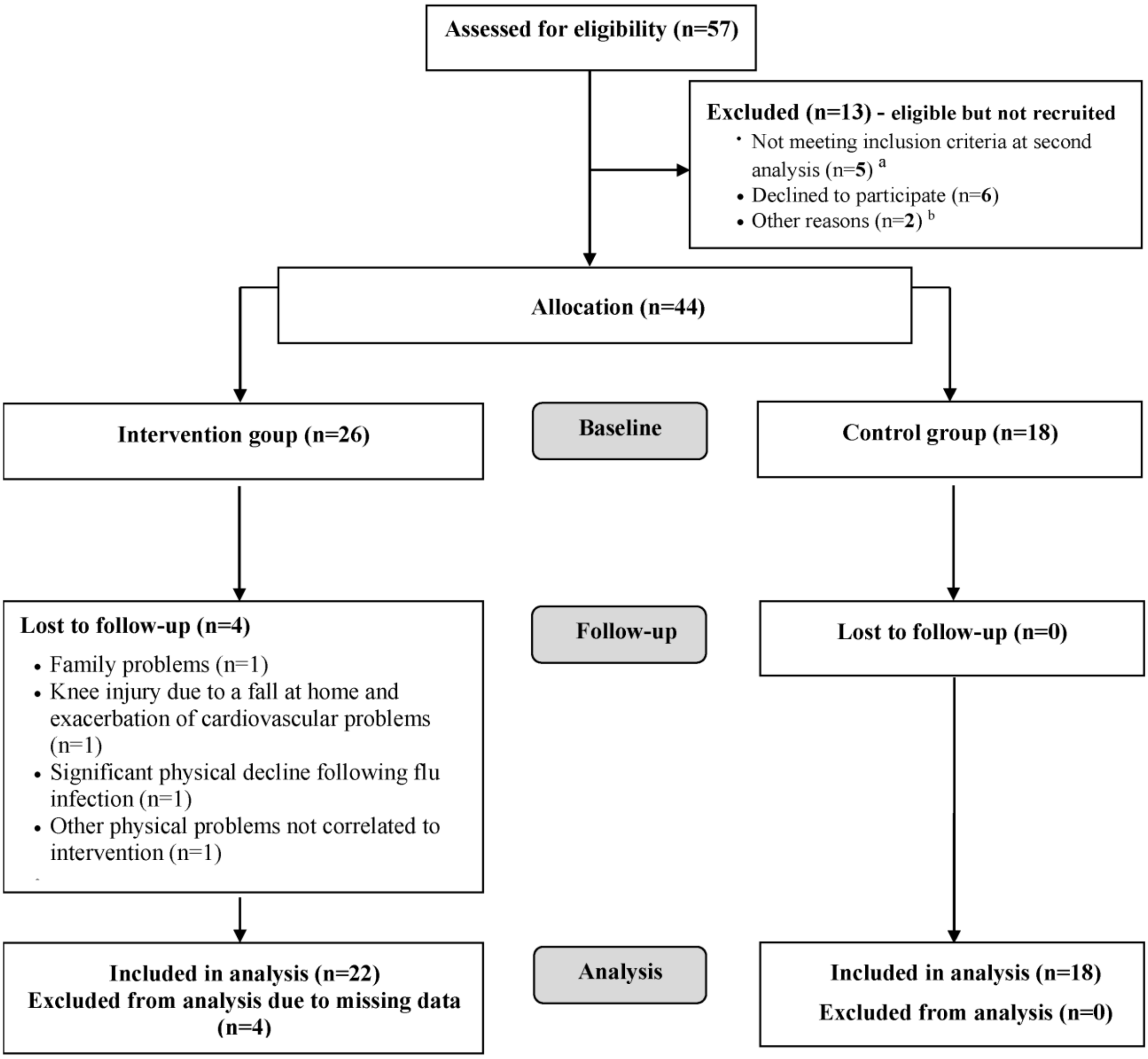
5.3 Statistical Analysis

The sample size was estimated by power analysis using the ECOS-16 questionnaire for the evaluation of HRQOL in post-menopausal women with osteoporosis as a primary outcome measure of the study. From published evidence, the ECOS-16 has a standard deviation of 0.8 at final follow-up assessment and a minimal clinically important difference of 0.69, which leads to an estimate of the size of the effect as 0.863 (Badia et al., 2004). Considering an alpha error of 0.05 and a power of at least 0.8, the minimum size of the sample is estimated in 18 patients per group, with a total of 36 patients. Power analysis was carried out with G*Power 3.1.9.2 (http://www.gpower.hhu.de).

Patients in the APA group were compared with those in the CG on socio-demographic data and outcome measures using the *t* test, Mann-Whitney test, or χ^2 test, as appropriate. Changes in outcomes measures were examined separately in each study group using Mann-Whitney test. Because the study groups are expected to differ in a non-randomized study design, we used linear multiple regression to compare changes in scores at 6 months between the APA group and CG after adjusting for age, baseline score of the analyzed variable, and all significantly different variables between the 2 groups at baseline. Effect sizes (ES) were calculated using Cohen's d (Cohen, 1998). All tests were two-sided with a *p* value of less than 0.05 considered as statistically significant. All the analyses were carried out using IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA).

5.4 Results

A total of 57 patients were assessed for eligibility, 13 of whom were subsequently excluded from the study (Figure 1). At baseline, the study sample had 44 participants: 26 assigned to the APA group and 18 to the CG. After assignment to the intervention, four patients were lost to follow-up due to conditions arising after baseline measurements and not depending on the intervention (Figure 1). All the remaining 40 women completed the study and participated in more than 50% of sessions, 22 of the APA group and 18 of the CG. The adherence, calculated as number of sessions performed compared to the sessions proposed, was 75.8% (minimum: 56.4%; maximum: 97.8%).



[a] - 76 years old and hospitalization at the time of the call (n= **1**)
- Significant cognitive impairment and Parkinson's (n= **1**)
- Vertebral abnormalities that at second analysis did not result as fractures (n= **1**)
- Pre-existence of physical exercise administered (n= **1**)
- Severe arterial hypertension (n= **1**)

[b] - dead between selection and allocation (n= **1**)
- no-response to repeated convocations (n= **1**)

Figure 1. The Consort-Flowchart of participants through each stage of the trial.

Table 3 shows participants' characteristics at baseline. The two study groups were similar in all characteristics except for the average PA, as measured by Physical Activity Scale for Elderly (PASE) score: CG had a significantly higher level of physical activity, in particular spent in leisure time and household activity (PASE score: Respectively, 141.8 vs. 102.3 and 58.2 vs. 25.3). Overall, at baseline, the APA group presented more risk and prognosis factors for osteoporosis than the CG, but without significant differences. Over 90% of participants had at least one co-morbidity and all 44 patients were on drug therapy for OP and did not change the pharmacological treatment throughout the intervention period.

Table 3. Baseline characteristics of the participants, socio-demographic data, and outcome measures

Characteristics	**APA Group (*n* = 26) *N* (%) or mean ± SD**	**CG (*n* = 18) *N* (%) or mean ± SD**	***t* Test; *p***
Age	67.6 ± 4.6	67.4 ± 4.7	0.124; 0.902
Body mass index	24.7 ± 3.6	23.9 ± 3.4	0.820; 0.417
Classification of osteoporosis			
Primary	23 (82.1%)	17 (94.4%)	1.462; 0.227
Secondary	5 (17.9%)	1 (5.6%)	
Number of vertebral fractures	2.0 ± 1.2	1.8 ± 1.3	0.549; 0.586 not significant
Number of falls	3 (10.7%)	2 (11.1%)	
Osteoporosis of parents or siblings	12 (42.9%)	8 (44.4%)	0.011; 0.916
Early menopause (<45 y)	2 (7.1%)	0 (0%)	1.344; 0.246
Dietary deficiencies in vitamin D	0 (0%)	0 (0%)	-
Amenorrhea (>6 m)	0 (0%)	1 (5.6%)	1.590; 0.207
Anorexia nervosa	1 (3.6%)	2 (11.1%)	1.023; 0.312
Glucocorticosteroids	2 (7.1%)	0 (0%)	1.344; 0.246
Smokers	5 (17.9%)	1 (5.6%)	1.462; 0.227
Alcohol [a]	0 (0%)	0 (0%)	-
Physical activity (<30 min) [b]	13 (46.4%)	7 (38.9%)	0.253; 0.615
CIRS [c]	27 (96,4%)	17 (94.4%)	0.104; 0.747
Severity Index	0.2 ± 0.1	0.2 ± 0.1	−0.680; 0.500
Osteoporosis medication	28 (100%)	18 (100%)	-
PASE	102.3 ± 46.6	141.78 ± 70.7	−2.286; 0.027

Characteristics	**APA Group (*n* = 26) *N* (%) or mean ± SD**	**CG (*n* = 18) *N* (%) or mean ± SD**	***t* Test; *p***
Leisure time activity	25.3 ± 38.4	58.2 ± 50.1	−2.515; 0.016
Household activity	74.0 ± 33.7	80.1 ± 37.7	−0.570; 0.572
Work-related activity	3 ± 7.5	3.5 ± 8.1	−0.215; 0.831

Notes: APA = Adapted Physical Activity; CG = Control Group; SD = standard deviation; CIRS = Cumulative Illness Rating Scale (maximum value = 4, minimum value = 0); PASE = Physical Activity Scale for Elderly; a ≥1 glass of wine or beer per day; b <30 min of moderate/vigorous physical activity per day; c number of patients with CIRS values ≥ 3.

