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ORIGINAL ARTICLE

An open, supplement, registry study Arborvitae® for prevention of arthrosis-related pain during exercise

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ABSTRACT

BACKGROUND: This open registry study evaluated improvements in symptoms associated with osteoarthrosis (OA) managed with a standardized liquid supplement (Arborvitae®, Australia [ABV]).
METHODS: Two comparable groups of subjects using standard management (SM) for OA were evaluated: one with SM only and another using SM and supplemented with Arborvitae® 100 mL/day for 8 weeks followed by 60 mL/day for 4 weeks. Arborvitae Supplement® contains Pycnogenol®, papain and, as accessory components, Aloe Vera, procyanidins, and honey. SM was an evaluation reference. The aim of this study was the evaluation of the efficacy of Arborvitae® supplementation on signs/symptoms, particularly pain while walking and in reducing the need for rescue medications in osteoarthritis patients.
RESULTS: The two groups were comparable at inclusion. Sixty subjects completed the study: 30 in the SM group as controls and 30 in the Arborvitae® group. No tolerability problems or side effects were observed during the observation period. At 3 months, the walking distance was significantly higher in the ABV group in comparison with the control group ($P<0.05$). The Karnofsky Scale in the supplemented subjects improved more in the ABV group at 3 months ($P<0.05$); blood oxidative stress was lower with ABV in comparison with controls ($P<0.05$). The increased temperature of the knee (measurable by thermography) was decreased more with the supplement ($P<0.05$) considering the maximum temperature of the area and the average temperature of the skin over the affected knee ($P<0.05$). The use of rescue medications was significantly lower in the ABV group.
CONCLUSIONS: This registry indicates that ABV may be an effective supplementary management in controlling mild-moderate signs/symptoms associated with OA in otherwise healthy subjects.

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KEY WORDS: Osteoarthritis; Knee joint; Cartilage; Dietary supplements; Pain; Ultrasonography.

Osteoarthrosis (OA) of the knee is one of the most common clinical conditions affecting patients over 50 years of age, often overweight but it can also be present in younger, otherwise healthy subjects regularly practicing traumatizing sports. Several causes are associated with this condition that shows a significant variability in signs and symptoms. The association with other preclinical or clinical conditions (*i.e.* diabetes, obesity, consequences of previous trauma) may affect the clinical picture, symptoms and its evolution, particularly in older subjects.[1-4] Generally, in subjects with a painful knee, forced to relative immobilization or reduced physical activity for prolonged periods, borderline, subclinical conditions (hyperglycemia, hypertension,

hyperlipidemia, increased thrombogenicity, etc.) tend to evolve into specific conditions eventually leading to the need of management with drugs or other medical and surgical interventions.[1, 2]

On the basis of the Merck Manual,[2] the standard management (SM) of OA in these patients without other clinical problems is based on controlling concomitant risk conditions (excess weight, sedentary life, chronic traumatic conditions, postural problems).

Mobilization, physiotherapy (when and if possible) and the use of anti-inflammatory agents (generally NSAIDs on demand) are considered the core medication. Corticosteroids are almost never used unless there are indications of a severe, acute inflammation in progress. Most knee osteoarthrosis (KOA) in subjects in adults has degenerative or post-traumatic (*i.e.* repeated running of hard surfaces) causes.

Potential adverse effects may be associated with acute or prolonged medication with anti-inflammatory drugs (NSAIDs) or corticosteroids that may be considered an easier management option for symptomatic KOA.[2, 3]

Other management plans are widely used including supplementary treatment of OA.[4]

All management measures – particularly in the most acute phases – cause increasing costs.

Complementary therapy is rarely effective.[2, 4-10] Supplementation with highly standardized supplements of natural origin has improved the self-management of many patients with several conditions associated with arthrosis including OA.

Standardized supplements of natural origin have been recently tested in several clinical applications concerning inflammation showing great safety and efficacy.[5-9] Supplementation decreases the need of potentially more dangerous anti-inflammatory agents.[10] Pycnogenol® has been successfully used in OA in several clinical and supplement studies with good results on efficacy and tolerability even in prolonged studies.[10-19]

The aim of this open, registry study was to evaluate the efficacy of Arborvitae® supplementation on signs/symptoms, particularly pain while walking/running and on the efficacy of ABV in reducing the need for rescue medications in osteoarthritis patients with minimal or limited symptoms. Another comparable group of subjects using the standard management for this condition was considered as a comparative reference. Previous registries had indicated the good tolerability of the supplement and its efficacy in improving walking and decreasing pain.

