DOCTOR SALVADOR ALLENDE UNIVERSITY HOSPITAL
FINAL REPORT OF RESEARCH
TREATMENT OF OSTEOARTHROSIS WITH TOPICAL AND ORAL FOLREX

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INTRODUCTION

Osteoarthrosis is the most common arthropathy affecting the adult population, which increases with age (25%-85% of individuals). It is considered as the second most incapacitating disorder, only surpassed by cardiovascular diseases. Due to either the pain and deformity it causes or the functional limitations of joints, it eventually makes movement and daily life activities very difficult for patients, even more so for the elderly.

This is usually a generalized pathology, that is, it affects all joint cartilages, even though it is felt with more intensity on certain cartilages. The inappropriate use of the body in daily activities, as it is the case of laundrywomen's rizarthrosis, pressure axis alterations, or knee arthrosis due to genus valgus or genus varus, can lead in certain cases to compromising one or a few joints. The cervical spine, along with the lumbar area, is continuously subject to the stresses of modern life: static positions of clerks at work or sitting at the computer, watching TV for several hours. Currently there is a broad therapeutic spectrum ranging from the so-called NSAIDS (all generations) to physiotherapy and surgery modalities that focus on improving the symptoms of the disorder and functionality of patients, who in many cases are not exempt from other adverse effects.

Oxidative stress that leads to the formation of free radicals can be triggered by many and varied causes, and has a role in cell ageing, diabetes and degenerative processes including

ARTHROSIS and RHEUMATISM.

The key for the remission of rheumatic-type diseases lies in the control of the synthesis of anti-stress molecules or their precursors (natural antioxidants synthesized by the body itself).
The product Folrex is designed with specific antioxidant compounds activated via a biocatalytic process that enables better control of the production mechanism of said anti-stress molecules.

Spectacular results can be achieved thanks to its new formula based on the analgesic power of activated Folic acid. The use of activated Folic acid as an analgesic and anti-inflammatory offers many advantages as compared with NSAID analgesics, as it is an excellent biocatalyst and myelin protector.

The application of this product helps prevent the inhibitory effects of analgesic and anti-inflammatory drugs, as these inhibit DHFR (dihydrofolate reductase) and lead to a deficiency of this vitamin. [1] The action of several analgesics is based on the irreversible inhibition of

cyclooxigenases 1 and 2, without discriminating both isoforms and inducing, along with the anti-inflammatory and analgesic effects sought, a dysfunction in other tissues (kidneys, gastric mucosa, vascular endothelium, uterine endometrium) and platelet formation.
Conventional therapies also cause a poor concentration of the vitamin B12 and Folic acid mixture, which can lead to myelin degeneration. However, the use of activated Folic acid prevents the occurrence of said processes.

JUSTIFICATION OF PROJECT

Due to both the increasing prevalence of Osteoarthrosis in adults and the high rate of side effects caused by the most frequently used NSAIDs for the treatment of all clinical symptoms of said condition —added to the fact that all other therapeutic methods, clinical and surgical, are not exempt of discomfort for patients— alternative treatment processes are currently sought to ensure increased benefits to patients, fewer side effects, increased safety and therapeutic effectiveness.

The product Folrex is designed with specific antioxidant compounds activated via a biocatalytic process that enables better control of the production mechanism of said anti-stress molecules.

Chitin hydrolisate is formed by an N-Acetylglucosamine polymer. The chitin is found in fungi, yeast, marine invertebrates and arthropods, and is also the main component of their cell walls or shells. [3] N-Acetylglucosamine has effects on the structure of osteoarthritis, as it modifies the agents that trigger it. [4]

Arthrosis and all degenerative diseases involve the development of specific reactive oxygen species (free radicals) and N-Acetylcysteine is the best performing antioxidant for inhibition of these toxic substances that affect the musculoskeletal system.

GOALS

GENERAL:

To demonstrate the effectiveness, safety and benefits of the product Folrex in the treatment of Osteoarthrosis, and to make the corresponding technical decisions regarding its selection and inclusion to the armamentarium.

SPECIFIC:

Ensuring the clinical and functional improvement of selected patients with the application of Folrex (oral and topical).
Increase patients' independence in daily life.

To introduce the product Folrex in the treatment of Osteoarthrosis, on the basis of its benefits and effectiveness.

METHODOLOGY DESIGN:

We conducted a clinical trial stage III with randomly selected patients from the hospital's Geriatric and Traumatology departments, with clinical, radiology and, in some cases,

ultrasonographic Osteoarthrosis diagnosis, for the application of the natural product Folrex oral and topical. The trial involved initially 120 controls and 60 cases. The final number was 106 controls and 53 cases. All patients were monitored by the researchers, who conducted the assessment of all findings from radiographies and ultrasound scans with the support of radiologists.

Selection of cases:

A simple random sample was taken involving patients diagnosed with Osteoarthrosis and listed with odd numbers in the specialized Comprehensive Geriatric Assessment, Orthopaedic and Traumatology of the Hospital Universitario Dr Salvador Allende. The initial sample included two groups. The Case groups (60 individuals) were given Folrex oral and cream, and the Control group (120 individuals) was provided conventional treatment with analgesics and NSAIDs.

CRITERIA APPLIED:

For inclusion:

Patient or relative's consent for participation in the research trial.

Clinical and radiology confirmation of the degenerative joint changes of the specific and ultrasonographic area where appropriate.

Only primary forms of osteoarthrosis were included.

For exclusion:

Any secondary forms of osteoarthrosis

Having undergone any surgery for their disorders.

Having discontinued the treatment for any reason whatsoever (Side effects, worsening of condition, acute condition, lack of willingness to continue, passing away, etc.).