Table 4 shows the mean scores of all primary and secondary outcomes at the beginning of the study and after six months of follow-up, and their respective mean changes from baseline. At baseline, the APA group was very disadvantaged compared with CG for most of the investigated outcomes. This finding was consistent with the difference in physical activity (PASE-score) observed between the two groups. However, while continuing to perform their general motor activities, the CG patients showed a slight worsening at follow-up and, in any case, did not improve. On the contrary, the APA group reached and exceeded the performance of the CG in HRQOL, fear of falling, and motor performance.

Table 4. Outcome measures at baseline, follow-up, and change at 6 months.

Variables	APA Group (N = 22)				Control Group (N = 18)				Between Groups a
	Baseline	Follow-Up	Change	Within Group pValue	Baseline	Follow-Up	Change	Within Group pValue	p Value
ECOS-16	2.49 ± 0.67	2.04 ± 0.57	−0.5 ± 0.5	0.001	1.97 ± 0.61	1.98 ± 0.59	0.0 ± 0.3	0.329	0.020
Pain score	2.68 ± 0.84	2.22 ± 0.84	−0.5 ± 0.7	0.014	2.23 ± 0.98	2.22 ± 0.80	0.0 ± 0.7	0.943	0.160
Physical Function score	1.95 ± 0.60	1.55 ± 0.49	−0.4 ± 0.5	0.003	1.59 ± 0.50	1.56 ± 0.56	0.0 ± 0.4	0.630	0.120
Psychosocial score	2.36 ± 1.01	2.07 ± 0.81	−0.4 ± 0.7	0.048	1.83 ± 0.70	1.89 ± 0.73	0.1 ± 0.4	0.617	0.200
Fear of Illness score	3.59 ± 0.91	2.86 ± 1.31	−0.7 ± 1.0	0.005	2.50 ± 0.99	2.64 ± 1.25	0.1 ± 0.8	0.297	0.020
PCS	2.31 ± 0.68	1.89 ± 0.64	−0.4 ± 0.5	0.002	1.91 ± 0.69	1.89 ± 0.64	0.0 ± 0.4	0.955	0.067
MCS	2.98 ± 0.79	2.46 ± 0.88	−0.5 ± 0.6	0.002	2.17 ± 0.70	2.26 ± 0.77	0.1 ± 0.5	0.262	0.027
EuroQoL VAS	65.00 ± 18.00	70.24 ± 18.67	6.0 ± 16.6	0.126	71.11 ± 15.01	73.06 ± 18.24	1.9 ± 12.1	0.503	0.589
FES-I	29.09 ± 8.18	24.41 ± 6.71	−4.7 ± 7.4	0.006	23.83 ± 6.60	24.72 ± 8.00	0.9 ± 2.5	0.181	0.059
Lumbar back pain VAS	4.87 ± 2.33	3.65 ± 2.75	−1.2 ± 2.6	0.029	3.73 ± 2.76	4.03 ± 2.51	0.3 ± 3.3	0.758	0.719
Tinetti Scale Total	24.77 ± 5.42	27.59 ± 0.80	2.8 ± 5.2	0.003	25.83 ± 3.13	25.11 ± 3.71	−0.7 ± 2.4	0.203	0.002
Balance	14.00 ± 2.96	15.68 ± 0.65	1.7 ± 2.8	0.005	14.67 ± 1.75	14.11 ± 1.97	−0.6 ± 1.7	0.190	0.001
Gait	10.77 ± 2.56	11.91 ± 0.29	1.1 ± 2.5	0.042	11.17 ± 1.69	11.00 ± 1.85	−0.2 ± 1.4	0.606	0.014
6-MWT	395.62 ± 66.23	447.80 ± 57.31	52.2 ± 42.1	<0.001	420.52 ± 60.65	411.99 ± 56.99	−8.5 ± 45.2	0.420	<0.001
Borg Scale	3.19 ± 1.75	1.68 ± 1.09	−1.5 ± 1.5	0.001	2.75 ± 2.15	2.33 ± 1.50	−0.3 ± 2.0	0.605	0.024
Chair Sit-and-Reach right	90.19 ± 12.32	96.36 ± 1.77	6.5 ± 8.0	0.002	94.64 ± 0.44	94.00 ± 10.10	−0.6 ± 11.0	0.660	0.106
Chair Sit-and-Reach left	89.98 ± 11.22	97.05 ± 11.05	7.3 ± 7.6	0.001	94.72 ± 10.68	93.53 ± 8.89	−1.2 ± 9.3	0.831	0.026

Notes: PCS = Physical Component Summary; MCS = Mental Component Summary; VAS = Visual Analogue Scale; a Changes in measures between baseline and follow-up are compared using linear multiple regression with correction for age, baseline scores of the analyzed variable, and PASE

More specifically, HRQOL, measured by the ECOS-16 questionnaire, significantly increased in the APA group in all summary scores, whereas it remained unchanged in the CG (comparison within groups). After adjustment for age, baseline ECOS-16 and PASE, the ECOS-16 total score, "fear of illness" score, and MCS score showed statistically significant changes also in the comparison between groups. Differently, the quality of life, estimated with the generic EuroQoL VAS questionnaire, remained unchanged within and between groups.

In general, after six months of follow-up, a significant enhancement in the APA group and no changes in the CG were also found for all secondary outcomes (comparison within groups). In particular, in the APA group, the fall-related self-efficacy (FES-I) improved significantly by almost five points ($p < 0.01$) while in the CG it worsened on average by almost 1 point. These findings agree with the results obtained for lumbar back pain (APA group −1.2 points, $p < 0.05$; CG +0.3 points, ns) and the Tinetti Scale used to measure gait and balance (APA group +2.8 points, $p < 0.01$; CG: −0.7 points, ns). After adjustment for unbalanced variables, the comparison between groups maintained significant effects for the Tinetti Scale (both balance and gait subscales).

As regards the performance in motor tests, the functional exercise capacity significantly increased in the APA group (6-MWT: on average +52.2 m, $p < 0.001$), with a significant decrease of the perceived exertion (Borg Scale −1.5 points, $p = 0.001$) after the intervention. The flexibility of the column also showed an improvement in the APA group for both the right and left side (Chair Sit-and-Reach, respectively: −0.6 and −1.2). No significant differences were observed in the motor test performance of CG between baseline and follow-up. The comparison between groups confirmed the significant effects of the intervention for all motor tests, except for the right Chair Sit-and-Reach.

Table 5 shows the effect size calculated for each of the evaluated variables. According to the statistical reference parameters proposed by Cohen to interpret the results, a “big” effect (>0.8) of the intervention was observed for six outcomes (HRQOL, fear of falling, balance, functional exercise capacity, flexibility of the column at the left side) and a “medium” effect (>0.5) for four outcomes (lumbar back pain intensity, gait, perceived exertion, flexibility of the column at the right side) (Cohen, 1998).

Table 5. Effect sizes (ES) calculated using Cohen’s d

Parameter	Effect Size (d)
6-MWT	1.390
ECOS-16	1.204
FES-I	1.007
Chair Sit-and-Reach left	1.000
Tinetti Scale Balance	0.969
Tinetti Scale Total	0.871
Chair Sit-and-Reach right	0.739
Borg Scale	0.654
Tinetti Scale Gait	0.639
Lumbar back pain VAS	0.510
EuroQoL VAS	0.276

5.5 Discussion

The APA intervention had a significant effect on all the components of the quality of life, as measured by the disease-specific ECOS-16 questionnaire, in women with osteoporosis and vertebral fractures. In the comparison between APA group and CG, after adjustment for the confounding variables, the differences were statistically significant for the ECOS-16 total score and MCS partial score. HRQOL improvement had an effect size of 1.204

("big" effect according to the Cohen reference) and reached the Minimal Clinically Important Difference (MCID) that must be achieved to prove an improvement in clinical status. For the ECOS-16 score, the suggested MCID is 0.5 points, representing the least improvement in general health status: "Slightly better" (Badia et al., 2004). In contrast, the HRQOL, as measured by the generic instrument EuroQoL, did not improve after the intervention, confirming the results obtained by Papaioannou et al., who compared a disease-specific (QOQL) and a generic (Sickness Impact Profile) tool to measure HRQOL after a six-month home-based exercise program (Papaioannou et al., 2003). The EuroQoL questionnaire proved unsuitable for assessing the quality of life of our enrolled women, probably because the variables investigated are not discriminatory for patients who, already at baseline, had a certain degree of autonomy and mobility.