Materials and methods

This study included into an open, controlled registry, subjects with symptoms associated with knee osteoarthrosis supplemented with 'Arborvitae® drink Supplement® (Arborvitae Health and W. Bankstown, NSW, Australia). The supplement use (in association with SM) was compared to standard management (SM) for this condition (control group) for its effects in controlling/decreasing pain, in reducing the need for rescue medications, for its action on oxidative stress (OS) measured as plasma reactive oxygen metabolites and considering its effects on inflammatory markers.

Included subjects were otherwise healthy subjects with mild-moderate symptoms of knee osteoarthrosis (KOA), predominantly associated with knee arthrosis lesions documented by X-ray. The study included subjects within the age range between 40-65 years.

All subjects were followed and managed with the SM and a group of 30 subjects used liquid ABV in addition to SM as a supplement. The subjects drank 50mL of ABV each morning and evening - for the first 8 weeks of the registry and then 60 mL per day for the remaining 4 weeks.

The total follow-up and registry lasted 3 months. All patients were fully re-evaluated at 1 month and at 3 months (end of the study).

Subjects with KOA (without surgical indications) in the age range of 40-65 years and without any other clinical or risk conditions were included.

Exclusion criteria were acute or systemic disease, use of drugs or other supplements, recent fracture or surgery and osteopenia.

Study description

Sixty selected subjects with KOA received either SM or SM+ABV and the 2 groups were comparable.

As indicated by the producer, the bottle was shaken before drinking to blend the ingredients every time before pouring the measured dose into the glass.

Arborvitae Supplement® contains Pycnogenol® 2.6 g/L, papain 2.4 mg/L, Aloe Vera 300 mg/L and honey.

In this study the following parameters were considered: change in pain (visual analogue score), walking distance, the use of the rescue medication and safety issues.

In addition, oxidative stress and inflammatory markers were assessed. Also, we evaluated possible changes in knee superficial perfusion with Ultrafast Thermography (Flir 440, FLIR, Sweden).

The evaluation of oxidative stress is performed with a spectroscopic system measuring the level of PFRs (plasma free radicals) in a drop of blood (from fingers), a method validated in previous studies.[20] The d-ROMs test allows to determine the blood concentration of reactive oxygen metabolites (ROMs). In this test the ROMs concentration is proportional to the intensity of the red coloration, photometrically evaluated. The test is evaluated in Carr Units. Normal values are 250 to 300 Carr Units; above 300 Carr Units, there is oxidative stress. The range between 301 and 320 Carr Units is considered borderline.

All subjects were screened and evaluated to exclude any vascular problem.[21-24]

Methods of evaluation

The severity of pain was evaluated with a visual analogue scale line (VASL) ranging from 1 to 10.

The quality of life was evaluated with a simplified F-35 questionnaire (range 1 to 10).

The mood was evaluated with a BMIS Scale. It was within normal range at inclusion and during the study. The walking distance was evaluated as the distance in meters that patients could walk without pain and the furthest distance they were able to walk with the pain before they had to stop. A treadmill (at 3 km/h with a 10% inclination) was used after briefing and an initial, instructive test.

Thermography measured the average area temperature and the maximum temperature at the anterior surface of the most affected knee (Figure 1) with the patient standing at rest.

An additional parameter was the evaluation of the need for the rescue medication during the observation period. The rescue medication suggested was oral diclofenac (50 mg on demand).

Finally, the Karnofsky Scale (expression of global fitness) was measured at inclusion and end-study.

Supplement studies[25-29] define the activity of supplements and preventive, preferably non-clinical applications. They are organized with the full participation of the patients. The best fields of application for supplements are preclinical, borderline applications or the management of some risk conditions. Supplements are not generally used for primary treatment of signs/symptoms or clinical conditions unless there are specific claims. Supplement registries produce supplementary data to be compared to background, historical data (best available management) or to other management plans. In this registry, supplementation was used according to the following rules: 1) the use of the supplement was suggested to the registry subjects; the supplement use was not prescribed but presented

