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**PREVALENCE AND INCIDENCE OF OSTEOPOROTIC FRACTURES IN
PATIENTS ON LONG-TERM GLUCOCORTICOID TREATMENT FOR
RHEUMATIC DISEASES: The Glucocorticoid Induced OsTeoporosis TOol,
GIOTTO STUDY.**

S.S.D. MED/16 REUMATOLOGIA

Coordinatore: Prof. GIOVANNI TARGHER

Firma _____

Tutor: Prof. MAURIZIO ROSSINI

Firma _____

Dottorando: Dott.ssa MARIA VITIELLO

Firma _____

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**PREVALENCE AND INCIDENCE OF OSTEOPOROTIC FRACTURES IN PATIENTS ON LONG-TERM
GLUCOCORTICOID TREATMENT FOR RHEUMATIC DISEASES: The Glucocorticoid Induced Osteoporosis Tool,**

GIOTTO STUDY.

Dott.ssa Maria Vitiello
Tesi di Dottorato
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Università degli Studi di Verona
Area Ricerca – U.O. Dottorati di Ricerca Nazionali ed Internazionali
tel. 045.802.8608 - fax 045.802.8411 - Via Giardino Giusti n. 2 - 37129 Verona

SOMMARIO

L'obiettivo di questo studio è quello di valutare la prevalenza e l'incidenza di fratture osteoporotiche e di identificare i loro principali determinanti (malattia primaria, dosaggio glucocorticoidi, densità minerale ossea, fattori di rischio, trattamento specifico per osteoporosi indotta da steroidi) in un'ampia coorte di pazienti consecutivi di età > 21 anni, in terapia cronica con glucocorticoidi (≥ 5 mg di prednisone -PN- equivalente), afferenti presso centri di reumatologia situati in tutta Italia. Lo studio è uno studio nazionale osservazionale, multicentrico, trasversale e longitudinale.

Sono stati arruolati 553 pazienti affetti da Artrite Reumatoide, Polimialgia Reumatica e Malattie del Tessuto Connettivo e in trattamento cronico con glucocorticoidi.

Lo studio GIOTTO potrebbe fornire importanti contributi nella pratica clinica, in particolare evidenziando e quantificando la prevalenza della osteoporosi indotta da glucocorticoidi (GIOP) e delle relative fratture nella real life, la frequenza dei principali fattori di rischio, e strategie di prevenzione sub-ottimale.

ABSTRACT

Background: Osteoporosis and fractures are common and invalidating consequences of chronic glucocorticoid (GCs) treatment. Reliable information regarding the epidemiology of GCs induced osteoporosis (GIOP) are coming exclusively from the placebo group of randomized clinical trials while observational studies are generally lacking data on the real prevalence of vertebral fractures, GC dose and primary diagnosis.

Objectives: The objective of this study was to evaluate the prevalence and incidence of osteoporotic fractures and to identify their major determinants (primary disease, GCs dose, bone mineral density, risk factors, specific treatment for GIOP) in a large cohort of consecutive patients aged > 21 years, on chronic treatment with GC (≥ 5 mg prednisone –PN- equivalent), attending rheumatology centers located all over Italy.

Methods: This is a national multicenter cross-sectional and longitudinal observational study (The Glucocorticoid Induced Osteoporosis Tool, GIOTTO Study). 553 patients suffering from Rheumatoid Arthritis (RA), Polymyalgia Rheumatica (PMR) and Connective Tissue Diseases (CTDs) and in chronic treatment with GCs were enrolled.

Results: Osteoporotic BMD values (T score < -2.5) were observed in 28%, 38% and 35% of the patients with CTDs, PMR or RA at the lumbar spine, and in 18%, 29% and 26% at the femoral neck, respectively. Before GC treatment prevalent clinical fractures had been reported by 12%, 37% and 17% of patients with CTDs, PMR, and RA, respectively. New clinical fragility fractures during GC treatment was reported by 12%, 10% and 23% of CTDs, PMR and RA patients, respectively. Vertebral fractures were the prevailing type of fragility fracture. More than 30% of patients had recurrence of fracture. An average of 80% of patients were in supplementation with calcium and/or vitamin D during treatment with GCs. Respectively, 64%, 80%, and 72% of the CTDs, PMR and RA patients were on pharmacological treatment for GIOP, almost exclusively with bisphosphonates.

Conclusions: The GIOTTO study might provide relevant contributions in clinical practice, in particular by highlighting and quantifying in real life the prevalence of

GIOP and relative fractures, the frequency of the main risk factors, and the currently sub-optimal prevention. Moreover, these results emphasize the importance of the underlying rheumatic disease on the risk of GIOP associated fractures.

CONTENTS

Introduction	pg. 7
Methods	pg. 20
Results	pg. 22
Discussion	pg. 24
Conclusions	pg. 30
References	pg. 31
Attachments	
• Tables	pg. 46
• Legend of the Figures	pg. 47
• Figures	pg. 48

INTRODUCTION

Glucocorticoid therapy (GCs) is frequently used in the treatment of rheumatic diseases, as Rheumatoid Arthritis (RA), Polymyalgia Rheumatica (PMR), and Connective Tissue Diseases (CTDs) such as Systemic Lupus Erythematosus (SLE) (1,2,3).

In RA the use of low-dose GCs has a well-defined effect on disease activity (4). In early RA, many evidences demonstrate that the treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in association with GCs may induce high and persistent remission rates (5). This disease-modifying effect of GCs is supported by different studies (5-12). These studies have demonstrated that GCs have an action in retarding the progression of erosive joint damage in early RA (prior to any joint damage) and a control of disease activity (5-12). The CAMERA II study, in which patients with RA and treated with 10 mg/day of prednisone, has demonstrated that in RA patients the co-treatment with GCs has a role in the *treat-to-target* and *tight control* strategy (13). Many reviews have concluded that low dose of GCs (<7,5 mg/day) can represent a “bridging-therapy” while waiting for csDMARDs begin to have effect (8,13). This conclusion is recommended by EULAR in early RA in 2010 and then in 2014 update (14-16). The 2012 update ACR recommendations treatment of RA concerned only about the use of conventional DMARDs and biological therapies, while did not recommend the use of GCs (17). In RA the combination therapy with GCs (at stable low dose of 7,5 mg/day) and traditional DMARDs frequently results in a suppression of inflammation, and allows a lasting clinical remission (5).

In the EULAR 2016 recommendations update, the term “low-dose” is deleted and replaced by “short-term”, leaving the choice about dose regimens and route of administration to the individual rheumatologist and patient (18). In addition, the Task Force underlines that GCs should be gradually reduced and ultimately stopped, usually within 3 months from treatment start and only exceptionally by 6 months. Long-term use of GCs, especially at doses above 5 mg/day, should be avoided because of the many adverse effects (osteoporosis, hyperglycaemia/diabetes mellitus, cardiovascular diseases and infections). Strehl et Al., in their study have agreed that the risk of harm is low for the majority of patients at long-term dosages of ≤ 5 mg prednisone equivalent per day, whereas at dosages of >10 mg/day the risk of harm is elevated. At dosages between >5 and ≤ 10 mg/day, patient-specific characteristics (protective and risk factors) determine the risk of harm. The level of harm of glucocorticoids depends on both dose and patient-specific parameters. General and glucocorticoid-associated risk factors and protective factors such as a healthy lifestyle should be taken into account when evaluating the actual and future risk (19).