System of Assessment

The initial assessment involved the clinical and radiological confirmation of the diagnosis.

All patients were required to fill out a questionnaire for the purpose of gathering general and specific data including the following:

Personal data: age, sex, skin colour, city/country of origin, clinical file number

Health history and toxic habits

Risk factors

History of joint disorder symptoms

Further findings via physical check-up and radiology analysis.

Once the diagnosis was confirmed, treatment with FOLREX and follow-up was conducted for a period of six months.

Both groups were monitored bimonthly in-house during the term of research.

The following variables were used for the purpose of establishing the effect of the drug in relation to the symptoms:

No change: any patients from both groups whose clinical symptoms remain identical during the period of research.

Slight improvement: any patients from both groups who experienced an improvement in at least one or two symptoms and signs, yet they still found it hard to deal with daily life activities.

Visible improvement: any patients from both groups who experienced improvements in all aspects of their health, which helped increase the quality of their daily life activities.

The level of joint damage was set by ultrasonographic criteria and radiology report:

Level I: Slight joint damage correlated with slight arthritic changes detected by radiology assessment.

Level II: Moderate joint damage and moderate arthritic changes detected by radiology.

Level III: Severe joint damage and severe arthritic changed detected by radiology.

The Barthel Index (see annexe) was applied for the purpose of functional assessment, which measures AVD. For gonarthrosis cases, a goniometer was used to measure the degree of flexibility of the knee before and after the treatment with Folrex.

At a later stage, comparative analysis of results were conducted, discussed and displayed in tables. This enabled us to reach conclusions and provide recommendations.

All data gathered was processed with a Pentium IV computer running the application pack Office 2003.

All results obtained were applied Pearson's Chi Square test using the programme EDIPAT.
Tabular and graphic representation of indicators enabled the analysis and synthesis with an increased level of generalization to provide for the initially set goals.

Ethical aspects

All patients who participated in this research expressed their willingness to participate and were not exposed to any risks that could jeopardize their physical or psychological health. All data gathered from patients involved in the research will remain strictly confidential. All patients involved provided the required informed consent.

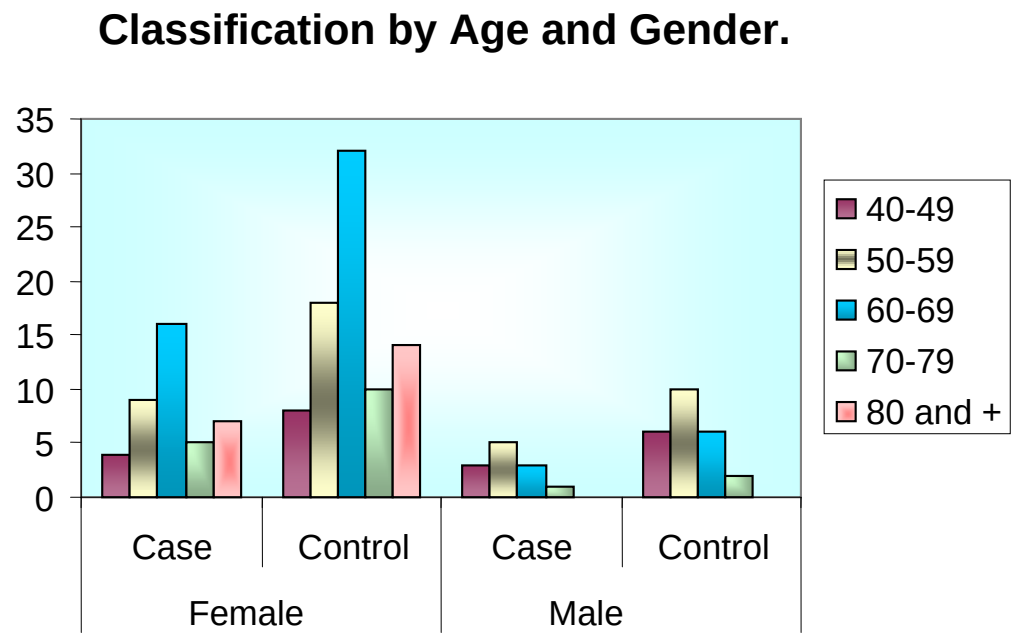
ANALYSIS OF RESULTS

Osteoarthritis is a disease that features a high level of occurrence and which increases with age, with high predominance in females. It is also very expensive. For example, the cost of treatment in Western countries is estimated to range between 1% and 2.5% of the gross domestic product, which shows the economic burden of this problem, as well as the impact in terms of mortality, morbidity and disability, the corresponding decrease of quality of life of patients as a result of the pain and physical limitation endured, which are well above any other groups of diseases including cardiovascular, digestive, respiratory, etc. (1)

Table I. Classification by Age and Gender.

Age	Female		Male		Total
	Case	Control	Case	Control	
40-49	**4**	**8**	3	6	**21**
50-59	**9**	**18**	5	10	**32**
60-69	**16**	**32**	**3**	**6**	**57**
70-79	**5**	**10**	1	2	**18**
80 and +	**7**	**14**	-	-	**21**
Total	**41**	**82**	12	24	**159**

Source: Folrex survey.



