

The supplementation included a group treated with Flexiqule and another group treated with Flexiqule added with CA (200 mg/day).

The aim of the study was to evaluate the clinical effects of Flexiqule (Alchem) on the knee joint cartilage (on pain, symptoms and mobility). Also, in this new formulation, the standardized extract of centella asiatica (CA) was added (Flexiqule-C) with the aim to improve cartilage surfaces in 6 months.

CA has been shown – in pilot studies – to increase the volume and regularity of the knee cartilage and its regrowing in relatively younger subjects without severe compromise of the joint.

SUBJECTS-METHODS

Subjects included into the registry did not regularly used any other treatments.

The use *on demand* of drugs during the follow up was considered one of the study targets.

The *rescue medication* was considered Voltaren (diclofenac, 50 mg cp).

All subjects had a good mobility. No other disease and the BMI of all included subjects was <26.

The 3 groups were formed on the basis of:

1. *Standard management* only
2. *Standard management + supplementation* with 2 cp Flexiqule/day for 6 months
3. *Flexiqule (2 cp/day) added with CA.*

A treadmill test (3Km/h with 10% inclination) was used to measure the walking distance without pain and the total, possible walking distance.

The product Flexiqule C includes 150 mg of boswellia in each capsule (daily dose 300 mg/day), 25 mg of ginger (daily dose of 50 mg/day) and centella 100 mg/day (daily dose of 200 mg/day).

The association of symptom-controlling and anti-inflammatory agents with centella asiatica (able to remodulate the cartilage surface, by collagen apposition and regulation, in the joints) is an original observation and concept from our group, based on previous morphological studies. Knee osteoarthritis had radiographic criteria (Kellgren/Lawrence grade 2 or 3, changes and baseline joint space width of at least 2 mm). No other significant disease or alterations was observed in the results of blood tests at inclusion, and no other drugs or supplements were used during the observational registry period by the subjects. A good understanding of the supplement study plan and the will to follow the SM and/or the supplementation program was considered essential. The aim of the subjects was to avoid using NSAIDs or use these compounds as little as possible, only as a rescue medication. The product rationale (in Flexiqule +CA) is then based on the synergistic action of its key ingredients, targeting three key features of osteo-arthritis: pain, inflammation and cartilage damage. This combination is aimed at better controlling

pain and inflammation at knee level improving symptoms and, eventually, pain-free mobility in these patients. *Boswellia serrata* extract contains boswellic acids, exerting an important anti-inflammatory action through the inhibition of lipo-oxygenase (and then of leukotriene synthesis), of PMN leucocyte migration and elastase. Ginger extract has an important anti-inflammatory and analgesic activity due to different mechanisms such as COX-2 control, leukotriene synthesis inhibition and an action on TRPV1 receptor.

Centella Asiatica has a significant role in avoiding irregular scarring and in modulating cartilage regrowth by regular collagen apposition, avoiding keloidal scarring at the affected areas in the articular cartilage.

Ultrasound scanning at the knee may have some limitations due to the non-transparency (at ultrasound) of the joint structure. Also, the relative deformation of the joint in OA patients does not always allow a correct visualization of the lateral space between tibia and femur by ultrasound in all subjects.

Only subjects with a visible cartilage surface and without severe calcifications by ultrasound were included into this registry. Calcifications may stop ultrasound by producing acoustic shadows at the V-shaped space. The V-shaped space broadly corresponds in the image to the synovial cavity.

Vascular problems had been excluded.

Ultrasound findings. Knee ‘V’ spaces (lateral and medial with a transversal, ideal latero-medial section) were studied and considered as target evaluation points (Figure 1.1). Out of a large number of valid ultrasounds parameters the most valuable items to follow-up in time were considered and grouped according to their relative reproducibility; the most consistent observations were:

- periosteal cartilage (PC) thickness;
- irregularity of the PC;
- presence of periosteal “steps”;
- high ultrasound range (white) components;
- elastosonography (considering tissue density and elasticity);
- channel space;
- presence of diffuse vascularization and inflammation.

Diffuse calcifications, severe deformities or irregularities – making imaging impossible at the V level of the knee – were exclusion criteria. The thickness of the PC was measured according to a method previously used to define the intima-media thickness at the carotids, described in detail in previous papers (Figure 1.1).¹³⁻¹⁸ A 10- to 14-MHz high-resolution ultrasound probe was used (Preirus, Hitachi, Tokyo, Japan, with a Hitachi elastosonography software). The patient was resting supine during the test.