In the report of Chatzidionysiou et Al, a systematic literature review informing the 2016 update of the recommendation for the management of RA has been performed. The Authors conclude that addition of GCs to csDMARDs therapy may be beneficial, but the benefits should be balanced against the risk of toxicity. Under tight control conditions, methotrexate (MTX) monotherapy is not less effective than csDMARDs, but better tolerated (20). A small study by Menon et Al. has shown a greater combination of csDMARDs with intrarticular GCs than with csDMARDs alone in patients with RA with less than 2 years disease

duration, although this is an open label study with high bias risk (21). In the CareRA trial, early RA patients, without prognostic factors, have benefited from the addition of GCs (COBRA-slim) to MTX with no differences in safety observed (22). A non-inferiority trial has compared two different GCs strategies; the COBRA-light strategy (prednisolone at 30 mg/day, tapered to 7,5 mg/day in 9 weeks) in combination with MTX; and the COBRA strategy, using prednisolone at 60 mg/day (tapered to 7,5 mg/day in 6 weeks) in combination with both MTX and sulfasalazine. The lower dose of GCs was efficacious in suppressing clinical disease activity and improving functional ability, but non-inferiority could not be claimed formally (23, 24). The degree of radiographic progression is similar in the two groups (COBRA and COBRA-light). This study has high risk of bias too, and no comparison with application of conventional GCs was performed.

In a double-blind RCT with patients with established RA, low-dose prednisone with modified release added to existing DMARD treatment in patients with active disease has a significant effect on disease activity and health-related quality of life compared with placebo (25).

In their study, Shimizu et Al. have analyzed data from the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) database, a large-scale, prospective cohort database of RA patients, with the goal of identifying changes in the proportions of biologic DMARDs (bDMARDs) users receiving MTX and glucocorticoids and changes in the doses of these medications over time in daily clinical practice (26). The proportion of patients using glucocorticoids decreased after the introduction of bDMARDs among users of all four bDMARDs (infliximab, etanercept, adalimumab, tocilizumab). Glucocorticoid doses also

decreased in all bDMARD groups, with no significant differences observed between groups. Several reports have focused on concomitant glucocorticoid use after initiation of bDMARDs (27,28,29). Notably, in the STREAM study, a steroid-sparing effect was observed as a benefit of Tocilizumab therapy (30). In the IORRA cohort, concomitant glucocorticoids were decreased and discontinued in 63.7% and 18.0% of baseline glucocorticoid users, respectively, suggesting that a higher proportion of patients attempted to decrease glucocorticoid use. However, few RA patients are able to discontinue glucocorticoid use, even after initiation of a bDMARD. Of the 21,672 RA patients registered in the U.S. National Data Bank, 35.5% used glucocorticoids at the time of the survey and 65.5% had used them at some point in their lifetime (31). Even among patients who had achieved remission and patients with well-controlled disease activity, 21% to 25% still used glucocorticoids. Likewise, the study of Shimizu et Al. revealed that 51.4% of patients continued to use glucocorticoids even though their disease activity was well-controlled after approximately 2 years of bDMARD treatment. The IORRA cohort study revealed that, in daily clinical practice, after the introduction of a bDMARD, MTX and glucocorticoid doses are commonly titrated down as disease activity decreases. These dose adjustments vary depending on which bDMARD is used.

Several studies have explored the safety and the tolerability of glucocorticoids treatment in RA patients. In their editorial Buttgerit and Bijlsma support the chronic use of low-dose of GCs as a realistic option for some patients (32). The Authors recommend the use of low-dose of steroids both in early RA and in established RA. In support of this recommendation, a recent report of Roubille et

Al. has investigated, in a cohort of very early RA from a real-life setting monitored for 7 year, the association between exposure to GCs treatment and classical major safety events related to GCs (death, cardiovascular diseases, severe infections, fractures). The patients were stratified in two groups: with or without GCs treatment. This 7-years analysis does not show any significant difference between patient with early RA with and without low-dose of GCs treatment in terms of major safety events. Also in established RA, there are many patients obviously being more or less constantly treated with GCs. The German National Database of the Collaborative Arthritis describes that, in a total of 8084 patients with RA, 48% received a mean dose of 5 mg prednisone equivalent per day, whereby 8,5% were treated with daily dosages < 5 mg, 37,7% with 5-7,5 mg and 2,1% with > 7,5 mg (33). So, during treatment of both early and established RA, the risk of adverse effects induced by conventional GCs can be minimised when following the established recommendations (34,35,36), and by considering each patient to be an individual person characterised by the presence or absence of certain risk factors and/or preventive measures. This will ultimately result in an adapted patient-specific therapy. Although these studies support the good safety profile of low-dose of GCs for early RA, the GCs risk/benefit balance has little evidence base, with most recent data provided by observational studies. These studies provide the opportunity to explore the real-life tolerability profile of GCs, with doses and duration commonly used in daily practice, but often present bias such as confounding by indication (37).

The GCs tolerability profile has been reported to depend both on the duration of exposure and dose (38). Indeed, in addition to a better tolerability profile of a low

dose than high-dose regimen (36), long-term use of low-dose GC has been associated with increased mortality as compared with shorter exposures (39). Most notably, two recent studies have suggested a dose-dependent increase in mortality in RA (40,41); del Rincón et Al (40) revealed a daily threshold dose of 8 mg at which all-cause mortality increased with GCs dose, and in the German register Rheumatoid Arthritis oBservatiOn of BIologic Therapy (RABBIT), use of GCs >5 mg/day was associated with increased mortality risk, independent of RA activity (41). Moreover, a 10-year follow-up study examined cardiovascular events and deaths in early patients with RA with no history of cardiovascular diseases who were included in a recent open-label randomised trial of low-dose prednisolone (7.5 mg/day) over the first 2 years of early RA Better Anti-Rheumatic Pharmacotherapy (BARFOT+): low-dose prednisolone use was associated with increased incidence of cerebrovascular events and, although not significant, increased mortality (42). Long-term follow-up of Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA II) patients with early RA who received prednisone at 10 mg/day for at least 2 years revealed increased cardiovascular risk and, although not significant, increased mortality (43).

Cardiovascular tolerance of GC remains controversial. In one meta-analysis of observational studies, GCs usage was associated with increased risk of all cardiovascular events, including myocardial infarction, heart failure and stroke (44). In another systematic literature review, low-dose GC (<10 mg/day) was associated with major cardiovascular events in four of six studies (45). GCs therapy has been associated with increased risk of severe infections (46, 47). One systematic review has noted the paucity of data on the association between low-

dose GCs (<10 mg/day prednisone) and risk of infections (48). In one recent study evaluating patients with RA aged >65 years, the risk of serious infections was increased 30%, 46% or 100% with 5 mg prednisolone used continuously for the last 3 or 6 months or 3 years, respectively, as compared with no use (49). The increased risk of severe infections was also proportional to the cumulative dosage over 2–3 years.