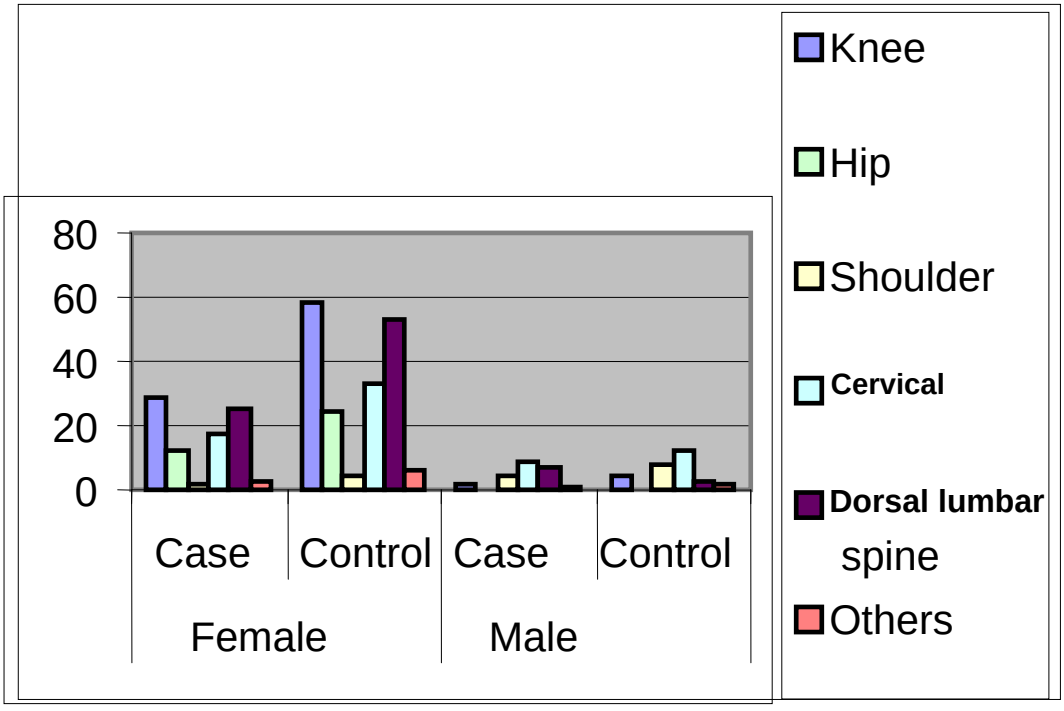
The table shows that the largest section of patients in both groups were females aged between 60 and 69. All other age groups behaved proportionally with a higher predominance of females in both groups. Upon comparison with available literature, all reports show the clear majority of female sufferers of Osteoarthrosis, coinciding in age sub-group size, as degenerative processes increase with age, specifically those affecting the Osteoarticular System. Similar reports were provided by Danilo et al in their research on the prevalence of SOMA diseases in the Cerro Municipality in 2006. (1, 2)

Table II. Distribution of Affected Joint by Gender.

Affected joint	Female		Male	
	Case	Control	Case	Control
Knee	**29**	**58**	2	4
Hip	**12**	**24**	-	-
Shoulder	**02**	**4**	04	8
Cervical spine	**17**	**33**	09	**12**
Dorsal lumbar spine	**25**	**53**	07	**3**
Other	**03**	**6**	01	**2**

Source: Folrex survey.

DISTRIBUTION OF AFFECTED JOINT BY GENDER



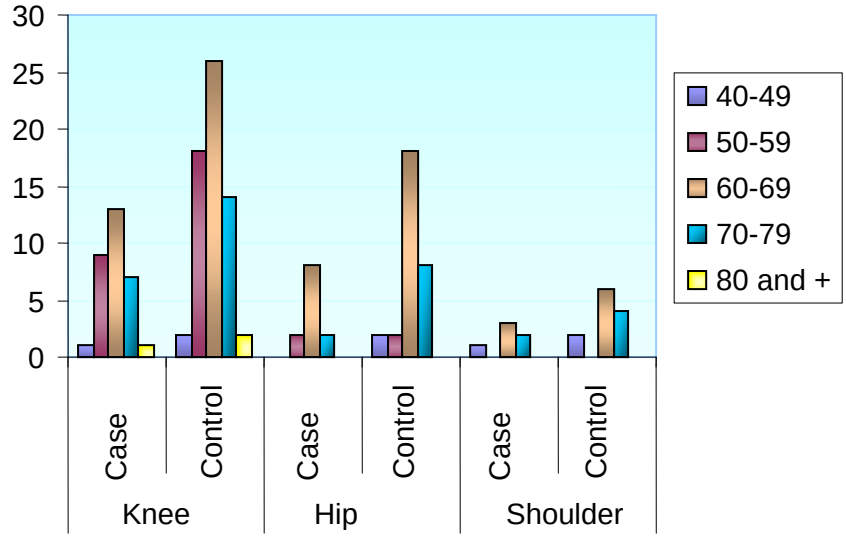
Both in cases and controls, we notice that there was a clear predominance of injuries to the dorsal lumbar spine and knees, followed by the cervical spine and hips, which, specifically the latter, affect more female than male patients. Available literature reports major predominance of knee and dorsal lumbar spine problems, featuring great exposure to loads, overweight and older age. Furthermore, most patients from both groups had more than one joint condition, and more so with age, which coincides with the findings on Prevalence of Disability due to SOMA degenerative diseases by the *Policlinico* Maceo - Cerro Municipality - City of Havana, as well as by all reviewed literature, where the term is widely used when there are more than two affected joints, which increase with age and body weight. (3,4)

Table III. Affected Joints, Knee, Hip and Shoulder by Age Group.

Age	Knee		Hip		Shoulder	
	Case	Control	Case	Control	Case	Control
40-49	**1**	**2**	-	2	1	2
50-59	**9**	**18**	2	2	0	0
60-69	**13**	**26**	**8**	**18**	**3**	**6**
70-79	**7**	**14**	2	8	2	4
80 and +	**1**	**2**	-	-	-	-
Total	**31**	**62**	12	30	6	12

Source: Folrex survey.