The intervention produced significant improvements for all secondary physical outcomes: Significantly higher scores were obtained for balance, gait, functional exercise capacity, perceived exertion, and flexibility. By improving physical performance, women probably increased self-esteem and self-confidence and this could have contributed to the improvement of QoL observed for mental dimension of ECOS-16 (MCS score). For fear of falling and lumbar back pain, the APA group significantly improved after the intervention, but differences were not significant in the comparison between groups. However, the APA group, which was very disadvantaged at baseline for both conditions, strongly reduced the gap with the CG at follow up, achieving for fear of falling a big effect (1.007). For the lumbar back pain our intervention was less effective. Very few studies are currently being carried out to evaluate the effects of exercise programs in patients with vertebral osteoporosis fractures. The most recent literature review of the Cochrane Database identifies only seven (Giangregorio et al., 2003). The impact of physical exercise programs on OP appears to vary depending on the frequency, duration, and intensity (Rossini et al., 2016). In accordance with our results, Bergland et al. and Evstigneeva et al. achieved beneficial and significant effects of exercise programs on the quality of life, balance, and functional mobility of patients with osteoporosis-related vertebral fractures, although using different assessment tools and physical exercise delivery times of only three months, compared with ours (Bergland et al., 2011; Evstigneeva et al., 2016). The instruments we used for the evaluation of motor performance (6-MWT, Borg scale, Chair Sit-and-Reach, Tinetti scale) are routinely applied in other fields of medicine or sports and to a lesser extent for patients with OP (Tinetti, 1986; Demers et al., 2001; Macko et al., 2005; Enright, 2003; Shipp et al., 2000; Jones et al., 1998). Our findings show that these tests—easy, quick, and economical to use—are suitable to evaluate the beneficial effect of PA even in women with osteoporosis-related vertebral fractures.

The FES-I scale was used in other studies for the measurement of fear of falling in subjects suffering from OP with or without vertebral fractures (Olsen et al., 2014; Stanghelle et al., 2018). Olsen et al., investigating as a primary outcome the fear of falling, achieved a significant effect of exercise on the decrease of FES-I score. In our experimental conditions, the difference of FES-I score between APA group and CG was at the limit of the statistical significance ($p = 0.059$) (Table 4). This contrasting result is probably due to the smaller sample size of our study that had as primary outcome HRQOL (sample size according to power analysis: 36 subjects), while Olsen et al., using the fear of falling as primary outcome, estimated the size of the sample at 64 subjects. Nevertheless, in our study, the effect size calculated for the FES-I (1.007) was greater than that of Olsen et al. (0.4 and 0.7, respectively, after three and 12 months from baseline), which may suggest a higher appropriateness of the exercises given or an optimal duration of our intervention to reach the maximum effect (Olsen et al., 2014).

Our study had an average adherence of 75.8%, higher than that of other studies of similar duration (Giangregorio et al., 2013; Papaioannou et al., 2003). This is an encouraging result which, together with the satisfaction expressed by the participants, demonstrates the feasibility of the proposed APA program. The feasibility of this intervention is also ensured by the type of exercises proposed that require simple equipment (i.e., mats, sticks, sponge balls, elastic bands) and not particularly large spaces. The only specific requirement is that of personnel trained in the provision of physical exercise. It is known that adherence to exercise appears higher among studies that include supervision (Giangregorio et al., 2013), and the role of trainers is essential to motivate and encourage participation. Another point of strength is the absence of withdrawals due to adverse events, a result that supports the adequacy and safety of the administered exercise protocol, whose intensity was calibrated on the characteristics of the patients and monitoring of their responses. According to a "patient-centered" approach, particular attention was paid to the choice of exercises, which had the objective of instructing patients to establish a workload and number of repetitions adapted to their individual functional capacity. Through feedback, the patient was educated to self-correction, to gain confidence in her abilities, to mitigate fears and hesitations in order to obtain motor autonomy.

The main limitation of the study is due to a possible selection bias related to the quasi-experimental trials, which were non-randomized studies. In order to favor the recruitment, we left the patients free to choose to participate in the intervention or control group. This approach allows for a selection bias that has been partially mitigated by the inclusion of patients referred to the same rheumatology unit, with similar demographic and clinical variables. However, the two groups were different at baseline, having the intervention group a lower level of physical activity and minor fitness compared with the control group. For this reason, in order to make the results of the two groups as comparable as possible, we applied corrective actions through an adequate statistical analysis. In the comparison between groups, we analyzed the outcomes for group differences through a multivariate analysis model, by adjusting for age, baseline PASE score, and each unbalanced variable. Non-randomization is certainly an important limit, but, in a public health context, with a view to implementing APA, it is also important to know whether an intervention can work for the patients who choose it. The patients included in our intervention group, due to non-randomization, probably represent only a part of patients with osteoporotic vertebral fractures, but having obtained beneficial effects on these women, probably more fragile than the generalized osteoporotic patients, is a result of some interest and relevance in the perspective of generalizing the pilot study intervention to a wider population.

Currently, in Italy, there is much interest and debate concerning the role of APA as a tool for prevention of chronic diseases and their consequences (Romano Spica et al., 2015; Weintich et al., 2014). Various regional health authorities, including Emilia Romagna, have encoded protocols of APA specifically designed to provide opportunities for people with chronic diseases such as back pain, neurological disorders, and arthrosis, but not for OP with vertebral fractures (Calugi et al., 2016; Regione Emilia Romagna 2016; Taricco et al., 2014). The implementation of APA programs is made available to a network of gyms, uniformly distributed throughout the territory, which, after the accreditation of the regional health authorities, can administer the APA protocols of proven efficacy to chronic patients addressed by the general practitioner or the specialist doctor (Regione Emilia Romagna, 2016; 2014).

5.6 Conclusions

The purpose of this study was primarily to propose an APA program of physical exercises specifically designed for osteoporotic women with particular fragility due to vertebral fractures. The feasibility, the safety, and the positive effect of the proposed exercise protocol on quality of life, fear of falling, balance, and functional exercise capacity show that APA programs, based on protocols similar to ours, should be extended also to patients with osteoporosis and a history of vertebral fracture. The results of this study can certainly be used to support policy makers who can favour the conditions to implement APA projects in their territory, through measures included in Health Plans of Public Health Authorities. To our knowledge, the studies that reported exercise protocols for osteoporotic patients are very few (Sinaki, 2012). The APA protocol reported here (Appendix) may be useful for future projects to be implemented in a wider setting.

6. Study III

A Randomized Clinical Trial to Evaluate the Efficacy and Safety of the ACTLIFE Exercise Program for Women with Post-menopausal Osteoporosis: Study Protocol

6.1 Introduction

A number of randomized controlled trials proved the efficacy of exercise programs versus no exercise, sham programs or drugs in women with OP (Howe et al., 2011). Exercise programs were administered individually as home training (IHT) or in gyms as group training (GGT). However, to our knowledge, there are no studies comparing the effects of an exercise program specifically designed for women with post-menopausal OP when administered as IHT versus GGT. There are studies that compared the benefits of the two settings for exercise programs designed for the prevention of other conditions. Exercise aimed at improving pain and function in chronic nonspecific low back pain is more effective when delivered in gyms with supervision (Hayden et al., 2005; Liddle et al., 2004). Studies compared the Otago exercise programs for fall prevention proved a better efficacy in group activity for variables related to physical and mental health (Helbostad et al., 2004; Kyrdalen et al., 2014).
Regular participation in a PA program is vitally important for the geriatric population to prevent decline in mobility function (Hicks et al., 2012). However, adherence to an exercise program is problematic in all age groups, but particularly among older adults.

For instance, a meta-analysis of 127 exercise interventions for older adults demonstrated that, within the first three to six months, 40–65% of the participants will drop out (Dishman et al., 1996). In a previous study, investigated predictive factors of improved back-pain status among older adults with chronic back pain participating in a 12-month GGT program, has been found that adherence was the key predictor of improved back pain (Singh et al., 2002). Adherence, in turn, was independently associated to accessibility to gyms. Thus, the question arose whether IHT could be a valid alternative of GGT since, from the theoretical point of view, it could overcome problems related to accessibility to gyms or timetable rigidity.