In their systematic review of guidelines for Glucocorticoids in RA (34), Palmowski et Al., have identified several potentially important clinical issues that are not addressed in any of the guidelines. The first of these issues is the timing and frequency of glucocorticoid administration. The interval between doses of DMARDs and biologic drugs used in the treatment of RA is generally longer than that of glucocorticoid dosing, and they are overall less affected by endogenous hormonal regulatory circuits. In contrast, the effects of daily glucocorticoid therapy are highly influenced by their strong dependency on circadian rhythms. Thus, choosing the right administration schedule for glucocorticoids may have a considerable impact on both efficacy and safety, by minimizing adverse effects on the hypothalamic–pituitary–adrenal axis or by allowing equal symptom control with lower doses. The concept of considering timing of glucocorticoids administration in order to optimize the individual benefit/risk ratio is often referred to as “chronotherapy”. Although several studies have been reporting promising results concerning the potential benefit of chronotherapy for more than 50 years (51,52,53) and various authors have emphasized its importance (54,55,56). A rather recent approach to this issue is the use of modified/delayed release prednisone (57), which will be another important point to be considered in

future recommendations. A second topic scarcely considered by any guideline to date is the potential influence of patient-specific factors on the optimal treatment regimen. These patient-specific factors include comorbidities, co-medications, or other (relative) contraindications. None of the available guidelines comment specifically on treatment of elderly RA patients. Both incidence and prevalence of RA increase with age, and therefore elderly patients with RA represent a large segment of the RA population (58). In general, the elderly have more comorbidities than young people, and this is even truer for elderly patients with RA. Such patients receive multiple concomitant drugs, which may influence RA treatment choices (59,60). Also elderly patients with RA are more likely than younger patients to experience glucocorticoid-related adverse effects such as osteoporosis, diabetes mellitus, or hypertension.

GCs represent the gold standard treatment in PMR. GCs reduce symptoms and suppress inflammation within a few weeks. GCs act by the inhibition of the circadian release of pro-inflammatory cytokines (such as IL-6), reduce the duration of morning stiffness (2). Although it is not accepted an universal regimen of daily doses of GCs in PMR, the EULAR/ACR 2015 recommendations for the management of PMR suggest to use the minimum effective GCs dose within a range of 12.5–25 mg prednisone (PN) equivalent daily as the initial treatment of PMR, and then at 10 mg for 4-8 weeks before being tapered by 1 mg every 4-8 weeks provided no flares occur (61). In addition, the experts panel discourages conditionally the use of initial doses ≤ 7.5 mg/day and strongly recommends against the use of initial doses >30 mg/day. The panel recommends to consider the early introduction of methotrexate (MTX) in addition to GCs, particularly in

patients at a high risk for relapse. MTX may also be considered during follow-up of patients with a relapse, without significant response to GCs or experiencing GC-related adverse events (61).

GCs are extensively used also for the treatment of CTDs, such as systemic lupus erythematosus (SLE) and their complications or flares.

GCs are used in the treatment of acute SLE as well as in the maintenance of remission and are often continued long-term. The most commonly used GCs in the treatment of SLE are prednisone and methylprednisolone; other GCs such as triamcinolone and dexamethasone are used less frequently (62). Although GCs have been administered in divided doses, particularly at medium to high doses, single morning administration appears advisable to minimise both adverse effects and suppression of the pituitary axis (63). Therapeutic protocols of GCs for SLE range from low (0.1–0.2 mg/kg/day), to medium (0.2–0.5 mg/kg/day), to high doses (0.5–1 gm/kg/day) and intravenous pulses (doses ranging from 250 to 1000 mg/daily for 3 consecutive days) and are used for induction and maintenance of remission (62). Low-dose GCs (0.1–0.2 mg/kg/day) are generally used as maintenance treatment, often even in the absence of active disease. Low to medium (0.2–0.5 mg/kg/day), doses are also used in the treatment of mild disease activity, particularly cutaneous, musculoskeletal, haematological and constitutional manifestations.

In their review Mosca et Al., conclude that, although many drugs have been introduced in the treatment of SLE, GCs still represent a cornerstone in the treatment of SLE in all its clinical aspects and different levels of severity (64).

As mentioned above, the use of GCs is associated to the occurrence of side effects, including hypertension, diabetes mellitus, cataract (65,66). The more common side effects of GCs in low (<7.5 mg/day) to moderate doses (7.5-30 mg/day prednisolone equivalent) are osteoporosis, diabetes, cataracts, thinning of the skin, weight gain and fat redistribution. At higher doses, infections, myopathy, psychological disturbances and osteonecrosis are seen (67,68,69).

One of the principal complications of long-term GCs use is an important alteration of bone metabolism. The bone loss associated with GCs generally involves trabecular and cortical bone, with increased bone resorption but mainly decreased bone formation (70). The bone loss is likely to proceed more rapidly and involves first the trabecular compartment because trabecular bone has more available surface upon which the cycle of resorption and formation occurs. Rapid bone loss is most marked on endocortical surfaces (71). Doses of GCs >5 mg PN equivalent per day are associated with bone loss due to reduced bone formation. Doses of <5 mg per day may be skeletal sparing, but it is unpredictable if doses <5 mg are efficacious (72). Indeed GCs play a dual role: they induce bone loss, but on the other hand they suppress systemic inflammation with a subsequent beneficial effect on bone mass (3). Fracture risk is positively related to daily dose and increases during the first 6 months of therapy (73), and the relative risk of fractures for patients in GCs therapy is higher for forearm, hip and vertebral sites (73). Some confounding factors such as activity of the disease, age of the patient, sex, baseline BMD previous fracture history, may influence the rate of bone loss (36). The effects of GCs on fracture risk as well as being dose-related, also depend on the duration of the therapy (74).

It is well known that GCs determine a decrease in osteoblastogenesis and interfere with osteoblastic differentiation and maturation (75). In addition, GCs inhibit the Wnt/ β -catenin pathway, which is critical for the differentiation of mesenchymal cells toward mature osteoblasts, with a consequent reduction of osteoblastogenesis (75,76). Also the osteocytes are influenced by the action of GCs. GCs induce the apoptosis of osteocytes by the activation of Caspase 3 (76). Recent studies demonstrate that treatment with GCs is related to an increased autophagy of osteocytes (77,78). In the GCs-induced osteoporosis the osteocyte-lacunar-canalicular network is altered (75); this change together with the osteocyte apoptosis may explain the alteration of biomechanical properties in the bone (76). The third type of cells influenced by GCs are osteoclasts. GCs determine an increase in osteoclastogenesis and a prolongation of osteoclasts lifespan (76) by the increased expression of the macrophage colony stimulating factor (M-CSF) and the receptor activator of NF- κ B ligand (RANK-L) (75). The canonical Wnt system has extracellular inhibitors: Dickkopf1 (DKK1) and Sclerostin. DKK1 determines an inhibition of osteoblastogenesis (79). Furthermore, the lack of stimulus of β -catenin on the OPG production by osteoblasts determines the imbalance of RANKL/OPG in favor of RANK-L and therefore of bone resorption. In conclusion, DKK1 inhibits bone formation while induces bone resorption (80,81).

Sclerostin is expressed by osteocytes with an important role in regulating bone formation by osteoblasts. Sclerostin is a monomeric glycoprotein, which antagonizes the canonical Wnt pathway in osteoblasts (82) by the inhibition of differentiation, activity and survival of osteoblasts (83). Recent studies in cultures

of osteoblasts treated with dexamethasone have shown an alteration of osteoblastic differentiation through the inhibition of the canonical Wnt/ β -catenin pathway (84,85,86,87), and an overexpression of Wnt-antagonists (86,88,89).