Affected Joints, Knee, Hip and Shoulder by Age Group.



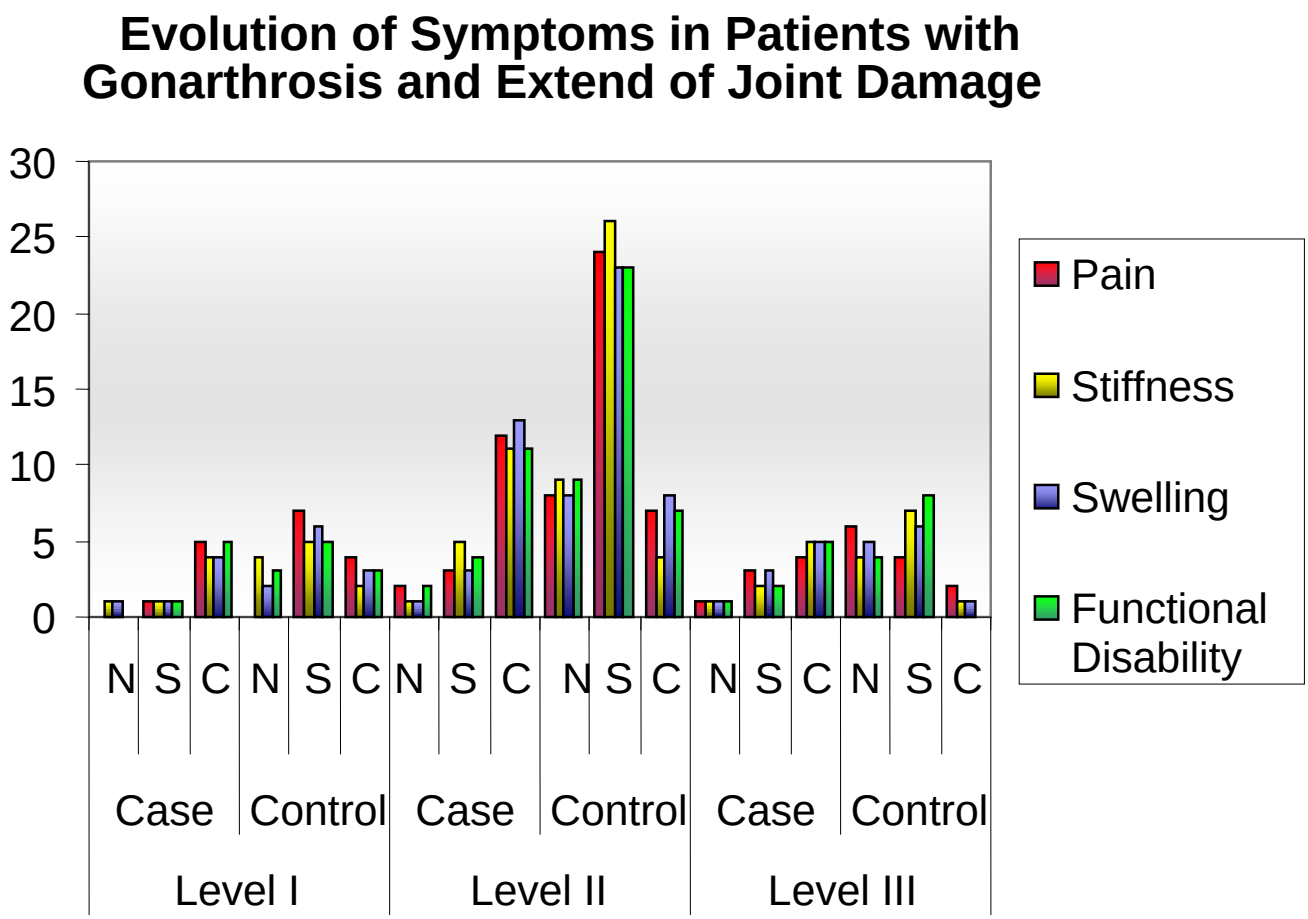
A clear predominance of knee and dorsal lumbar spine injuries were detected in both case and control groups, followed by the cervical spine and hips, which, specifically the latter, affect more female than male patients. Available literature reports major predominance of knee and dorsal lumbar spine problems, featuring great exposure to loads, overweight and older age.

Table IV: Evolution of Symptoms in Patients with Gonarthrosis and Extend of Joint Damage

Joint damage	Level I						Level II						Level III					
Number of patients	Cases 6			Controls 11			Cases 17			Controls 39			Cases 8			Controls 12		
Evolution	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C
Pain	-	1	5	-	7	4	2	3	12	8	24	7	1	3	4	6	4	2
Stiffness	1	1	4	4	5	2	1	5	11	9	26	4	1	2	5	4	7	1
Swelling	1	1	4	2	6	3	1	3	13	8	23	8	1	3	5	5	6	1
Functional disability	-	1	5	3	5	3	2	4	11	9	23	7	1	2	5	4	8	-

Source: Folrex survey.

Legend: N: no changes S: slight improvement C: clear improvement



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Arthrosis is a chronic, degenerative and irreversible arthropathy, featuring cracks, fragmentation and erosion of the joint cartilage, with loss of the intercell substance's chondromucoprotein, reduction of the chondroitin sulphate, among other metabolism disorders that lead the cartilage to lose its properties, above all the uniform distribution of pressures and repair of tissue damage —which lead to the occurrence of progressive injuries aggravated by several factors. This is a common disorder, and knees are the most affected joints. Pain is the predominant symptom, generally functional or mechanical, which appears as soon as movement is started and eases with rest —the main symptom that takes patients to see their doctors. In the research, the main symptoms reported by both groups were pain (100% of patients) followed by stiffness, swelling and functional disability. In many cases in both groups, all symptoms were reported, specifically those involving major joint damage. As shown on the table, the largest group and percentage of cases moved in all symptoms to the

range of clear improvement with practically equal proportion in all levels of joint damage for all the most relevant symptoms in pain control procedures.