This paper aimed at presenting the protocol of a randomized trial for evaluating the efficacy of a physical activity program (12-month duration) designed to improve the quality of life in women with post-menopausal OP when administered IHT or GGT. We relied on the most recent scientific evidence in this field, to develop the exercise program designed to improve the quality of life in this population (Giangregorio et al., 2014; Marini et al., 2019; American College of Sport Medicine, 2018). We hypothesize that efficacy and safety of the exercise program are equal when administered as GGT or IHT. However, differences in terms of intensity, supervision, progression and adherence between the two groups may have different impact on the outcome measures.

6.2 Materials and Methods

This study is carried out within the project "Physical ACTivity: the tool to improve the quality of LIFE in osteoporosis people" (ACTLIFE) funded by European Commission within the Erasmus+ Sport program (Grant Agreement N2017-2128/001-001). The study was approved from the Local Ethics Committee (Comitato Etico Indipendente di Area

Vasta Emilia Centro, CE-AVEC) of the Emilia-Romagna Region (reference number AVEC: EM601-2019_696/2018/Sper/IOR_EM2). The trial was registered in ClinicalTrial.Gov (NCT04179903).

6.2.1. Study Design

The study is a randomized trial with two parallel groups: in the first group the 12-month ACTLIFE exercise program is performed as IHT, while in the second as GGT. It is single blinded since professionals who evaluate patients are not aware to which exercise group patients are assigned. Patients are assessed at baseline and after 6 and 12 months.

6.2.2. Participant Recruitment

Sedentary patients with primary post-menopausal OP are recruited by the Centro Osteoporosi e Malattie Metaboliche dello Scheletro (COMMS) of the Istituto Ortopedico Rizzoli of Bologna, Italy. The participation to the study was proposed to all women attending COMMS for a medical visit who met the inclusion criteria. In addition, to facilitate patients' recruitment, the study was advertised on local media requesting the women who might be interested to contact the COMMS for a preliminary evaluation.

A letter was sent to a participant's home in an anonymous envelope, asking the patient to contact the person in charge of the study (or his staff). The letter described the scientific purposes, not specifying the type of study.

During the study, all pharmaceutical treatments, and their modifications were recorded. Patients were recommended to adhere pharmacological treatment for OP, as prescribed.

6.2.3. Inclusion and Exclusion Procedures

The inclusion/exclusion criteria (Table 1) were identified during a preliminary medical visit and functional assessment. If eligible, patients were requested to sign the informed consent form. Subsequently, they were recruited and given an individual study code (number based on the order of inclusion in the study). Personal data were recorded only on the informed consent form together with the individual study code. Patients were identified only with the individual study code in all the other forms and databases used in the study.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
▪ Signed informed consent ▪ ▪Post-menopausal women aged ≥ 40 years ▪ Lumbar spine or femur T-score ≤ -2.5 ▪ SPPB* ≥ 6 ▪ Having exercised less than 30 minutes per week in the last 6 months	▪ Secondary osteoporosis ▪ Severe impairment of communicative and/or sensorial functions ▪ Heart failure (NYHA** class ≥ 2) ▪ Unstable angina ▪ Pulmonary disease requiring oxygen therapy ▪ Symptomatic orthostatic hypotension ▪ Hypertension in poor pharmacologic control (diastolic >95 mmHg, systolic >160 mmHg) ▪ Previous implant of prosthesis at upper or lower limbs ▪ Relevant neurological condition impairing motor or cognitive function

Inclusion Criteria	Exclusion Criteria
	▪ Any other condition that the General Practitioner considers to contraindicate the participation in an exercise program of moderate intensity

* SPPB = Short Physical Performance Battery [18,19]; **NYHA = New York Heart Association (Dolgin et al., 1994).

6.2.4. Description of Procedure and Randomization

The professional who enrolled the patients assigned them to the GGT or IHT group after contacting a dedicated person responsible of the maintenance of the randomization list. The randomization list was defined using the random numbers generator available on the web site of the Emilia-Romagna Region (http://wwwservizi.regione.emilia-romagna.it/generatore/). For each of the two groups (IHT and GGT), 26 numbers from 1 to 52 were generated.

6.2.5 Allocation, Concealment and Blinding

The random assignment to IHT or GGT groups was performed by different personnel than those who performed the assessments at baseline, six and 12 months.

The list of allocation of the patients to one of the two groups was kept locked and separated from the rest of the material used to collect patients' information. At any time, professionals who performed the assessments were not aware to which group patients had been assigned. Patients were clearly instructed not to reveal to the trainer who performed the assessment which exercise group they were in.

6.2.6 Sample Size

Sample size was estimated considering the questionnaire ECOS-16 (Badia et al., 2004) as a primary outcome measure of the study. From published evidence, ECOS-16 has a standard deviation of 0.8 at final follow-up assessment and a minimal clinically important difference of 0.69. This leads to an estimated effect size of 0.863. Considering an alpha error of 0.05 and a power of at least 0.8, the minimum size of the sample was estimated in 18 patients per group, for a total of 36 patients. Considering a 15% drop-out (estimated on the basis of the experience of a previous study by Marini et al., 2019, focused on patients with OP vertebral fractures), preferring to be even more conservative, we estimated an appropriate sample size of 26 patients for each group, for a total number of 52 participants. Power analysis was carried out with G*Power 3.1.9.2.

6.2.7 Data Collection and Measures

Instruments to record primary and secondary outcome measures and the time of their used are summarized in Table 2.

Table 2. Outcome assessment

Outcome Assessment	**Baseline (T0)**	**6 Months (T1)**	**12 Months (T2)**
ECOS-16	x	x	x
BMI	x		x
BIA	x		x
WHODAS	x		x

Outcome Assessment	Baseline (T0)	6 Months (T1)	12 Months (T2)
FES-I	x	x	x
Falls	x	x	x
PASE	x	x	x
6-MWT	x	x	x
Delos	x		x
Handgrip	x	x	x
Occiput-wall distance	x	x	x
Chair sit and reach	x	x	x
Range of motion (shoulder, hip, knee)	x	x	x
Adherence		x	x

6.2.8 Primary Outcome

The primary outcome was QoL measured with the Short Osteoporosis Quality of Life Questionnaire (ECOS-16) (Badia et al., 2004), specifically designed to measure the health related QoL in post-menopausal women with OP. It was based on the combination of Osteoporosis Quality of Life Questionnaire and Quality of life questionnaire of the European Foundation for Osteoporosis. Specific-disease instruments have been proved to be of paramount importance to evaluate responses to treatments (Patrick et al., 1989; Testa et al., 1996). Validity and reliability of ECOS-16 had also been previously proved for the Italian version of the questionnaire (Salaffi et al., 2007). This measure was repeated at baseline, 6 and 12 months.

6.2.9 Secondary Outcomes

Secondary outcomes were measured, which were recognized to influence QoL.

Body Mass Index (BMI) was calculated as the ratio of body weight squared (kg/m2) and the impedance measurements were performed with bioimpedance analysis (BIA 101 Anniversary®, Akern, Florence, Italy) (Piccoli et al., 2005; Vienna et al., 1999; Savastano et al., 2010) to evaluate body composition (fat mass, muscle mass and bone mass).

The WHO Disability Assessment Schedule (WHODAS) (Ustun et al., 2010) is composed of 36 items to represent the six activity and participation domains (cognition, mobility, self-care, getting along, life activities, participation). The Italian version of the instrument has been previously validated (Federici et al., 2017; Federici et al., 2009).

Falls Efficacy Scale International (FES-I) (Yardley et al., 2005) is a 16 items questionnaire to assess fear of falling during simple and complex motor and social activities; this instrument has also been validated in Italian (Ruggiero et al., 2009). Furthermore, history of fall was recorded by self-reported falls (number) in the previous three months.

Physical Activity Scale for Elderly (PASE) (Washburn et al., 1999; Washburn et al., 1993), which has also been validated in Italian (Covotta et al., 2018), is a scored survey designed specifically to measure the weekly physical activity in adult and aged population. Its score combines information on leisure, household and occupational activity.

Individuals' functional capacity is estimated by measuring several domains. Gait performance was evaluated by the 6-Minute Walk Test, which has been proven to be a valid and reliable instrument (Demers et al., 2001; Macko et al., 2005). It is a test very easy to administer and allows to measure patients' residual functional capacity in a number of pathological conditions (Gruet et al. 2010; Kervio et al., 2003; Kervio et al., 2004; Enright et al., 2003), including OP (Shipp et al., 2000).