While several *in vivo* and *in rodents* studies about the effect of GCs on Wnt signaling are widely available, studies in humans are poor, and results are discordant and controverse, probably because conducted with different doses and underlying diseases.

Reliable information regarding the epidemiology of GC induced osteoporosis (GIOP) are coming exclusively from the placebo group of randomized clinical trials while observational studies are generally lacking data on the real prevalence of vertebral fractures, GC dose and primary diagnosis.

In the 2017 ACR recommendation for the prevention and treatment of GIOP (90), Buckley et Al., outline the treatment recommendation for GIOP. The Authors consider it is crucial to identify those patients taking GCs for whom the benefits of preventive therapy sufficiently outweigh potential harms, since GCs treatment is a potentially reversible risk factor for GIOP. Firstly, in all adults and children, an initial clinical fracture risk assessment should be performed as soon as possible, but at least within 6 months of the initiation of long-term GCs treatment. For all patients receiving GCs treatment, optimizing calcium intake and vitamin D intake, as well as a lifestyle modifications, are recommended. Oral bisphosphonates are recommended as the preferred first-line therapy in most clinical situations given their antifracture benefit, safety, and low cost, unless there are contraindications, intolerance, or concerns about patient adherence to treatment

The main objective of this multicenter study was to evaluate, with a transversal and longitudinal approach, in the real life, the prevalence and incidence of osteoporotic fractures and to identify their major determinants in a sample of patients with different rheumatic diseases in chronic treatment with GCs. Secondary objectives were to quantify the prevalence of the major risk factors for osteoporotic fracture: age, underlying disease, sex, bone mineral density (BMD), dietary intake of calcium, specific anti-osteoporotic therapy, estimate of vitamin D, physical activity, smoking, alcohol, family history, comorbidity and falls.

METHODS

This is a national multicenter cross-sectional and longitudinal observational study (The Glucocorticoid Induced Osteoporosis Tool, GIOTTO Study). 553 patients suffering from RA, PMR and CTDs and in chronic treatment with GCs were enrolled in the Italian rheumatologic centers of Verona, Vercelli, Mantova, Pavia, Modena, Bologna, Firenze, Pisa, Siena, Ancona, Roma, Napoli, Foggia, Lecce, Reggio Calabria, Catania, and Cagliari (fig. 1).

The study was purely observational so no additional treatments or tests to that normally applied in these patients, were provided or requested.

Each center has enrolled patients presenting consecutively in their outpatients clinics and within the following inclusion criteria:

- for the “transversal phase”: women or men age > 21 years and receiving GCs at least from one year at a dose of at least 5 mg/day of PN or equivalent
- for the “longitudinal phase”: patients in therapy with GCs (at least 5 mg/day) for less than three months and in which was expected a therapy with GCs for at least one year at a dosage of at least 5 mg/day of PN or equivalent.

All subjects with at least one of the following characteristics were excluded from the study: a diagnosis of metabolic bone diseases or other forms of secondary osteoporosis (uncontrolled hyperthyroidism, M. Cushing, malabsorption syndrome, primary hyperparathyroidism), severe renal insufficiency (serum creatinine > 2 mg/dl), severe liver failure. Patients on aromatase inhibitors, androgen deprivation therapy and heparin are also excluded (fig. 2).

Additional diagnostic tests (instrumental or biochemical) deemed appropriate by the investigator for the clinical practice were provided. The prevalence or incidence of fractures are referred to so-called clinical fractures (but also to any vertebral fractures detected incidentally by radiographic investigation of the column or the DXA investigation of the spine).

The data collection cards (CRF) used collected information about the medical history, clinical, diagnostic and therapeutic data, and in particular: demographics; physiological and pathological history; assessment of the state of the rheumatic disease and concomitant Health Assessment Questionnaire; previous drug therapy; previous and ongoing glucocorticoid therapy; specific anamnesis for osteoporosis: date of first diagnosis; date of first atraumatic fracture; pain symptoms; previous fractures (before or after the start of therapy GC)/fractures at the baseline visit; outcome laboratory examinations; previous/ongoing drug therapy for osteoporosis; risk factors; assessment of the quality of life (EQ-5D); simplified questionnaire of calcium and vitamin D intake and physical activity (fig. 3,4,5,6,7).

The study was approved by the Ethics Committee and by the local coordinator. All patients provided written informed consent.

Descriptive statistics analysis included: sample size, mean, standard deviation, median and range for continuous variables; absolute and relative frequency distributions for categorical variables.

RESULTS

A total of 553 patients with RA, CTDs (mainly SLE = 93%) or PMR in chronic treatment with GCs have been recruited. Table 1 shows the main clinical features of the patients depending on the disease.

The prevalence of the main risk factors for osteoporosis and fracture, according to the disease that requested GCs chronic therapy, is shown in Table 2.

The prevalence of osteoporosis according to DXA (T-score <-2.5) was at the spine in 28%, 38% and 35% of patients with CTDs, PMR or RA; instead at the femur it was respectively 18%, 29% and 26% (Fig. 8).

A prevalence of anamnestic clinical fractures has been found in 12%, 37% and 17% of patients suffering from respectively CTDs, PMR, or RA before any treatment with GC (Fig. 9A).

During treatment with GC new clinical fragility fractures were reported in 12%, 10% and 23% in patients suffering from CTDs, PMR and RA, respectively (Fig. 9B).

The prevailing type of fragility fracture has been the vertebral one, in particular multiple vertebral fractures in patients suffering from PMR (Fig. 10A).

More than 30% of patients had recurrence of fracture. A second relapse of a fragility fracture was found in 20% of patients with CTDs and 10% of those with RA (Fig. 10B).

In addition, considering only calcium and/or vitamin D, an average of 80% of patients were in supplementation during treatment with GCs; only few of them were already on treatment before the beginning of the GCs treatment (Fig. 11A).

64% of patients with CTDs, 80% of patients with PMR and 72% of patients with RA, were treated with specific drugs for the prevention or treatment of GIOP, and in particular with anti-resorptive drugs (alendronate or risedronate) (Fig. 11B).

The patients included in the prospective longitudinal phase of the study, which met the inclusion and exclusion criteria, were 83. Their assessment did not show any significant results in addition to those shown by the retrospective longitudinal analysis of 553 cases.

DISCUSSION

The main aim of this multicenter study was to evaluate the prevalence and the incidence of osteoporotic fractures in a cohort of patients with different rheumatic diseases and in therapy with chronic GCs.

In this study we have observed that the prevalence of osteoporosis in RA patients according to DXA, in terms of T-score $< - 2,5$, was at the spine of 35%, while at the femur was 26%. In previous studies the frequency of generalized osteoporosis in patients with RA ranges from 12.3 to 38.9 % in the lumbar spine and from 6.3 to 36.3 % in the hip (91-93). The KORONA database showed that the frequency of osteoporosis was 46.8 % (94). This frequency was higher in comparison to some other studies, which reported a prevalence of 22–24 % (95,96). In a large Italian multicenter cross-sectional study that included 925 female RA patients the Authors described that the frequency of osteoporosis in the whole sample was 28.8% at lumbar spine and 36.2% at femoral neck (92).