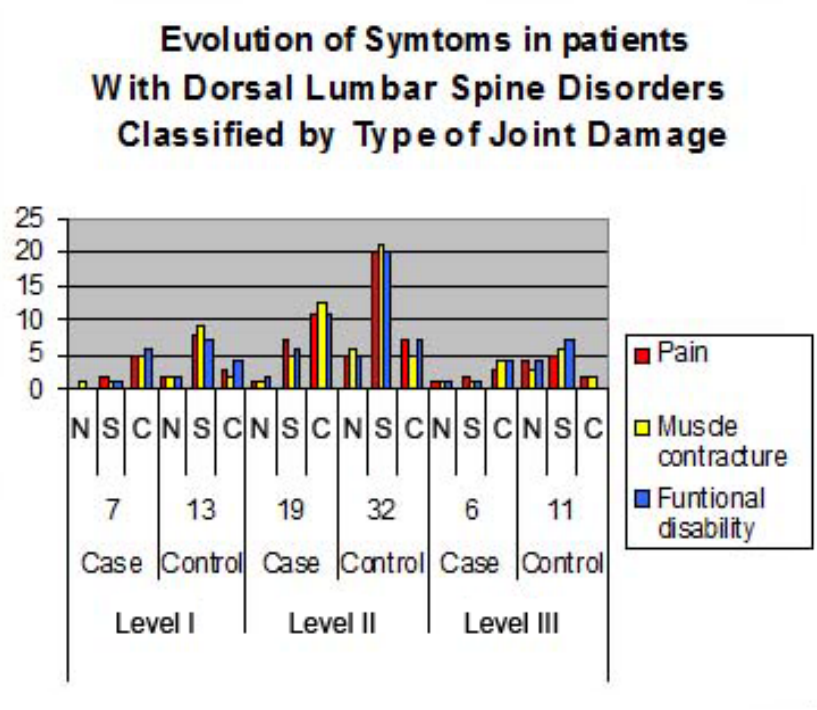
The control group behaved differently. We believe that the beneficial effect of Folrex is due to the double presentation and application of the product, which causes a systemic effect if taken per os as well as a local effect if applied topically, which increases the likelihood of boosting the chances of clear improvement of symptoms. A major influence on this are the different components that help soothe pain and all other symptoms thanks to the analgesic, anti-inflammatory and antioxidant effects of its formulation (N-Acetylglucosamine, N-Acetylcysteine, Germanium 132). As discovered in the research, these components can also help to restore the joint cartilage mostly in early stages of joint damage. The analgesic and NSAIDs used in the control group are compared with results reported in the literature, with no variation to report. (4, 5)

Table V: Evolution of Symptoms in Patients with Dorsal Lumbar Spine Disorders Classified by Type of Joint Damage

Joint damage	Level I						Level II						Level III					
Number of patients	Cases 7			Controls 13			Cases 19			Controls 32			Cases 6			Controls 11		
Evolution	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C
Pain	-	2	5	2	8	3	1	7	11	5	20	7	1	2	3	4	5	2
Muscle contracture	1	1	5	2	9	2	1	5	13	6	21	5	1	1	4	3	6	2
Functional disability	-	1	6	2	7	4	2	6	11	5	20	7	1	1	4	4	7	-

Source: Folrex survey

Legend: N: no changes S: slight improvement C: clear improvement



P:000

In cases of arthrosis of the dorsal lumbar spine, lateral joints display the common degenerative process for all joints, the interfacetal joint cartilage of vertebras is destroyed, followed by subcondral bone sclerosis and the occurrence of osteophytes as detected on radiographies.

Said destruction of the joint and cartilage, osteophytes, deformities and reduction of the intra-articular space lead to the occurrence of pain and muscle contractures in vertebras.

Upon analysis of the table, we can note that most symptoms in the Cases group – Damage I and II experienced a clear improvement in over 60% of all symptoms, which is a significant ratio that provides evidence of the benefits of the use of the product Folrex for treatment of this disorder, as compared with the Controls group, in which most symptoms only experienced a slight improvement.