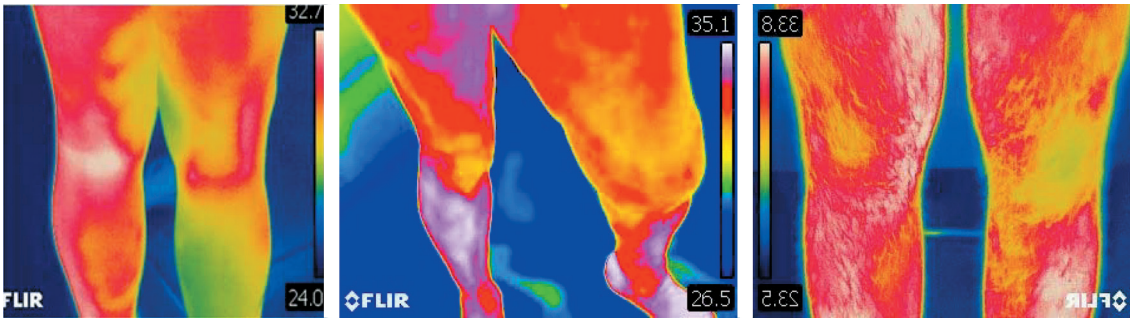

Figure 1.—Thermography patterns showing thermal asymmetry at the symptomatic knees.

as an option, possibly capable of improving the management of OA; 2) the supplement was only used on top of what was considered at the time to be the best-management/care available for that condition; 3) the use of the supplement should not have interfered with any other treatment or preventive measure; 4) the period of follow-up is considered variable, according to the needs and availability of registry subjects. The observation period could be therefore variable, not prefixed. Ideally, the supplement administration should be used as long as needed to see results or changes; 5) the type of evaluation for these studies is always a registry; 6) the supplement is available in the market, does not need a prescription, and may be voluntarily acquired by the study subjects. A quantity of product is made freely available for underprivileged subjects; 7) the evaluation of the compliance concerning the use of the supplement is a significant value indicating how many subjects are actually willing to use the product; 8) there is no defined group allocation, no randomization organized by the monitors; 9) subjects decided, on the basis of the initial briefing, the management group they wanted to join including the control (non-supplement) group. No placebo was used.

This study was a small-scale, independent, pilot, registry study; the evaluation product was not prescribed but recommended. This type of registry is more corresponding to real, practical conditions than most clinical studies that artificially select groups of patients in very selected conditions, often not corresponding to an epidemiological reality.

Statistical analysis

For all the data the average and dispersion variables were calculated. *T*-test for interdependent data was calculated to compare baseline values *versus* 3 months. The ANOVA (with Bonferroni correction) was used to compare the differences between baseline and end-registry values. The correlation coefficients were also determined among walking distance and anthropometric/laboratory variables with the ellipse analysis. On the basis of previous studies, it was considered that at least 20 subjects were necessary to overcome the spontaneous inter-individual variability in each management group.

Results

The registry groups resulted comparable for age and symptoms distribution (Tables I, II) at inclusion. In all subjects, blood pressure was normal — with all main physiological parameters — at inclusion and at the end of the study: also, routine blood tests, were within normal values at inclusion and at the end of the study.

No side effects were observed, and no tolerability problems were reported.

Oxidative stress was significantly decreased in the ABV group in comparison with controls after 1 and 3 months ($P<0.05$) (Table II). ESR and CPR (slightly increased in a small number of patients), were significantly decreased with ABV in comparison with controls; $P<0.05$).

Pain (VASL) was significantly decreased and controlled with the supplement after 1 and 3 months ($P<0.05$) compared to controls.

Walking distance without pain was significantly improved with the supplement at 1 and 3 months in comparison with controls; the total walking distance (Table II) was also significantly increased ($P<0.05$) with AVB at 1 and 3 months in comparison with controls.

Knee thermography showed a significantly more important decrease in the number of subjects with higher knee temperature at the more affected knee with ABV at 1 and 3 months ($P<0.05$).