In our study the prevalence of osteoporosis in patients with CTDs (mainly SLE) was at the spine of 28% and 18% at the hip. Recently, Carli et Al. observed that more than 50% of SLE patients chronically treated with GCs had a reduced BMD and 28% had osteoporosis (97). In previous studies the prevalence of osteoporosis ranged from 1,4 to 68% of patients with SLE (98,99). Two recent studies have demonstrated that bone loss occurs mainly in SLE patients treated at least with 7,5 mg/day prednisone, while treatment with lower doses of prednisone is not associated with bone loss (100,101).

The frequency of osteoporosis in patients with PMR in previous studies ranges between 14.9 and 85%. In our experience, in these elderly patients osteoporosis was generally found in 38% at the spine and 29% at the hip.

Risk of fracture in patients who received long-term GC is about 33–50%, which depends on daily and cumulative dose (102). This diversity can be explained by the use of different age groups in the study populations, the menopausal status of the participants, and the use of GCs. In addition, we observed that the prevalence of anamnestic clinical fractures before any GCs treatment was 12% in patients with CTDs, 37% in patients with PMR and 17% in patients with RA. This finding may be explained by the role of underlying inflammation. In general population, even small elevations of C reactive protein within the normal range increase non-traumatic fracture risk (103). In some studies, variations within the low levels of inflammatory markers and cytokines predict bone loss and elevated inflammatory markers are prognostic for fractures (104,105). There is a strong biological rationale for these observations. Osteoclastogenesis is under the control of RANK-ligand, which is mainly produced by osteocytes in normal bone remodelling, but also by lymphocytes and fibroblasts in other situations (106) and inflammation. Osteoclastogenesis can be enhanced by many cytokines: interleukin (IL) IL-6, IL-23, Tumor necrosis factor α (TNF- α). TNF- α transgenic mice are models of osteoporosis with dramatic decrease in bone mass and deterioration of bone microarchitecture.

These findings show that inflammation has a deleterious effect on bone remodelling, inducing an increased resorption and a decreased formation, before any effect of GCs themselves.

As mentioned in the introduction, the Wnt pathway is critical for bone formation (107). Several studies have reported a rise in Wnt inhibitors (sclerostin and DKK1) expression in rodents and cell culture systems following GCs treatment (81,88,108,109). The evidence for a substantial link in human patients has been discordant with decreased serum sclerostin at one week in GCs patients (110) and increased serum sclerostin at later time points (111), with a consequence of inflammation-related decrease in bone formation (112). Similar disparities are seen with sclerostin and disease states: increased levels are reported in Cushing's syndrome patients, (113) whereas cases of chronic hypercortisolism presented with decreased sclerostin (114).

Moreover, alterations in other Wnt inhibitors, such as DKK1, might be involved in inflammation-related bone loss (115).

The effects of GCs treatment on serum levels of DKK1 have been studied in many diseases with discordant results. Brabnikova Maresova et al. have shown increased values of DKK1 during short-term GCs treatment (110). On the contrary, long-term studies showed a decrease of serum levels of DKK1 (111). The reasons for these controversial results are unknown, probably factors as GCs dose and duration treatment, and any underlying diseases may play a role (85). The clinical significance of a reduction of DKK1 might be relevant. Gifre et al. have speculated that the osteocytes and/or the osteoblasts may attenuate the effect of GCs on the cell by lowering the secretion of DKK1, as a protective mechanism against cell death (111). In this way, the modulation of DKK1 signaling by GCs treatment limits both the onset of osteoblasts apoptosis than the differentiation of the adipocytes, and the bone mass loss (88).

In their study, Beier et Al. explored a mechanism involving induction of sclerostin as a facilitator of the negative effects of GCs on bone quality (116). The Authors concluded that bone loss associated with steroid-induced osteoporosis is a consequence of sclerostin-mediated restriction of Wnt signaling, which may mechanistically facilitate glucocorticoid toxicity in bone.

Also autoimmunity might have a role in bone remodelling. For example, in RA the adaptive immune system produces antibodies against rheumatoid factor (RF) and/or against cyclic citrullinated peptides (antibodies to citrullinated protein antigens or ACPA). The plasma levels of ACPA are an index of disease activity and joint damage (117). A recent study has shown that ACPA can stimulate osteoclast differentiation, and that in patients with RA that are ACPA-positive there is a more frequent evidence of bone loss and thinning of cortical thickness than patient with RA and APCA-negative (118). Recently, a significant correlation has been observed between osteoporosis-RA related and risk of erosions (119,120).

The incidence of new fragility fractures during GCs treatment in our cohort of patients was 12% in CTDs, 10% in PMR, and 23% in RA. The prevailing type of fractures was the vertebral one, in particular multiple vertebral fractures observed especially in patients with PMR. It is known that the risk of fractures is increased by twofold in patients with GCs, and the risk of vertebral fractures is even higher. In a study comparing 244.235 oral GCs users and 244.235 controls, the risk of hip fracture was 1.6, and the risk of vertebral fracture was 2.6; many studies have confirmed these numbers (73,121,122). The global prevalence of fractures in patients receiving long-term GCs has been reported to be 30–50%. In 551 patients

receiving long-term GCs, the prevalence of vertebral fractures was 37%, with 14% of patients having 2 or more asymptomatic vertebral fractures; 48% of patients aged ≥ 70 years and 30% of those aged < 60 years had at least one vertebral fracture (123). The increase in fracture risk is immediate, as early as 3 months after the initiation of therapy and reverses sharply after discontinuation of GCs (73). This can be related to the added effects of GCs on bone remodelling previously uncoupled by the inflammation itself, and the dramatic effect on bone strength through induced apoptosis of osteocytes. Data also suggest a rapid increase in rate of falls after start of oral GCs (73). In epidemiological studies, the increased risk of fractures is observed even at low doses of prednisone, that is, 2.5–5 mg per day. The appropriate care of patients receiving such low doses is not well defined. There is a dose-dependent increase in fracture incidence. Interestingly, the fracture risk is related to the current daily dose, more than to the cumulative dose (124): this may be related to the difficulty of an accurate calculation of this cumulative dose.

Secondary objectives of this study were to quantify the prevalence of the principal risk factors for osteoporotic fractures. The prevalence of comorbidities was very high, especially in PMR. No physical activity was found in about 40% of the patients, independently by the rheumatic disease, and the prevalence of falls was high, in particular in RA and PMR (about 20%). Immobilization due to pain from inflamed joints and impairment of physical activity are known key factors related to low BMD and are common in patients suffering from rheumatic diseases (125). The risk of falls may be higher in RA patients because of lower limb joint disease and muscle weakness (due to GCs therapy and disuse) (126). An increased fall

risk in 89% of the RA patients was found (127). Potential interventions to reduce falling in this kind of patients, include control of disease activity, rehabilitation or exercise therapy, balance training, occupational therapy, home assessment and treatment of vitamin D deficiency. A study of Bearne et al. suggested that a “brief rehabilitation” can improve the quadriceps sensorimotor function (128).

In addition, in our patients we found high prevalence of low sunlight exposure and low calcium intake. Vitamin D deficiency is common in patients with rheumatic disease, and associated with disease activity (129-131). We evaluated also the regular intake of calcium and vitamin D supplements before and during therapy with GCs. We observed that only a few patients were on supplementation before starting GCs therapy, while about 80% of patients taking calcium or vitamin D supplements during GCs therapy, as recommended (132).