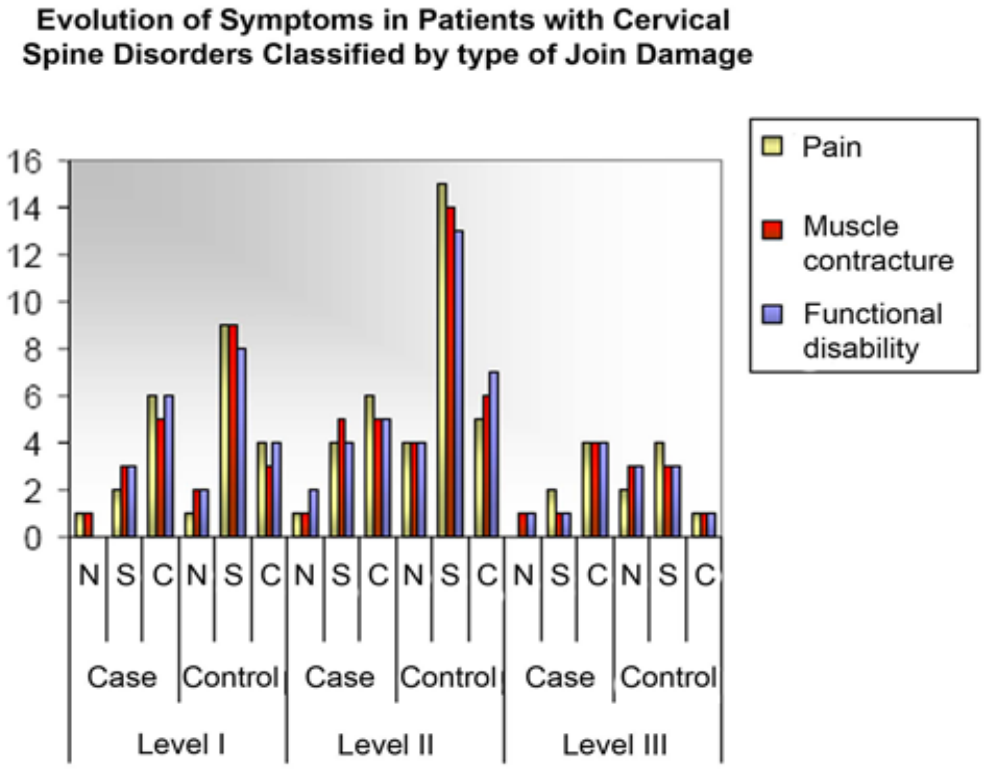
This emphasizes the recovery of the functional capacity of the dorsal lumbar region, which has a strong impact on movement, mobility, spine flexion and development of daily life activities and, as a result, greater independence in the Cases group. (6)

Table VI: Evolution of Symptoms in Patients with Cervical Spine Disorders Classified by Type of Joint Damage

Joint damage	Level I						Level II						Level III					
Number of patients	Cases 9			Controls 14			Cases 11			Controls 24			Cases 6			Controls 7		
Evolution	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C
Pain	1	2	6	1	9	4	1	4	6	4	15	5	-	2	4	2	4	1
Muscle contracture	1	3	5	2	9	3	1	5	5	4	14	6	1	1	4	3	3	1
Functional disability	-	3	6	2	8	4	2	4	5	4	13	7	1	1	4	3	3	1

Source: Folrex survey

Legend: N: no changes S: slight improvement C: clear improvement



P:002

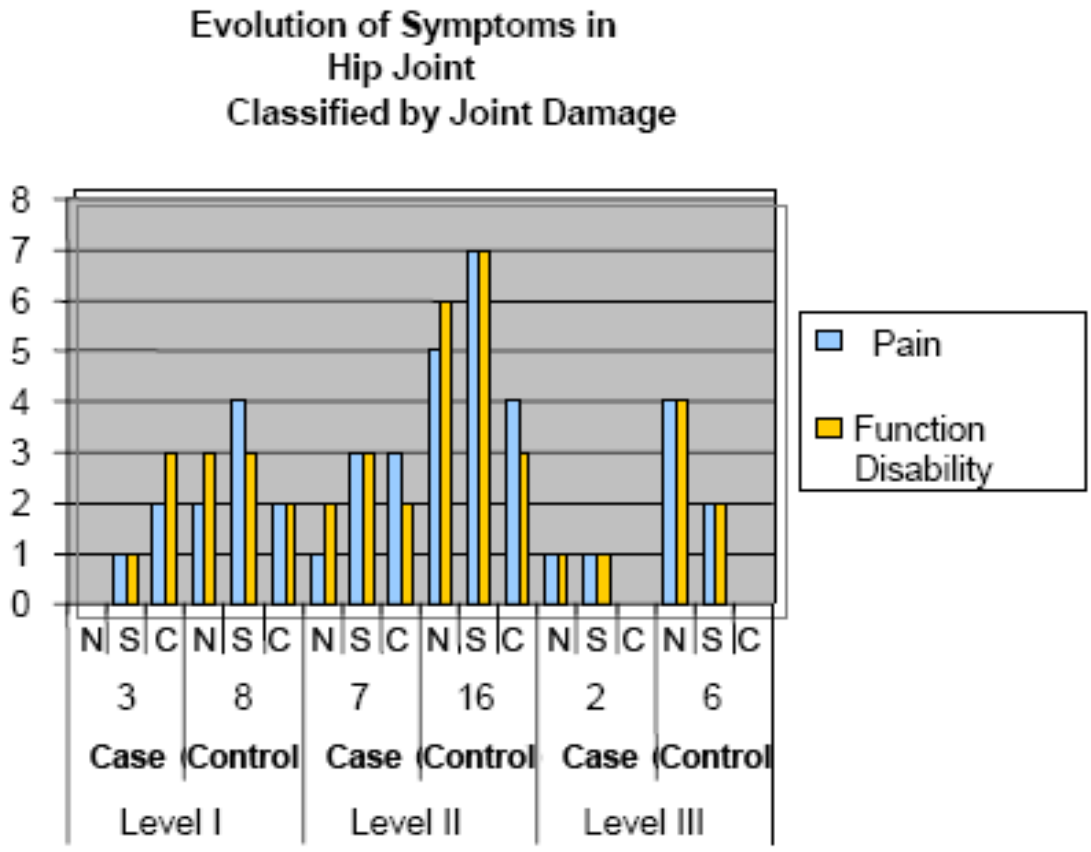
In the table we can compare the response of both groups to the treatment, with results that show a clear improvement, which is greater in the Folrex group. Osteoarthrosic occurrences in the cervical spine are a common complaint from patients of several age groups in daily medical practice, due principally to pain, muscle contracture and functional problems on the neck, which prevent patients to carry out comfortably their daily activities. The limitation of mobility in the neck often occurs along with other paresthetic symptoms triggered by compression of brachial plexus roots, which makes it necessary to distinguish it from other entities, such as discal hernias, carpal tunnel syndrome, etc. (6)