To better understand individuals' functional capacity modifications, we also included measures of standing balance, muscle force and joint mobility, which are considered prerequisites of motor functioning. Standing balance is estimated by the validated Stability Index (Riva et al., 2013) for both right and left lower limbs. For these measures, the Delos Postural Proprioceptive System® (Delos S.r.l., Torino) were used. For muscle force, the hand grip (Prasitsiriphon et al., 2018; Xue et al., 2010) was bilaterally measured by Hydraulic Hand Jamar Dynamometer®. This measure has been strongly associated to frailty in elderly population (Prasitsiriphon et al., 2018). The occiput-wall distance was used to estimate postural alignment (Balzini et al., 2003). The measure was the distance between the head and a wall, while the subject stood with their heels touching a wall. Sit-and-reach tests were used as indirect measures to assess hamstring and low back flexibility. This test measured the fingertips-to-tangent feet distance of the subjects when they were sitting on a chair (Jones et al., 1998).

Finally, joint mobility of shoulder, hip and knee, which are fundamental prerequisites of healthy and safe motor behavior, were assessed by routinely used clinical measures (Kendal et al., 1993; Clarkson et al., 2013). Shoulders were evaluated in sitting position, requesting the subject to actively flex both the extended arms while holding a 1.2 m stick. The minimum distance between the hands was measured when the stick was over the vertex of the head. When subjects were unable to bring the stick in the requested position, even with the largest holding, the stick length was conventionally attributed. Hip and knee ROMs were bilaterally evaluated in lying position asking an active flexion of one joint while the other was kept in neutral position. Maximum flexion degree is reported.

Patients’ adherence to the exercise program was recorded by home or gyms weekly logs and measured as the percentage of exercise sessions actually performed/total number of scheduled exercise sessions.

The reasons of interruption and abandons were carefully evaluated during the study period. All patients were also instructed to contact the project staff to communicate adverse clinical events or other reasons of non-participation, whenever this was deemed necessary. Finally, patients’ satisfaction is assessed at the end of the study by a specifically designed questionnaire based on seven-point Likert scale (Jaeschke et al., 1989; Goldsmith et al., 1993) investigating the perceived quality and self-efficacy of the ACTLIFE program.

6.2.10 Intervention

The exercise program was administered to both GGT and IHT groups. It was aimed at improving joint mobility, muscle force, static and dynamic balance, motor coordination and endurance. For each subject of both groups, the program was structured in 2-days/week 1-hour sessions and lasts 12 months.

Moreover, subjects were requested to choose an additional third day of the week to carry out at least one of the following activities: brisk walking, cycling or swimming to reach the weekly amount of exercise of 150 minutes recommended by World Health Organization (WHO, 2010).

Each session was structured in the following sections: warm-up, strength, balance, flexibility and cool down. The exercise program was redundant to allow the trainer to adapt the exercise program to the participants' needs and preferences. The protocol defines the strategies to instruct patients and to check the correct and safe execution of the motor tasks and the criteria for varying workload and number of repetitions to adapt to each individual functional capacity. For both groups, the exercise program was administered by a graduate trainer in Science and Techniques of Preventive and Adapted Physical Activity.

GGT was performed in adequately equipped gyms, which had stipulated formal agreements with the University of Bologna under the direct supervision of a graduate trainer. Every 6-8 weeks, the trainer upgraded the exercise program on the basis of the improvement obtained by the gym group.

For the IHT group, the trainer explained to the participant the PA program to be performed at home in one or more individual sessions. At the end of these initial instructional session(s), the participant was also given educational material on the purpose of the exercises and how to perform them correctly. Participants were requested to strictly adhere to the given instructions. Subsequently, the trainer contacted the IHT participants at pre-established time intervals: once a week for the initial two weeks and twice a month for the following 11 months to encourage participants to exercise regularly and to get information on the health status. Every 6-8 weeks, an appointment was scheduled to review the exercise program. All contacts of trainers with IHT participants were recorded.

Monthly logbooks were used to record the adherence to the exercise program by noting down the execution of this session both at home and in the gym. For the former, a recording was made by the participant, for the latter by the trainer. The logbooks were subsequently collected by research staff or returned by mail with pre-paid envelopes. Finally, a telephone number and a week time schedule in which a trainer was available for further explanations and suggestions were given to them.

6.2.10 Statistical Analysis

The qualitative variables are summarized in terms of frequency, the quantitative ones in terms of mean and standard deviation for both groups and for the three times of assessment. For the analysis of the results, the principle of intention to treat is used, adjusting for adherence to the exercise program.

To compare the general characteristics between the two groups, the Student's t-test is used for parametric quantitative variables, the Mann Whitney test for non-parametric variables and Chi-square test for qualitative dichotomous ones.

To compare the changes between the two settings among baseline and follow-up assessments the analyses of variance for repeated measures followed by of Sidak post-hoc comparisons tests for paired samples were used for the quantitative variables and the Friedman test, followed by the Wilcoxon test for paired samples with Bonferroni correction for non-parametric ones.

6.3 Discussion

Several lines of evidence have consistently proven the importance of regular participation in specific exercise programs to prevent/minimize the osteoporotic bone deterioration and its consequences in post-menopausal women (Papaioannou et al., 2010; Todd et al. 2004; Howe et al., 2011). However, to the best of our knowledge, no study has yet examined exercise programs for women with post-menopausal OP when administered as IHT or GGT. From a theoretical point of view, each setting may have advantages and disadvantages (Helbostad et al., 2005; Hicks et al., 2012; Helbostad et al., 2004). Older frail people may have a reduced functional capacity and have difficulty following the rhythms of group activity. Travel to and from the gym may be problematic, especially during the winter months, and/or require regular, often unavailable, commitments from family members or caregivers. For women with good health and functional status attending gyms at scheduled intervals may be problematic due to family or work obligations. On the other hand, the activity in the gym has a greater level of supervision and, probably, will ensure a greater amount of exercise to actually be performed. Numerous factors have been demonstrated as barriers to regular exercise in older adults, including perceived poor health, poor self-confidence, low motivation and perceived exercise enjoyment (Lee et al., 2008). Experts in group dynamics have suggested that participation in regular group activities can lead to true behavior change through a pathway of social interaction, group bonding and behavior imitation (Yalom et al., 1985). In other patient populations (i.e., patients with cancer), group exercise has been shown to result in improved quality of life, greater self-confidence, increased motivation and a sense of camaraderie with other participants (Losito et al., 2006). Finally, clinicians may consider the exercise safer when performed under supervision of a professional trainer and, therefore, more willing to advice GGT than IHT.

Some limitations of the present protocol must be considered because they may influence the interpretations of the findings of the study. The study did not consider a control group performing sham or no activity since we focused on comparing GGT versus IHT. Therefore, we cannot empirically prove the efficacy of the exercise program administered either as GGT or IHT. However, the vast and substantial published evidence (Consensus Development Conference, 1993; Cooper et al., 2013; Choi et al., 2013; Bessette et al., 2008; Papaioannou et al., 2010; Todd et al. 2004; Howe et al., 2011) have led the medical community to recommend patients with OP physical activity extensively. Thus, the implementation of a control group appeared to the authors to be not feasible and not acceptable from an ethical point of view. Participants are post-menopausal women recruited on the basis of inclusion/exclusion criteria (Table 1). Most of them may be under pharmacological treatment not only for OP but also for other chronic conditions with high prevalence in post-menopausal women. We cannot exclude that both associated chronic conditions and pharmacological treatments may influence the outcome of the study. Therefore, data related to comorbid conditions and pharmaceutical treatment were recorded at baseline and during the entire study.

6.4 Conclusions

Although guidelines for OP prevention recommend to exercise regularly, there are no specific indications on the best setting to exercise. The results of this study could be relevant for future indication of the best setting and strategy to ensure the adherence to the physical activity and add to the current evidence base for clinicians, exercise trainers and policy makers.

7. Conclusion and future directions

From the present doctoral thesis emerges the feasibility, the safety and the positive effects of adapted physical activity protocols specifically designed and administered by trainers educated to deal with these conditions. The results have enabled us to better understand the relationship between osteoporosis and quality of life, and most importantly, that APA can be a good strategy helping to improve the QoL of osteoporotic people.

The results obtained in the present thesis contributed in providing new scientific evidence to expand the knowledge in order to propose and define future perspectives and studies. Furthermore, it is worth pointing out the role of these studies in defining future strategies to be applied by the involvement of policy makers, in order to primarily improve people's quality of life.

Daily PA and a carefully planned exercise program enhance bone health by increasing bone mineral density during all stage of life. For these reasons, APA interventions are recommended in the prevention and treatment of OP and to decrease the risk of future bone fractures (American College of Sports Medicine, 1995). Exercise is the only strategy that has the potential to improve all modifiable fracture risk parameters (fall risk, fall impact, bone strength), if it is tailored to each individual's needs and the right type and dose is prescribed. Accordingly, PA is excellent for both disease prevention and for those with limited financial means, benefiting from both public health and the individual QoL. Nowadays the burden of osteoporosis consequences affecting both physical as well as mental health, is not yet sustainable either socially or financially. Therefore, exercise programs for individuals with OP are crucial as a means of achieving the goal.