In our study prevention or treatment of GIOP with specific drugs for osteoporosis appear sub-optimal, and generally restricted to anti-resorptive approach with bisphosphonates (133), despite it is well known that inhibition of bone formation and increased apoptosis of osteocytes play a consistent and crucial role in the pathogenesis, while changes in bone resorption during GCs use are variable. Although it has been shown that bisphosphonates reduce vertebral fractures during the first 2 years of GC treatment, there are no data on long-term use, and, of some concerns in GIOP, bisphosphonates reduce bone turnover, including bone formation, which is already downregulated by GCs. Effectively, the use of the anabolic agent teriparatide was found more effective in reducing vertebral fractures than alendronate (134).

CONCLUSIONS

In conclusion, the GIOTTO study might provide relevant contributions in clinical practice, in particular by highlighting and quantifying in real life the prevalence of GIOP and relative fractures, the frequency of the main risk factors, and the currently sub-optimal prevention. Moreover, these results emphasize the importance of the underlying rheumatic disease on the risk of GIOP associated fractures.

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Table 1: Features of Patients depending on the Rheumatic Disease (Mean \pm SD)

Rheumatic Diseases	N.	F/M	AGE (yrs)	BMI (Kg/m²)	CUMULATIVE DOSE (g)	LENGTH OF THERAPY (mo)
AR	183	157/26	64 \pm 13*	25 \pm 5	20,3 \pm 22,9	108 \pm 91
CTDs	249	206/43	57 \pm 16*	25 \pm 4	23,9 \pm 42,9	79 \pm 84*
PMR	91	71/20	74 \pm 6*	26 \pm 5*	6,3 \pm 10,1*	29 \pm 53*

* $p < 0,05$ between groups

Table 2: Prevalence of risk factors for osteoporosis or fracture, according to the Rheumatic Disease

RISK FACTORS	RA	CTDs	PMR
FAMILY HISTORY OF FRACTURE	15%	23%	13%
ALCOOL HABITS	20%	19%	34%
SMOKING (CURRENTLY/PREVIOUS)	HABITS 19%/23%	19%/17%	9%/26%
FALLS DURING LAST 6 MONTHS	20%	15%	19%
NO PHYSICAL ACTIVITY	42%	42%	39%
SUNLIGHT EXPOSURE <1/WEEK	37%	35%	18%
NO SEA HOLIDAY	66%	63%	60%
LOW CALCIUM INTAKE	30%	23%	34%
COMORBIDITIES	78%	76%	98%
VAS-EQ-5D <50%*	23%	18%	20%

*Visual analogue scale for recording European Quality of Life-5 Dimensions

Legend of the Figures

Fig.1: Enrolling centers

Fig.2: Inclusion/Exclusion criteria flow-chart

Fig.3,4,5,6,7: CRF used to collect information about the medical history, clinical, diagnostic and therapeutic data, and in particular: demographics; physiological and pathological history; assessment of the state of the rheumatic disease and concomitant Health Assessment Questionnaire; previous drug therapy; previous and ongoing glucocorticoid therapy; specific anamnesis for osteoporosis: date of first diagnosis; date of first atraumatic fracture; pain symptoms; previous fractures (before or after the start of therapy GC)/fractures at the baseline visit; outcome laboratory examinations; previous/ongoing drug therapy for osteoporosis; risk factors; assessment of the quality of life (EQ-5D); simplified questionnaire of calcium and vitamin D intake and physical activity

Fig. 8: Prevalence of osteoporosis at spine or femoral neck depending on the Rheumatic Disease

Fig.9: A) Prevalence of patients with fractures pre-GC treatment, according to the Rheumatic Diseases B) Prevalence of patients with new clinical fragility fractures in the different Rheumatic Diseases during GC treatment

Fig.10: A) Distribution of different types of fractures, in the different diseases, during GC treatment B) Prevalence of RA or CTDs patients with recurrence of fractures during GC treatment

Fig.11: A) Prevalence of patients with calcium and/or vitamin D supplementation, before or during GC treatment, according to the Rheumatic Disease B) Prevalence of patients on prevention or treatment of osteoporosis with specific drugs, depending on the Rheumatic Disease.

Fig.1



Fig.2

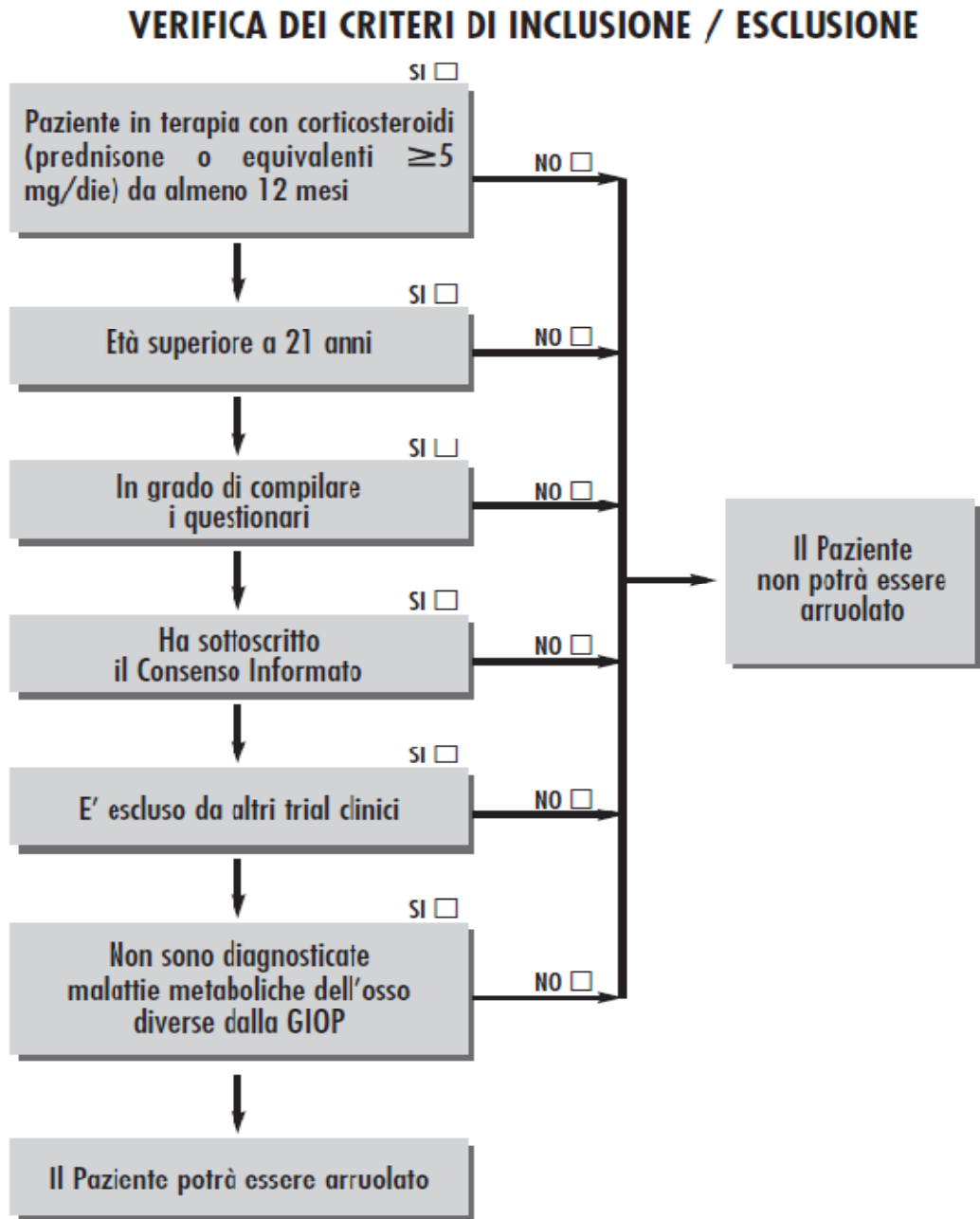


Fig.4

ESAMI STRUMENTALI PREGRESSI/PRESCRITTI PER OSTEOPOROSI								
A39 Densitometrie		<input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare:						
A40 Sito indagato * e data diagnosi	A41 BMD (g/cm ²)	A42 T score	A43 BMC (g)	A44 Marca/modello DEXA				
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*Sito indagato: 1 = colonna; 2 = collo del femore; 3 = femore in toto; 4 = total body