Table VII: Evolution of Symptoms in Patients with Hip Joint Disorders Classified by Joint Damage

Joint damage	Level I						Level II						Level III					
Number of patients	Cases 3			Controls 8			Cases 7			Controls 16			Cases 2			Controls 6		
Evolution	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C	N	S	C
Pain	-	1	2	2	4	2	1	3	3	5	7	4	1	1	-	4	2	-
Functional disability	-	1	3	3	3	2	2	3	2	6	7	3	1	1	-	4	2	-

Source: Folrex survey

Legend: N: no changes S: slight improvement C: clear improvement



P:003

Hip osteoarthrosis features the same metabolic and degenerative mechanisms of all other joints, it is a progressive disease and very little can be done to stop it. However, running a

treatment from the outset can help relieve pain, which is the main symptom reported by patients. The development of the condition causes a limitation of mobility that increases gradually to full stiffness and deformity. Table below shows cases in levels I and II that experienced a clear improvement as compared with control patients, the majority of whom only experienced slight improvement. For both level III groups including patients with severe joint damage, even though they were small groups, the number of no-change and slight improvement cases was identical. However, there was a majority of no-change cases in the control group. These cases of severe hip osteoarthrosis only experienced slight reduction of pain, as the functional disability prevents these patients from moving and carrying out normal daily activities, and need to use hip prosthesis to restore their functionality and regain quality of life. (7)

Table VIII

Clinical evolution of Cases and Controls in bi-monthly assessments of Pain and Functional Impotence

Evolution control		Level I						Level II						Level III					
Joint damage		Cases 25			Controls 46			Cases 54			Controls 111			Cases 26			Controls 36		
Month II %		I	L	E	I	L	E	I	L	E	I	L	E	I	L	E	I	L	E
	P	9	21	70	20	60	30	13	30	57	22	40	38	25	30	45	31	48	31
	FI	11	31	58	17	39	44	16	31	53	32	27	41	26	33	44	39	44	27
Month IV %	P	0	12	88	15	41	44	9	27	68	29	26	45	21	26	53	37	43	30
	FI	4	16	80	16	45	39	11	29	60	30	24	46	22	28	50	37	43	30
Month VI %	P	0	10	90	12	37	51	7	18	75	27	24	49	13	21	66	29	39	34
	FI	2	10	88	10	41	49	8	20	72	29	25	46	14	22	64	28	39	34