In the scenario cooperation between researchers and patients, such as in the studies objects of this thesis, are fundamental and the health authorities need to be aware and involved. Indeed, more information on how treatments impact patients in terms of physical function and everyday activity would benefit both healthcare professionals and persons with OP in making treatment decisions and improving overall outcomes (Kerr et al., 2017).

Finally, the development of standardized guidelines for exercise and bone health in older adults and those with osteoporosis will make important contributions to clinical guidelines for OP management and public health messages to prevent fractures which, despite their high prevalence, are currently not being prioritized by the National Health Care Systems. Therefore, action needs to be taken.

Future directions:

- The costs for health care are massive when osteoporosis has set in. Time and money can be saved if these fractures are prevented. Therefore, it is important for the public health sector to educate primary care workers about the value of physical exercise as a means to prevent chronic diseases, including OP;
- A recent study showed that fracture assessment of osteoporosis patients is decreasing in many countries, due to the COVID-19 pandemic (McCloskey et al., 2020). As OP creates a heavy burden on the health systems, it is crucial that it is diagnosed and not neglected due to the current challenges;
- In connection, restriction measures taken during the COVID-19 pandemic led not only to the increase in sedentary behaviour, but also to the interruption of PA both indoor and outdoor with possible negative consequences on the status of osteoporotic subjects. In light of this, feasible strategies such as home-based

exercise program, are urgently needed to preserve bone and muscle mass improving also the QoL of people with OP (Girgis et al., 2020);

- A challenge in prescribing PA as a treatment for osteoporosis is supporting adoption and compliance to exercise protocols. In this regard, it has been demonstrated that lack of time and access to transportation are the most commonly reported barriers to exercise participation in patients with OP (Rodrigues et al., 2016). Thus, clinicians and researchers should explore strategies to facilitate exercise participation in this population, such as the safety and efficacy of home-based impact exercise protocols;
- Exercise seems to have a positive influence on bone metabolism, further studies are needed to better assess the effectiveness of PA on bone metabolism taking into account the combined effects with pharmacological treatment in people with OP.
- Future research should work towards developing methods of objectively monitoring participation in PA and exercise specifically targeting osteogenesis, particularly the measurement of ground reaction forces in long-term interventions (McMillan et al., 2017);
- For future exercise studies, a longer time span is needed, in order to see if the overall patient's quality of life, and relative outcomes, are able to reach better improvement and able to be maintained.
- Stakeholders, taking into account the magnitude of effect on fracture risk in a population, should identify and contribute to modify risk factors for falling and set high-priority to OP and its consequences;
- In the future, the precise components (type, intensity, duration, frequency) of an effective exercise program for OP prevention and treatment should be stated,

disseminated and adopted by the policy maker in order to improve collective and individual's quality of life;

- Communication between healthcare professionals and people with OP should be improved in terms of the information and advice provided to patients as, having a greater awareness, may encourage people with OP to better comply and persist with treatment. In order to improve these interactions clinicians and other healthcare professionals are suggested to provide clear, simple explanations about the physiology, symptoms and potential impacts of OP on physical function at diagnosis, as well as the possibility of social and psychological issues that may also affect physical function (Kerr et al., 2017).;
- Effective pain management is a cornerstone in vertebral fractures management. Pain relief may be obtained by the use of a variety of physical, pharmacological, and behavioural techniques. Further studies are needed to address this issue;
- For future programs, it could be beneficial to use objectively methods, as activity monitors, to assess PA dose for a longer time period;
- Further research on long-term effects of physical exercise investigating the mechanism by which diet and drugs may influence the exercise, is recommended;
- To better identify the effective strategy in order to prevent and manage osteoporosis and its consequences, the attitudes and conceptions on exercise among OP patients need to be further investigated though mixed-methods analysis. In addition, qualitative research methods are fundamental to better understand the patient's perspective regarding the significance of the disease (illness);
- In order to minimise the confusion around exercise recommendations, physicians should provide evidence-based exercise guidelines rather than generic advice to

exercise, to walk or get more active, and should make referrals to exercise advice from expert trainers or exercise physiologists specialising in the treatment of OP;

- In view of the crisis in the treatment of OP, education for both clinicians and patients may represent the key factor to improve osteoporosis management efficacy.

Acknowledgments

I am presenting my now third thesis which has been the longest and most substantial so far however I would say also my best. The result of a multilevel, multicomponent, multidisciplinary, piece of work that has been going on for years.

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Finally, I wish to thank my family for their support and encouragement throughout my PhD.

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Appendix

Assessment tools

Patient reported outcome measures

Quality of life measurement: Ecos-16 and EuroQoL questionnaires

ECOS-16 QUESTIONNAIRE

During the last week and because of your back problems due to osteoporosis,

1. How often have you had back pain in the last week?

- ☐ 1. I have not had back pain
- ☐ 2. 1 day
- ☐ 3. 2-3 days
- ☐ 4. 4-6 days
- ☐ 5. Every day

2. How severe is your back pain?

- ☐ 1. I have not had back pain
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Intolerable

3. How much distress or discomfort have you had because it has been painful to stand for a long time?

- ☐ 1. No discomfort or suffering
- ☐ 2. Slight discomfort or suffering
- ☐ 3. Moderate discomfort or suffering
- ☐ 4. Severe discomfort or suffering
- ☐ 5. Very severe discomfort or suffering

4. How much distress or discomfort have you had due to pain from bending?

- ☐ 1. No discomfort or suffering
- ☐ 2. Slight discomfort or suffering
- ☐ 3. Moderate discomfort or suffering
- ☐ 4. Severe discomfort or suffering
- ☐ 5. Very severe discomfort or suffering

5. Has the back pain disturbed your sleep in the last week?

- ☐ 1. On no occasion
- ☐ 2. One night
- ☐ 3. Two nights
- ☐ 4. Three or four nights
- ☐ 5. Every night

6. How difficult has it been for you to carry out the household activities?

☐ 1. No difficulty
☐ 2. Slight difficulty
☐ 3. Moderate difficulty
☐ 4. Great difficulty
☐ 5. I was unable to do anything

7. Can you climb stairs to the next floor of a house?

☐ 1. No difficulty
☐ 2. Slight difficulty
☐ 3. I had to rest at least once
☐ 4. I could only climb the stairs with help
☐ 5. I was unable to climb the stairs

8. Do you have problems with dressing?

☐ 1. No difficulty
☐ 2. I can dress myself with slight difficulty
☐ 3. I can dress myself with moderate difficulty
☐ 4. I sometimes need help to dress myself
☐ 5. I cannot dress myself unaided

9. How difficult has it been for you to bend?

☐ 1. No difficulty
☐ 2. Slight difficulty
☐ 3. Moderate difficulty
☐ 4. Great difficulty
☐ 5. I am unable to bend down

10. How much has your walking been limited?

☐ 1. Not limited
☐ 2. Slightly limited
☐ 3. Moderately limited
☐ 4. Very limited
☐ 5. I am unable to walk

11. How difficult has it been for you to visit friends or relatives?

☐ 1. No difficulty
☐ 2. Slight difficulty
☐ 3. Moderate difficulty
☐ 4. Great difficulty
☐ 5. I have been unable to visit family or friends

12. Do you feel downhearted?

- ☐ 1. No
- ☐ 2. Rarely
- ☐ 3. Sometimes
- ☐ 4. Often
- ☐ 5. Always

13. Are you hopeful about your future?

- ☐ 1. Always
- ☐ 2. Often
- ☐ 3. Sometimes
- ☐ 4. Rarely
- ☐ 5. No

14. Do you feel frustrated?

- ☐ 1. No
- ☐ 2. Rarely
- ☐ 3. Sometimes
- ☐ 4. Often
- ☐ 5. Always

15. Are you afraid of falling?

- ☐ 1. No
- ☐ 2. Rarely
- ☐ 3. Sometimes
- ☐ 4. Often
- ☐ 5. Always

16. Are you afraid of getting a fracture?

- ☐ 1. No
- ☐ 2. Rarely
- ☐ 3. Sometimes
- ☐ 4. Often
- ☐ 5. Always

EuroQoL (EQ-5D-3L)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual activities *(e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

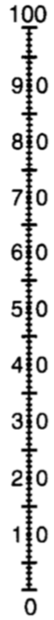
Pain/discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Best imaginable health state



Worst imaginable health state

Fear of Falling measurement: Fall efficacy scale

FES-I

Now we would like to ask some questions about how concerned you are about the possibility of falling. Please reply thinking about how you usually do the activity. If you currently don't do the activity (e.g. if someone does your shopping for you), please answer to show whether you think you would be concerned about falling IF you did the activity. For each of the following activities, please tick the box which is closest to your own opinion to show how concerned you are that you might fall if you did this activity.