Blood tests. Laboratory test results were normal in all subjects at inclusion and were used to rule out other clinical problems (including rheumatoid arthritis of other prob-

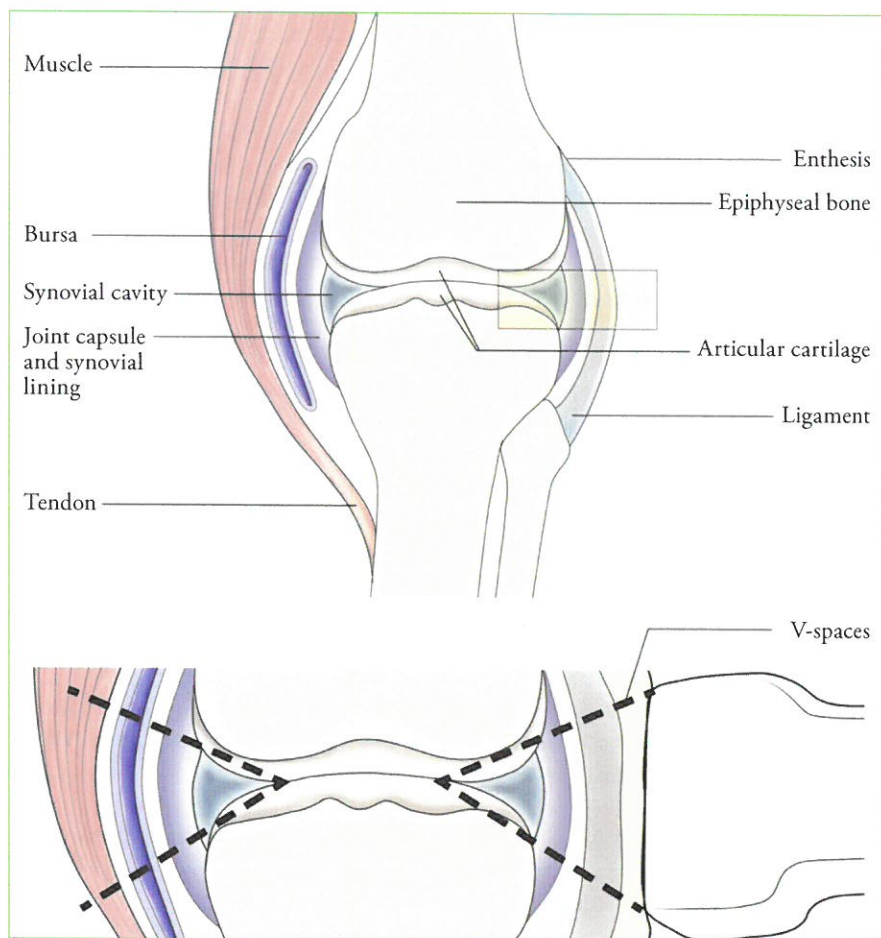


FIGURE 1.1. Legend, the knee joint with the V-spaces used to visualize the articular cartilage.

lems causing OA) or risk conditions (*i.e.* diabetes). All tests were within the normal range at inclusion (hematocrit, tests of liver and kidney function, urines).

Oxidative stress was measured with a drop of blood from a finger, as described in detail in previous studies.^{19, 20}

A minimal joint effusion was present in all subjects at inclusion (also shown by ultrasound).

No peripheral vascular problems were observed with a complete evaluation of the arteries and veins (Doppler Duplex).

The global physical evaluation was made using the Karnofsky Scale (Table 1.II) to define the relative level of incapacitation due to the painful knee arthrosis. The Kar-

nofsky score is easier to use and clinical better than WOMAC score, particularly for medical patients and more corresponding to the presence of physical limitations.

Standard management included, weight control, regular exercise (20 minutes daily, with soft knee/ankle flexion exercises and specific re-training for the leg joints after briefing by a specialized therapist). Also, adequate shoes and clothes, avoidance of static positions for long periods, working aspects (i.e., avoiding weights and wrong postures) and administration of adequate doses of calcium, vitamins C and D. Drugs and treatments were only used on demand or, if needed.