Source: Folrex survey

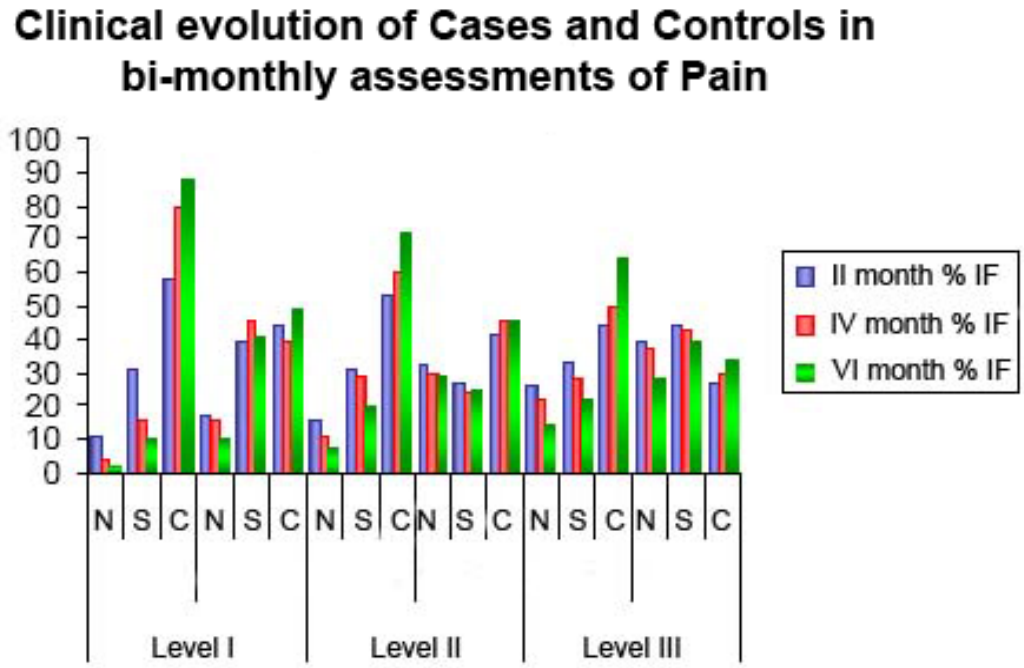
P: pain

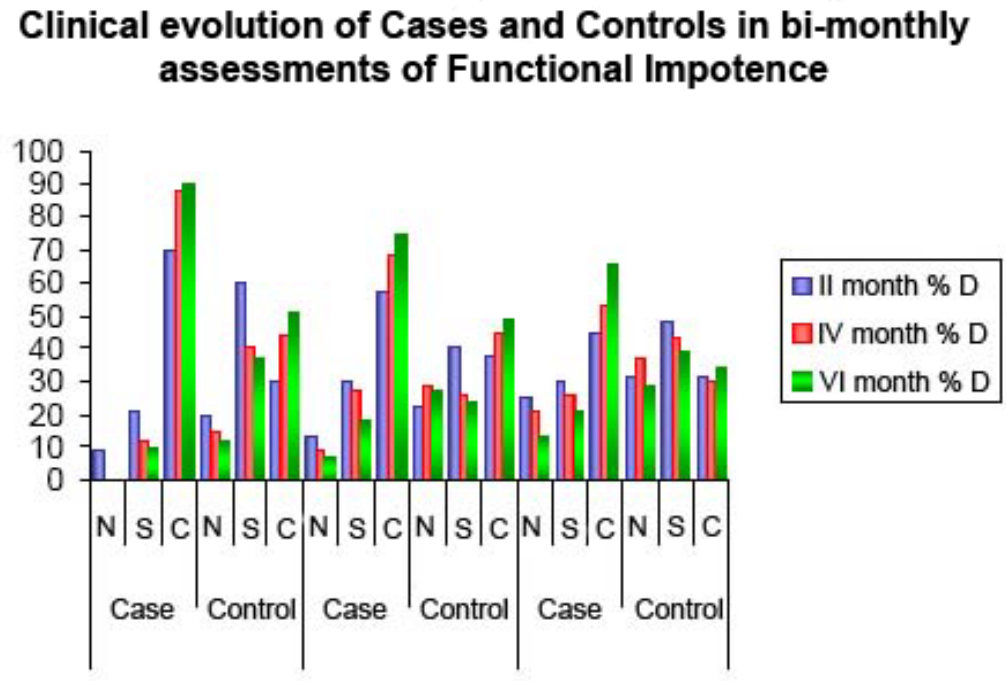
FI: functional impotence

II: second month of treatment

IV: fourth month of treatment

VI: sixth month of treatment





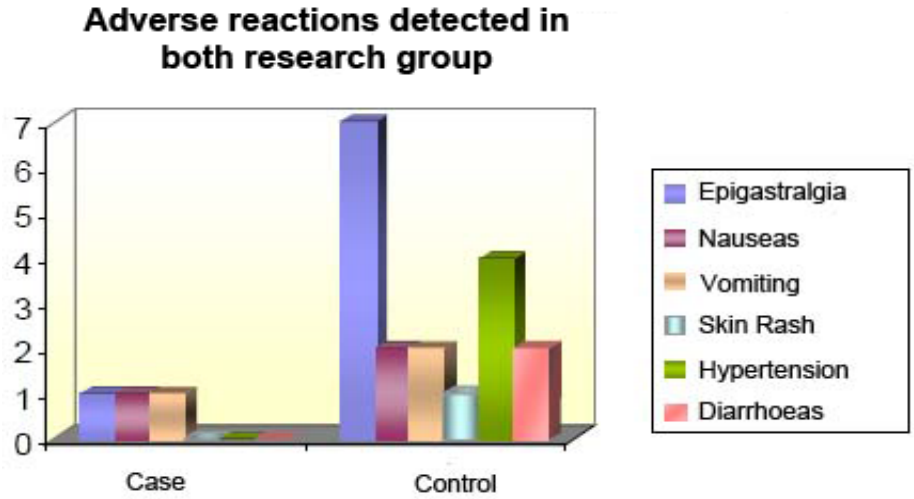
P:002

As observed in the table, the proportional curve of improvement highlights cases (specially Joint Damage Levels I and II) that enjoyed progressive improvement right from the first assessment, 50% of which felt great improvement, moving to clear improvement in Level I in the sixth month (up to 90% for pain and 88% for functional recovery). These patients displayed greater vitality, great relief of symptoms and improved capacity to carry out daily activities thanks to functional recovery —as compared with controls, which only reached high percentages of slight improvement in pain relief and functionality for all joint disorders. (8)

Table IX Adverse reactions detected in both research groups

Type of ARM	Case	Control
Epigastralgia	1	**7**
Nauseas	1	**2**
Vomiting	1	**2**
Skin rash	-	**1**
Hypertension	-	**4**
Diarrhoeas	-	2
Total	3	18

Source: Folrex survey



The use of drugs for relief of pain or improvement of muscle contracture, stiffness and functional impotence in degenerative processes affecting the musculoskeletal system, specifically Osteoarthritis, has led to the increase in consumption of NSAIDs and even corticoids —which, in combination with age and comorbidity, increases the number of adverse reactions. (9). On the table we can observe that control patients (which used currently available

NSAIDs for their treatment) displayed proportionally the largest amount of ARMs (adverse reaction to medicaments) as compared with case patients. This outcome leads us to believe in the benefits, efficiency and effectiveness of the natural product Folrex for the treatment of Osteoarthritis.

CONCLUSIONS

1. The predominant age range for both groups was 60-69, mostly females.

2. Knee, dorsal lumbar spine, cervical spine and hip joints experienced fewer symptoms in both groups.

3. Symptoms were: pain, stiffness, swelling. Symptoms clearly improved in Folrex-treated cases, featuring a higher rate for Joint Damage Level I and II. Controls, however, only manage to enjoy slight improvement.

4. Functional recovery was proportionally greater in Folrex-treated cases compared to controls.

5. The control group experienced the most severe adverse reactions.

RECOMMENDATIONS

1. Conducting multicentric research stage III.
2. Introduce Folrex in the Geroprotection field on the basis of its antioxidant properties .

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Pictures

Case 1: 57 year-old patient with Gonarthrosis Level I.

Angle at start of Treatment

Angle at completion of Treatment

Patient: 62 year-old woman with Gonarthrosis Level II

Angle at start of Treatment

Angle at completion of Treatment

64 year-old patient with Gonarthrosis Level II

Angle at start of Treatment

Angle at completion of Treatment