		Not at all concerned 1	*Somewhat concerned 2*	*Fairly concerned 3*	*Very concerned 4*
1	Cleaning the house (e.g. sweep, vacuum or dust)	*1* ☐	*2* ☐	*3* ☐	*4* ☐
2	Getting dressed or undressed	*1* ☐	*2* ☐	*3* ☐	*4* ☐
3	Preparing simple meals	*1* ☐	*2* ☐	*3* ☐	*4* ☐
4	Taking a bath or shower	*1* ☐	*2* ☐	*3* ☐	*4* ☐
5	Going to the shop	*1* ☐	*2* ☐	*3* ☐	*4* ☐
6	Getting in or out of a chair	*1* ☐	*2* ☐	*3* ☐	*4* ☐
7	Going up or down stairs	*1* ☐	*2* ☐	*3* ☐	*4* ☐
8	Walking around in the neighbourhood	*1* ☐	*2* ☐	*3* ☐	*4* ☐
9	Reaching for something above your head or on the ground	*1* ☐	*2* ☐	*3* ☐	*4* ☐
10	Going to answer the telephone before it stops ringing	*1* ☐	*2* ☐	*3* ☐	*4* ☐
11	Walking on a slippery surface (e.g. wet or icy)	*1* ☐	*2* ☐	*3* ☐	*4* ☐
12	Visiting a friend or relative	*1* ☐	*2* ☐	*3* ☐	*4* ☐
13	Walking in a place with crowds	*1* ☐	*2* ☐	*3* ☐	*4* ☐
14	Walking on an uneven surface (e.g. rocky ground, poorly maintained pavement)	*1* ☐	*2* ☐	*3* ☐	*4* ☐
15	Walking up or down a slope	*1* ☐	*2* ☐	*3* ☐	*4* ☐
16	Going out to a social event (e.g. religious service, family gathering or club meeting)	*1* ☐	*2* ☐	*3* ☐	*4* ☐

FES-I: Prof Lucy Yardley and Prof Chris Todd

Lumbar pain: Visual Analogue Scale (VAS)

Visual Analogue Scale (VAS) for lumbar pain

Considering a scale from 0 to 10 in which 0 correspond to absence of pain and 10 correspond to worst pain imaginable, how do you evaluate the intensity of your perceived lumbar pain?

10 The worst imaginable pain

0 No pain

Total score _______________

Measure with the ruler in mm.
□ Not assessable

Physical fitness

Six Minutes Walking Test and Borg Scale, Tinetti Scale, Chair Sit and Reach

Six Minutes Walking Test (6-MWT) and Borg Scale

SIX MINUTES WALKING TEST (6MWT)

PRE TEST	POST TEST
Heart Rate (bpm)	Heart Rate (bpm)
Dyspnoea (Borg scale)	Dyspnoea (Borg scale)
Fatigue (Borg scale)	Fatigue (Borg scale)
	Distance (m)
	Rest (number)

PRE TEST		BORG SCALE	POST TEST	
Dyspnoea	Fatigue		Dyspnoea	Fatigue
0	0	Nothing at all	0	0
0,5	0,5	Extremely weak	0,5	0,5
1	1	Very weak	1	1
2	2	Weak	2	2
3	3	Moderated	3	3
4	4	Somewhat strong	4	4
5	5	Strong	5	5
6	6		6	6
7	7	Very strong	7	7
8	8		8	8
9	9		9	9
10	10	Extremely strong	10	10

Tinetti Scale

TINETTI BALANCE ASSESSMENT TOOL

Tinetti ME, Williams TF, Mayewski R, Fall Risk Index for elderly patients based on number of chronic disabilities. Am J Med 1986:80:429-434

PATIENTS NAME ______________________ D.o.b. ___________ Ward ______

BALANCE SECTION

Patient is seated in hard, armless chair;

	Date		
Sitting Balance	Leans or slides in chair = 0 Steady, safe = 1		
Rises from chair	Unable to without help = 0 Able, uses arms to help = 1 Able without use of arms = 2		
Attempts to rise	Unable to without help = 0 Able, requires > 1 attempt = 1 Able to rise, 1 attempt = 2		
Immediate standing Balance (first 5 seconds)	Unsteady (staggers, moves feet, trunk sway) = 0 Steady but uses walker or other support = 1 Steady without walker or other support = 2		
Standing balance	Unsteady = 0 Steady but wide stance and uses support = 1 Narrow stance without support = 2		
Nudged	Begins to fall = 0 Staggers, grabs, catches self = 1 Steady = 2		
Eyes closed	Unsteady = 0 Steady = 1		
Turning 360 degrees	Discontinuous steps = 0 Continuous = 1		
	Unsteady (grabs, staggers) = 0 Steady = 1		
Sitting down	Unsafe (misjudged distance, falls into chair) = 0 Uses arms or not a smooth motion = 1 Safe, smooth motion = 2		
	Balance score	/16	/16

TINETTI BALANCE ASSESSMENT TOOL

GAIT SECTION

Patient stands with therapist, walks across room (+/- aids), first at usual pace, then at rapid pace.

	Date		
Indication of gait (Immediately after told to 'go'.)	Any hesitancy or multiple attempts = 0 No hesitancy = 1		
Step length and height	Step to = 0 Step through R = 1 Step through L = 1		
Foot clearance	Foot drop = 0 L foot clears floor = 1 R foot clears floor = 1		
Step symmetry	Right and left step length not equal = 0 Right and left step length appear equal = 1		
Step continuity	Stopping or discontinuity between steps = 0 Steps appear continuous = 1		
Path	Marked deviation = 0 Mild/moderate deviation or uses w. aid = 1 Straight without w. aid = 2		
Trunk	Marked sway or uses w. aid = 0 No sway but flex. knees or back or uses arms for stability = 1 No sway, flex., use of arms or w. aid = 2		
Walking time	Heels apart = 0 Heels almost touching while walking = 1		
	Gait score	/12	/12
	Balance score carried forward	/16	/16
	Total Score = Balance + Gait score	/28	/28

Chair Sit and Reach

CHAIR SIT AND REACH TEST

Equipment required

1. A chair with legs that have a forward angle so the chair will not tip forward easily.
2. Place the rear legs of the chair against a wall so the chair cannot slide backwards.
3. A ruler or tape measure.

Instructions for participant

1. Sit close to the front of the seat with the crease between the top of the thigh and the buttocks on the edge of the seat.
2. Have one leg extended straight with the heel on the floor and the foot flexed at 90 degrees to the leg.
3. Have the other leg bent at right angles at the knee with the foot flat on the floor.
4. Place one hand over the other with finger tips level.
5. Slowly reach forward as far as you can towards the toes in the outstretched leg.
6. Do not bounce forward.
7. Hold the maximum reach for 2 seconds.
8. Try with the other leg extended and see which one is able to allow the greater reach.

Measurement

- Allow the participant to have two warm up tries.
- Measure the distance from the tip of the middle finger to the middle of the toe of the shoe.
- If the fingers do not reach the toes, the measurement is a negative score.
- If the fingers pass the toes, the measurement is a positive score.
- If the participant's knee bends they must sit up, straighten the leg and start again.

Exercise protocol Study II

Exercise protocol

N°	Exercise	Advise	Duration	Material	Aim	Variants
1	Walk around the perimeter of the gym	In the first lessons insist on proper walking	3/5 min	Sticks	Cardiovascular conditioning and postural education	▪ slow walking with breath control; ▪ fast walk; ▪ walk with lunges; ▪ rolled walk; ▪ • tandem walk.
2	Walk with exercises for the upper and lower limbs		5 min	Balls or sticks	Cardiovascular conditioning, postural education, coordination	▪ with various upper limb circumduction; ▪ with upper limbs stretched along the sides, alternating elevation; ▪ with upper limbs stretched along the sides; open and close hands; ▪ hands on shoulders, limb distension sup. forward or lateral; ▪ bend knee to the chest; ▪ arm-leg coordination exercises with and without tools.
3	Elevate and lower the shoulder stump		10 repetitions x 2 series		Shoulder mobilization	Executable even when seated
4	Protraction and retraction of shoulders		10 repetitions x 2 series		Shoulder mobilization	Executable even when seated
5	Hands on shoulders, circling clockwise and counterclockwise		10 repetitions x 2 series		Shoulder mobilization	Executable even when seated
6	Upper limbs in candlestick position: pushed back (with the back leaning against the wall)	Attention at the lumbar spine: avoid over-lordosis	10 repetitions x 2 series		Shoulder mobilization	Executable even when seated