TABLE I.—*Details of subjects (no drop outs: all included subjects completed the registry). Inflammatory markers were increased in a limited number of subjects (ESR and CRP).*

Group	Number	Age;SD	Range	Sex	Tolerab	Compliance
SM+ABV	30	51.3;2.3	46-61	12 females	Optimal	>97% of INC correct dosing
Increase infl. markers	6					
SM	30	50.2;2.1	46-60	10 females	Optimal	
Increase infl. markers	7					

TABLE II.—*The main target measurements.*

		Inclusion	1 M	3 M
Blood pressure	SM+ABV	Normal	Normal	Normal
	SM	Normal	Normal	Normal
BMI (<26)	SM+ABV	<26	<26	<26
	SM	<26	<26	<26
Oxstress	SM+ABV	388;12	331;13*	326;16*
Carr Units;SD	SM	381;13	356;14	349;19
Blood routine tests	SM+ABV	NV	NV	NV
	SM	NV	NV	NV
ESR	SM+ABV	16;1.1	12;1.2*	11;0.9*
mm/h;SD	SM	16.5;1.2	14.2;1	12.4;0.2
CRPmg/L;SD	SM+ABV	2.58;0.4	2.04;0.3	1.12;0.3*
	SM	2.62;0.3	2.1;0.4	2.3;0.3
Severity of pain (VASL 1-10);SD	SM+ABV	6.88;0.5		3.3;0.4*
	SM	6.8;0.9		5.4;0.2
Walking distance meters without pain	SM+ABV	177;33	203;16*	267;28*
(treadmill) m;SD	SM	181;13	193;17	207;22
Total walking distance m;SD	SM+ABV	269;33	359:32*	458;22*
	SM	265;27	305;23	355;19
Knee thermography (higher temperature)	SM+ABV	30/30	11/30*	6/30*
(>3 °C)	SM	30/30	19/30	14/30
Need for drugs on demand	SM+ABV	--	11/30*	2/30*
	SM	--	16/30	8/30
Karnofsky Scale %;SD	SM+ABV	86.4;2.3%		97.2;1.1%
	SM	86;2.2%		94;3.2
QoL SF35;SD (corrected into 1-10)	SM+ABV	4.3;0.4	6.9;0.2*	8.1;0.3*
	SM+ABV	4.1;0.6	5.5;0.3	6.7;0.3
BMIS mood	SM+ABV	Normal V	Normal V	Normal V
	SM	Normal V	Normal V	Normal V

BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; QoL: quality of life; BMIS: brief mood introspection scale. *P<0.05 *vs.* controls (SM).

The need for rescue medications was also significantly decreased with ABV in comparison with the SM (P<0.05).

The Karnofsky Scale (expression of global fitness) was significantly increased with ABV at 3 months in comparison with the SM, and almost normalized with the supplement (P<0.05).

The Quality of life score also improved better with the supplement (P<0.05).

Mood measured in all subjects at inclusion and at the end of the study (with the BMIS questionnaire) was within normal values at inclusion and at 3 months.

Discussion

This study indicates potential, significant applications of this new standardized supplement formulated as a drink. Previous clinical registries in KOA (in healthy subjects, with limited symptoms) had indicated a good tolerability of Pycnogenol® supplementation with an important level of efficacy in improving walking distance and in decreasing or controlling pain.[17] The present pilot registry on this new liquid formulation including Pycnogenol® indicates that it is possible to control most moderate-mild symptoms due to KOA with ABV, without using drugs.

However, this type of evaluation needs time. This process may be seen in studies lasting at least 6 months or more. The improvements on the knee joint cartilage structures can be documented noninvasively with high-resolution ultrasound.

Cartilage thinning and the presence of superficial irregularities may produce irregular friction in the cartilages with significant symptoms (including pain and altered mobility). Alterations of the cartilage-joint structure can be detected and measured by ultrasound (*i.e.*, measuring the thickening and plaques in carotids or femoral arteries usually suggest the presence of compa-

rable plaques and thickening in the coronary and cerebral vessels). More studies in this direction may indicate other possible ultrasound parameters to study in parallel with symptoms and with functional measurements (walking). The evaluation of the cartilage surface modification in knee osteoarthritis is still limited and this, present study presents a new functional clinical system to obtain objective measurements (walking, running) particularly in cases with early knee lesions and limited symptoms in subjects who have a life with routine patterns of exercise that may be greatly disrupted by even minimal knee pain on walking/running.

The cost-efficacy of the management with Pycnogenol® and particularly ABV is competitive with other managements using products (particularly drugs) that may produce significant side effects. Supplementation may avoid the use of more complex and potentially dangerous products leading to potentially costly complications.

Conclusions

This pilot registry study with the new liquid standardized supplement Arborvitae® indicates that mild-moderate signs and symptoms of KOA, associated with initial arthrosis lesions of the knee cartilage, in relatively young, otherwise healthy subjects using ABV may improve in 3 months of supplementary management without tolerability problems, improving their mobility and the capacity to run without significant pain.

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