Fig.5

TERAPIA FARMACOLOGICA PER OSTEOPOROSI (antirassorbitiva/anabolica)						
A45 Terapia prima dell'inizio del trattamento con GC				<input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare:		
A46 Codice (☞ - vedi pag. codifiche)	A47 Nome commerciale	A48 Dose/Unità	A49 Frequenza somministr. ☞	A50 Data inizio		A51 Data fine
_ _				_ mm	_ anno	_ mm _ anno
_ _				_ mm	_ anno	_ mm _ anno
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_ _				_ mm	_ anno	_ mm _ anno

☞ Frequenza di somministrazione: 1 = giornaliera; 2 = settimanale; 3 = mensile; 0 = altro

A52 Terapia durante il trattamento con GC							<input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare:		
A53 Codice (☞ - vedi pag. codifiche)	A54 Nome commerciale	A55 Dose/Unità	A56 Frequenza somministr. ☞	A57 Data inizio		A58 Data fine	A59 In corso		
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_ _				_ mm	_ anno	_ mm _ anno	<input type="checkbox"/> SI		

☞ Frequenza di somministrazione: 1 = giornaliera; 2 = settimanale; 3 = mensile; 0 = altro

Fig.6

FATTORI DI RISCHIO				
A68 Familiarità (primo grado) <input type="checkbox"/> ND <input type="checkbox"/> Nessun antecedente familiare <input type="checkbox"/> SI, specificare:				
<input type="checkbox"/> Per fratture dell'anca				
<input type="checkbox"/> Per fratture vertebrali				
<input type="checkbox"/> Altro, specificare _____				
A69 Consumo di alcolici <input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare: n. bicchieri die [][]				
A70 Fumo <input type="checkbox"/> Non fumatore <input type="checkbox"/> Ex fumatore (da più di 6 mesi): n. sigarette die [][]				
<input type="checkbox"/> Fumatore: n. sigarette die [][]				
A71 Cadute negli ultimi 6 mesi <input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare numero: [][]				
A72 Attività fisica <input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare:				
Tempo giornaliero medio				
	< 30 minuti	30 minuti - 1 ora	1- 2 ore	> 2 ore
A73 Passeggiare	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A74 Andare in bici	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A75 Giardinaggio	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A76 Altro _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Esposizione alla luce solare				
A77 Uscite all'aperto (per un tempo superiore a 30 minuti) nel periodo compreso tra aprile e settembre:				
<input type="checkbox"/> Mai	<input type="checkbox"/> Meno di 1 volta a settimana	<input type="checkbox"/> 1 - 2 volte a settimana	<input type="checkbox"/> Più di 2 volte a settimana	<input type="checkbox"/> Ogni giorno
A78 Vacanze al mare per più di una settimana? <input type="checkbox"/> ND <input type="checkbox"/> NO <input type="checkbox"/> SI, specificare:				
<input type="checkbox"/> 15gg.	<input type="checkbox"/> 30gg.	<input type="checkbox"/> 60gg.	<input type="checkbox"/> 120gg.	<input type="checkbox"/> >120gg.
QUESTIONARIO A PUNTEGGIO PER L'INTROITO DI CALCIO				
Riportare nei quadratini a destra i punti corrispondenti alla porzione quotidiana media degli alimenti citati. Nel quadratino finale sommare i punti segnati nei quadratini dei punti A, B, C, D, E				
A65 A. Latte intero o scremato punti [][]				
Un bicchiere = punti 1 Mezzo litro = punti 5				
Una tazza = punti 2 Yoghurt (confezione piccola) = punti 2				
Una ciotola = punti 3				
A66 B. Formaggi (almeno una porzione piccola da 50 grammi) punti [][]				
Ricotta, mascarpone = punti 1				
Bel Paese, fontina, taleggio, provola, ecc. = punti 2				
Grana, pecorino, emmenthal = punti 4				
A67 C. Altri alimenti punti [][]				
Sardine, acciughe = punti 1				
Broccoli, cime di rapa, legumi (100 grammi) = punti 1				
Almeno un litro di acqua minerale con elevato contenuto di calcio* = punti 2				
* ACQUE MINERALI AD ELEVATO CONTENUTO DI CALCIO (Denominazione e Luogo di provenienza)				
Acetosio San Paolo - Roma Lavedo - Bolzano Sant'Agata - Caserta				
Acqua Regina - Pistoia Lete - Caserta Sargente di Tabiano - Parma				
Acqua Santa di Chianciano - Siena San Faustino - Perugia Teleso - Benevento				
Cinciano - Siena San Marco - Latina Uliveto - Pisa				
Ferrarelle - Caserta Sangemini - Terni Valle d'Oro - Verbania				
Fucoli - Siena				

EQ-5D

Per aiutarla ad esprimere il suo stato di salute attuale, abbiamo disegnato una scala graduata (simile ad un termometro) sulla quale il miglior stato di salute immaginabile è contrassegnato dal numero 100 ed il peggiore dallo 0.

Vorremmo che indicasse su questa scala quale è, secondo lei, il livello del suo stato di salute oggi, tracciando una linea dal riquadro sottostante fino al punto che corrisponde al suo stato attuale di salute.

AAA
Il suo stato di salute oggi



HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

da Ranza R. et al. Clin Exp Rheumatol 1993; 11(2): 123-8

Porre una crocetta in corrispondenza della risposta che descrive meglio la Sua condizione. Le domande si riferiscono agli ultimi sette giorni.

Punteggio*	DOMANDA E' in grado di:	RISPOSTE			
		SENZA difficoltà	Con qualche difficoltà	Con MOLTA difficoltà	NON RIESCO
AS2	1. Vestirsi da solo, allacciarsi le scarpe e abbottonare gli abiti?				
Max	2. Lavarsi i capelli?				
AS2	3. Alzarsi da una sedia senza braccioli?				
Max	4. Salire e scendere dal letto?				
	5. Tagliare la carne?				
AS4	6. Portare alla bocca un bicchiere o una tazza piena?				
Max	7. Aprire una confezione di latte?				
AS5	8. Passeggiare su un terreno in piano?				
Max	9. Salire cinque gradini?				
	10. Lavare ed asciugare tutto il corpo?				
AS6	11. Farsi un bagno nella vasca?				
Max	12. Utilizzare i servizi igienici da solo?				
AS7	13. Raggiungere e prendere un oggetto del peso di circa due chili (per esempio, un sacchetto di zucchero posto sopra la sua testa)?				
Max	14. Chinarsi per raccogliere un indumento caduto a terra?				
	15. Aprire la portiera dell'automobile?				
AS8	16. Aprire un barattolo già aperto in precedenza?				
Max	17. Aprire e chiudere un rubinetto?				
	18. Fare delle commissioni e fare la spesa?				
AS9	19. Salire e scendere dall'automobile?				
Max	20. Svolgere lavori quali passare l'aspirapolvere o pulire un cortile?				
AT00	Totale _____ (punteggio totale ottenuto dalla somma dei punteggi diviso per 8)				

*PUNTEGGI HAQ: 0 = senza difficoltà; 1 = qualche difficoltà; 2 = molta difficoltà; 3 = non riesce. RIPORTARE IL PUNTEGGIO PIU' ELEVATO PER CIASCUN GRUPPO DI DOMANDE (MAX).