7	Hold the shoulder-height stick, raise it above the head, extending the upper limbs. and return	Attention at the lumbar spine: avoid over-lordosis	10 repetitions x 2 series	Stick	Shoulder mobilization	Executable even when seated
8	Holding the same handle, elevate the stick over the head with extended upper limbs, flex on the back of the neck, return to extended arms and finally, starting position	Back lat machine with starting position	10 repetitions x 2 series	Stick	Shoulder mobilization	Executable even when seated
9	Holding the same grip, stick at shoulder height, extend and flex the arms		10 repetitions x 2 series	Stick	Shoulder mobilization	Executable even when seated
10	Head flexion forward and return	To be avoided or suspended at the onset of vertigo	10 repetitions x 1 series		Neck mobilization	Executable even when seated
11	Tilt the head to the right, then to the left	Recommend to direct the ear towards the shoulder	10 repetitions x 1 series		Neck mobilization	Executable even when seated
12	Raise the leg and perform circling of the ankle		10 repetitions in clockwise direction and 10 in counterclockwise direction		Ankle mobilization	Executable even when seated. Executable even with extended lower limb
13	Firmly point the stick on the ground and retract the abdomen		3 repetitions for 8 seconds	Stick	Reinforcement of abdominal muscles	Executable even when seated.
14	Supine decubitus: feet on the ground and bent knees. One hand placed on the abdomen and the other on	Beware of possible COPD cases		Mat	Breath adjustment and diaphragm relaxation	

	the chest: breathing control					
15	Supine decubitus: keeping one leg bent on the chest with the other leg extended to the floor. Keep for 10 sec. the position and leg change	Attention to posture	5 repetitions x limb	Mat	Stretching	
16	Supine decubitus with feet resting on the ground and bent knees: anteversion and retroversion of the pelvis	Inhale in anterversion, exhale in retroversion	5 repetitions x 3 series	Mat	Spinal column mobilization	
17	"Rotation" of the pelvis: supine position, legs bent, arms stretched out, orient the legs to the right side and then left	During the movement, do not elevate the shoulder opposite to the twist	5 repetitions x 3 series (stay for a few seconds in position)	Mat	Spinal column mobilization	It can be done with the leg going to the ground, crossed over the other
18	Supine decubitus: perform slight flexion of the leg by pushing the hand against the ipsilateral and contralateral knee in order to resist		8 repetitions for 5 seconds	Mat	Reinforcement of abdominal muscles	Executable even when seated.
19	Supine decubitus: flex the leg to the chest, stretch it up and keep a few seconds. (alternate legs)	To be avoided in subjects with low back pain	10 repetitions x limb	Mat	Reinforcement of abdominal muscles	
20	Bridge: from supine with feet on the ground and knees bent, lift the buttocks upwards (in isometry)	Be careful not to accentuate the lordosis	5 repetitions for 5 seconds	Mat	Reinforcement of gluteus and abdominal muscles	

21	Supine decubitus with a flexed knee: crushing the sponge ball in isometry placed under the knee of the stretched leg. Alternate the lower limb	Keep the pelvis in retroversion	3 repetitions for 10 seconds x limb	Mat and sponge ball	Quadriceps reinforcement	
22	Supine decubitus: feet resting on the ground and bent knees. Bring one knee at a time to the chest alternating the lower limbs with support		5 repetitions for 2 series x limb	Mat	Reinforcement of abdominal muscles	In progression alternating in flight.
23	Supine decubitus: one limb flexed with foot resting on the ground, the other limb is extended. Lifting of the limb extended upwards and backwards	Attention to maintaining the retroversion of the pelvis	5 repetitions for 2 series x limb	Mat	Reinforcement of abdominal muscles and quadriceps	
24	Supine decubitus: progressively extend the knee bringing the foot up with the use of an elastic placed under the sole of the foot		5 repetitions x limb	Mat and elastic band	Stretching	Executable even when seated.
25	Supine decubitus: feet resting on the ground and knees bent, push the sponge ball between the knees		10 repetitions	Mat and sponge ball	Reinforcement of adductors muscles	Executable even when seated
26	Decubitus supine and bent knees, place a ball under the soles of the feet and roll it extending and flexing the legs		2 series of 8 extensions and 8 flexion	Mat and sponge ball	Reinforcement of lower limb muscles	Executable even when seated

27	Self-stretching of the cervical spine bringing the chin to the neck and bringing the top of the head upward, keeping the shoulders low (imagine holding a book on the head)	Keep the position with free breathing ; pay attention to those with respirator y problems	3 repetitions for 8 seconds		Stretching	Executable even when seated
28	Orthostatism in front of the espalier: hands on the peg at shoulder level and arms extended. Move the torso forward and backward			Espalier	Mobilization of scapulae	
29	Orthostatism in front of the espalier: hands on the peg at shoulder level and arms extended. One foot in support and another leg stretched with a hammer foot raised from the ground: adduction and lateral abduction	Keep body and pelvis still and aligned	10 repetitions for 2 series	Espalier	Reinforcement of gluteus and lower limb muscles	▪ flexion-extension lower limb on the sagittal plane; ▪ limb circling clockwise and counterclockwise
30	Orthostatism in front of the espalier: hands on the peg at shoulder level and arms extended Alternate marching by touching the peg of the espalier with your foot		10 repetitions for 2 series	Espalier	Reinforcement of lower limb muscles	
31	Orthostatism in front of the espalier: hands on the peg at shoulder level and arms extended. Sponge ball under the toe and heel resting on the ground: push the ball		10 repetitions for 2 series	Espalier and sponge ball	Reinforcement of lower limb muscles	

32	Orthostatism in front of the espalier: hands at shoulder level and arms extended, one foot completely resting on the ground and the other with toe on the first peg and heel to the ground. Both knees are stretched.		10 repetitions for 3 series x limb	Espalier	Stretching	
33	Orthostatism in front of the espalier: hands at shoulder level, one foot completely resting on the ground, the other on the highest possible rung with flexed knee. In this position, move as close as possible to the backrest with the torso extending the leg completely to the ground	Be careful not to accentuate the lordosis The torso moves forward while remaining well aligned	5 alternate repetition keeping the position for 6 seconds	Espalier	Stretching	
34	Orthostatism in front of the espalier: hands at shoulder level, with arms extended. Lift up on the toes and then on the heels maintaining the position		5 alternate repetition keeping the position for 6 seconds	Espalier		
35	Orthostatism in front of the espalier. Alternate marching by touching the peg of the espalier with your foot		10 alternate repetitions for 2 series	Espalier	Reinforcement of lower limb muscles and balance	• slow execution • fast execution

36	Arms stretched out in front of his chest with a ball in his hands. Keep your back straight and your elbows out. Press the ball in your hands to develop isometric force	Pay attention to the posture. If necessary, lean on the wall.	5 repetition for 2 series keeping the position for 5 seconds	Sponge ball	Reinforcement of the upper limb and pectoral muscles	Same position, but instead of squeezing it between palms, work with scapulae: slide forward one hand by rolling the ball forward, while the other hand remains fixed. Scapular musculature lengthening. Executable even when seated
37	Back leaning against the wall, arms stretched along the sides and push a sponge ball towards the wall, with the palms of the hands. Maintain isometric position	Knees slightly bent to not accentuate the lordosis	5 repetition for 2 series keeping the position for 5 seconds	Sponge ball	Reinforcement of the upper limb	Same position but with a ball under each of the two palms and instead of crushing them towards the wall roll them downwards lowering the shoulders, then I go up again: for stretching
38	Back against the wall, slightly bent knees and 90-degree elbows attached to the body. Forearms rise outwards and find themselves parallel to the ground	Perceive the movement of the scapulae	10 repetition for 2 series		Reinforcement of the upper limb	Executable with palms facing inward or upward. With / without ball
39	Orthostatism frontal to the wall: with a ball in hand, draw small circles on the wall keeping the arm extended forward	keep the shoulders lowered	20 sec per arm (10 in clockwise, 10 in anticlock wise)	Sponge ball	Reinforcement of the upper limb	
40	Hands behind the nape, stretch the back of the neck by bending the head forward		3 series keeping the position for 10 seconds		Stretching	Executable even when seated
41	Flex the head sideways, helping with the hand, first right then left		3 series for side keeping the position		Stretching	Executable even when seated

42	Squat on the wall		5 repetition for 2 series		Reinforcement of the lower limb	
43	Supine Decubitus, lower limb extended, flex the knee by "sliding" the heel towards the gluteus		10 repetition for 2 series		Reinforcement of the lower limb and abdominal muscles	
44	With the arm extended forward, gently pull the fingers towards you, palm facing forward		3 series for limb keeping the position for 10 minutes		Stretching	Executable even when seated
45	From the upright position with the legs spread to the same width as the shoulders, bring the right arm in front of the body, with the left hand grasp the elbow and pull to the left. Hold the position and repeat from the opposite side		3 series for limb keeping the position for 10 minutes		Stretching	Executable even when seated

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