Statistical analysis. Data and results were analyzed in comparison with the results from the SM considered as a baseline. All measurements were considered not regularly distributed and therefore, non-parametric. Intra- and inter-group comparisons were performed by non-parametric tests and using the ANOVA test, as appropriate. A P value <0.05 was considered statistically significant. According to previous studies on comparable groups, at least 20 subjects in each group were considered adequate to define a difference in target outcomes after at least 6 months of supplementation. The study was considered complete when at least 60 subjects completed the follow up for 6 months.

RESULTS

No side effects were observed with the supplementations. There were no drop outs. The groups were considered comparable (Table 1.I) for age, sex distribution and for their clinical patterns at inclusion (Table 1.II).

Cartilage thickness (considered the most important target measurement) was increased, significantly more in the Flexiquile-C group. There were no changes in controls using the SM only.

Also, the cartilage surfaces – visible on ultrasound scans – appeared more regular with a lower number of ‘steps’.

Ultrasound also indicated a more decreased level of effusion with the supplementation. Flexiquile-C was significantly superior in all parameters indicated in Table 1.II and 1.III to the other two groups including the Karnofsky scale score.

The pain score, the number of subjects with increased CRP (C-reactive protein), the general fitness scale, the need for pain-killers, oxidative stress, the pain-free walking distance and the ESR were all significantly better with the two supplementations in comparison with standard management. There was a significant, progressive improvement at 3 and 6 months.

Measurements in the Flexiquile-C group were all improved in comparison with Flexiquile. Flexiquile appears to be effective in controlling pain and symptoms but a restoration of the cartilage surface occurred only in subjects treated with centella asiatica.

TABLE 1.1.

Groups	Number	Females	Age
Ps supplement flexiqule	26	14	49.8;2.4
Standard management controls	26	16	48.7;2.7
Controls2 flexiqule with ca:	20	8	48-5;4.2

TABLE 1.2.

Groups	Numb of cases	Cartil thickness 6 Months	Pain Inc 0-4	Pain At 3 and 6 Months	Raised Cpr		Fitness 3-6 Months Scale 0-4 (At Incl<2)	Karnofsky	
					Inc	3-6 Months		Scale Incl	6 Months
Supplement Flx 6 Months	26	+14.2% +15.4%	3.33;0.2	0.82;0.2* 0.75;0.1*	7/26	2/26* 1/26*	3.4;0.2* 3.5;0.1*	91;2	94.5;1
Controls 6 Months	26	+0.22% +0.2%	3.3;0.1	1.89;0.2 1.8;0.1	8/26 5/25	5/26 2.7;0.2	2.1;0.1	90.3;2	92.3;1
Flexiq+ Cent.as. 6 Months	20	+19%	3.24;0.1	1.8;0.1 1.4;0.1*	6/15	3/20 1/20	3.4;0.2 3.6;0.2*	89.2;1	94.6;2*

Cartilage thickness (considered the most important target measurement) was increased, significantly more in the Flexiqule-C group. The increase (was measured by High Resolution Ultrasound); Table values express increase in % (from the initial thickness value = 100%). *= Better than controls.

TABLE 1.3.

Groups	Numb Of Cases	Use Of Pain Killers	Oxstress Carr Units		Painfree Walking Distance (M)		Erythro Sediment.	
			Incl	6 Months	Incl	3-6 Months	Rate Incl	3-6 Months
Supplement Flx 6 Months	26	4/26* 1/26*	367;12	331;11* 320;12*	75;12	189;24* 212;12*	23.4;2.1	11;1.2* 8-5;2*
Controls 6 Months	26	11/26 10/26	361;11	362;13 371;22	81;12	119;15 124;12	22;2.1	17.5;2 15.4;2.2
Flexiq+ Cent.as. 6 Months	20	— 1/20*	366;14	358;11 334;11*	80;14	122;22 198;14*	23;4.4	14;1.2 8.3;3

*= Better than controls.

The increased regularity of the articular surfaces – due to the modulation of collagen within the cartilage – may be effective in controlling better not only the joint function but also symptoms.