Fig.7

CONTA ARTICOLARE (articolazioni dolenti e tumefatte)				
	N° Articolazioni dolenti		N° Articolazioni tumefatte	
	DESTRA	SINISTRA	DESTRA	SINISTRA
A102	Scapolo - omerale			
A103	Gomito			
A104	Polso			
A105	Metacarpo - falangee			
	I			
	II			
	III			
	IV			
	V			
A106	Interfalangee prossimali (mani)			
	I			
	II			
	III			
	IV			
	V			
A107	Ginocchio			
	A108 TOTALE DOLENTI _____ (0 - 28)		A109 TOTALE TUMEFATTE _____ (0 - 28)	

A110 VES (Velocità di Eritrosedimentazione) mm/h

A111 PCR (Proteina C-Reattiva) mg/dl

A112 DAS 28 (Disease Activity Score)

da Pincus ML et al. *Arthritis Rheum* 1995; 38: 44-8

$$DAS28 = 0,56 \cdot \sqrt{(t28)} + 0,28 \cdot \sqrt{(sw28)} + 0,70 \cdot \ln(ESR) + 0,014 \cdot GH$$

Dove: t28 = n° articolazioni dolenti (conta a 28 articolazioni);

sw28 = n° articolazioni tumefatte (conta a 28 articolazioni);

Ln(ESR) = Logaritmo naturale della VES;

GH = Stato di salute globale del paziente (scala VAS 0-100)

Attività elevata di malattia: >5.1; moderata: >3.2;
bassa: ≤3.2; remissione: <2.6.

GH Stato di salute globale

Il peggior stato di salute possibile

A113 Vorremmo che Lei indicasse il Suo stato di salute globale negli ultimi 3 giorni (tracciare una LINEA orizzontale)

Il miglior stato di salute possibile

da Pincus ML et al. *Arthritis Rheum* 1995; 38: 44-45

Fig.8

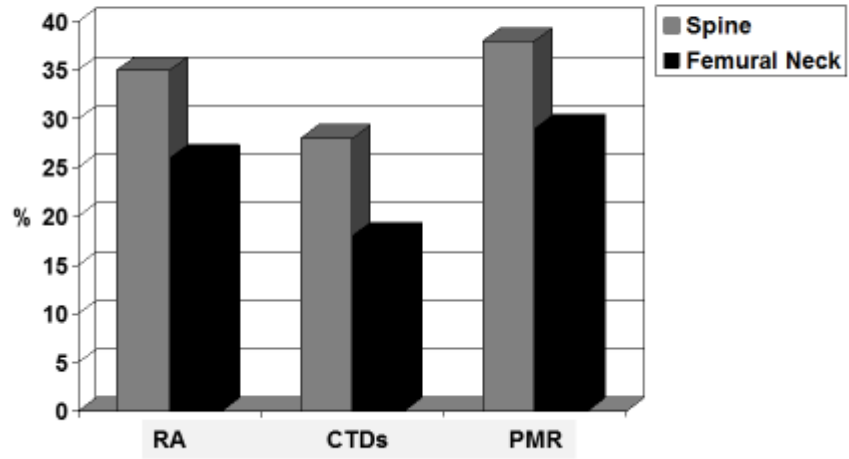


Fig.9

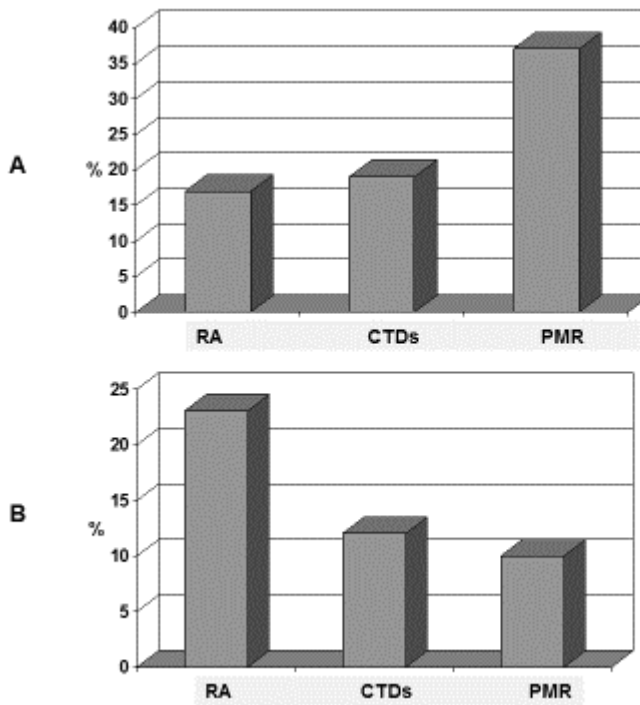


Fig.10

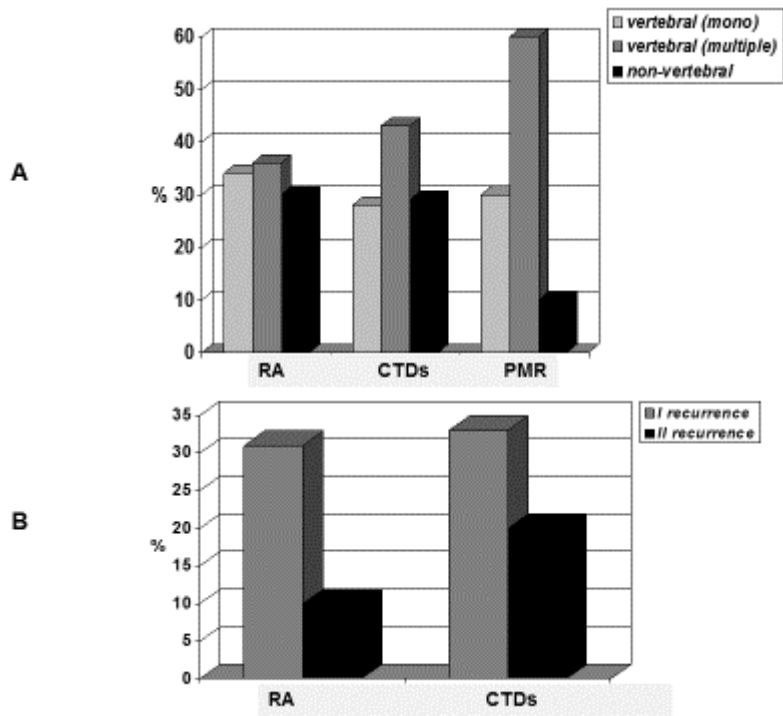


Fig.11