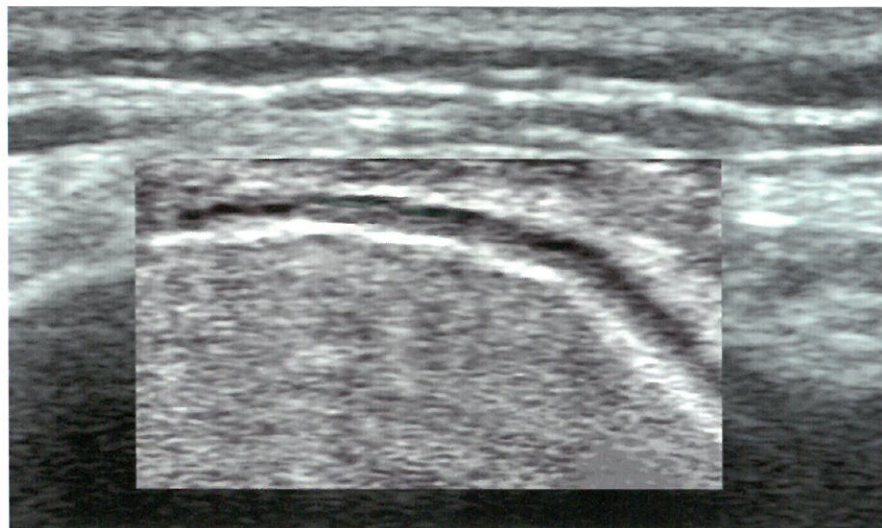


FIGURE 1.2. A sample of articular cartilage.

The surfaces are clearly visible and the thickness of the 'white', echogenic surface can be measured.

DISCUSSION

This study indicates an important applications of this new PS supplements composition in the management of OA with a significant healing activity.

The most important observation is that these products – all very safe and well tolerated – can be used for long periods; no significant complications or problems occur.

This combination of elements appears to be very effective. Previous clinical registries had shown a very good tolerability of the association boswellia and ginger and its significant efficacy in improving walking distances and decreasing pain and the need for drug treatments.

This registry indicates that the cartilage – with the administration of centella asiatica – may undergo a progressive remodeling process that usually may last months and that could be noninvasively detected and measured with high-resolution ultrasound. Cartilage thinning and alterations and superficial irregularities may produce irregular frictions within the cartilage surfaces with significant local symptoms (including pain and altering mobility). Detecting and measuring alterations in one visible section of the cartilage-joint structure has a sampling value for all joints (*i.e.* thickening and plaques in carotids or femoral arteries usually suggest the presence of diffuse, comparable plaques and thickening in the coronary and cerebral vessels).

More studies in this direction may indicate other possible ultrasound parameters and may improve this specific technology.

The evaluation of 'reverse' cartilage modifications in knee OA is still limited by technology and this study presents a new system to obtain objective measurements, repeatable in time.

The biological activity of *centella asiatica* is expressed on the healing or improvements of the affected cartilages; this process may require 4-6 months to be detected. The cost-efficacy of supplementary management with pharma-standard products appears to be competitive with other managements (i.e. including intra-articular injections) using expensive products (i.e. ialuronic acid) that may also produce significant side effects. Supplementation avoids more complex and potentially dangerous drugs, products and management options (for instance NSAIDs) leading to potentially medically and socially costly complications.

Standard management and physiotherapy are also very useful and effective but require visits to specialized centers with a significant loss of time and costs.

Role of centella: the collagen-remodulating activity of *centella* has been known for decades in modern medicine. The control of excessive proliferations leading to keloids is a significant target of *centella asiatica* in several studies (i.e., wound healing, scarring after burns in children).

Atherosclerotic plaques may be considered a cheloidal proliferation and the use of *centella asiatica* helps to stop the progression of carotid and, generally atherosclerotic plaques. Also, the use of *centella asiatica* makes plaques less fragile or prone to embolization by incorporating collagen in the right amount and with the right appositional structure.

Conclusions. This study – including different management plans for symptoms linked to OA, in otherwise healthy subjects – indicates usefulness of PS supplements in the treatment of OA. In particular, remodeling of the knee cartilages as a consequence of the use of *centella asiatica* is effective and safe, especially for relatively younger subjects.

With this new supplement combination the effects of cartilage remodeling may occur in months and the most common signs/symptoms tend to disappear in a shorter period of time (less than 3 months) allowing a faster and more progressive recovery.

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