ORIGINAL

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The effect of a pharmaceutical per os supplement based on methylsulfonylmethane, hydrolyzed collagen, bromelain, D-glucosamine, chondroitin sulfate, L-arginine, L-lysine, plant extracts of boswellia, myrr and turmeric, and Vitamin C on Achilles tendinopathy

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ABSTRACT

This is a prospective clinical study in order to evaluate the effect of nutraceutical treatment of Achilles tendinitis. Recreational and professional athletes with acute Achilles tendinitis were recruited and divided into a Treatment (n=8) and a Control (n=8) group. Treatment group received food supplement based on Methylsulfonilmethane (MSM), Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin (turmeric acid) and Myrrh for a month. Subjective (VAS score) and objective (VISA-A and Ankle-Hindfoot scales) were evaluated. The Treatment group demonstrated statistically significant pain relief (VAS) at 1st month and better functional outcomes (VISA-A) compared to Control group. It seems that administration of nutraceuticals additional to any other conservative or surgical intervention enhance the final outcome in Achilles tendon pathologies.

KEYWORDS: Food supplements, Achilles tendinitis, Achilles tendinopathy

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Introduction

Terminology

Achilles tendon pathologies can either be due to an acute injury, mostly occurring in relation to sports, or have a chronic background. Acute traumatic loading of the Achilles tendon is associated with acute inflammatory reaction of its paratenon called *Achilles tendinitis.* Cyclic chronic loading during walking or running activities may lead to repetitive microtrauma of the tendon substance and alterations of the tendon microcirculation. Accumulation of chronic microdamage to the tendon itself will cause degeneration of its substance called *Achilles tendinosis*. Degeneration and calcification of the tendon insertion into the calcaneus bone is referred as *Achilles enthesopathy*. It is caused either due to systematic pathology such as autoimmune disorders especially ankylosing spondylitis and psoriatic arthritis or due to repetitive local microtrauma such as in long distance runners. The last two types of chronic Achilles pathology are placed under the general term of *Achilles tendinopathy*. (1-3)

Current treatment options

All the above-mentioned pathology of Achilles tendon is expressed predominately with pain followed by swelling and stiffness. Achilles tendinopathy initial treatment is often conservative, and the available therapeutic options are based on sparse evidence, including physiotherapy, splinting, taping, cryotherapy, extracorporeal shockwave therapy (ESWT), peritendinous injections with corticosteroids or Platelet Reach Plasma products (PRPs), non-steroidal anti-inflammatory drugs (NSAIDs) and food supplements. (4-8)

The role of food supplements in Achilles tendinopathy regarding pain relief and function improvement has not yet been clarified. In a clinical trial, a statistically significant improvement of pain, in terms of Visual Analog Scale (VAS) and Ankle-Hindfoot Scale (AHS) was observed in patients treated with methylsulfonylmethane, collagen, bromelain and vitamin C in association with ESWT compared to ESWT alone. (9)

Study target

Given the known adverse events of prevalent pharmacological treatments for pain such as NSAIDs, and the poor results of local infiltration with corticosteroid and PRP products, we intended to assess the effect of food supplements based on methylsulfonylmethane, collagen and arginine on pain and function in acute cases of Achilles tendinitis in addition to the standard of care. It is the senior author's belief that chronic cases of Achilles tendinopathy are refractive to any conservative treatment alone. In such cases, conservative therapies could be adjuvant to surgical treatment.

Patients and Methods

Design, Setting and Recruitment

This is an arm of an observational non-interventional prospective multicenter international study conducted in ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy with satellite centers in Greece, Spain and Romania. However, due to the COVID-19 pandemic, the multicenter study was not accomplished, so we used our data in the Hellenic population. Patients were recreational or professional long distance runners recruited at the 5th Orthopaedic Department, Hygeia Hospital in Athens, Greece.

Food supplement was based on Methylsulfonilmethane (MSM), Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin (turmeric acid) and Myrrh. The supplement was offered by the Hellenic branch of Galenica Pharmaceutical Industry under the commercial name of *Tendisulfur Forte*. The usual course of treatment was two drug sachets daily for 30 days according to information provided by the manufacturer. Each sachet contained Methylsulfonilmethane 5000 mg, Collagen 2000 mg, Arginine 2000 mg, Lysine 1000 mg, Vitamin C 1000 mg, Glucosamine 300 mg , Chondroitin sulfate 300 mg, Boswellia 200 mg, Curcumin 200 mg and Myrrh 100 mg. Subjects who participated according to the authors' judgement and the current clinical practice, were divided into two groups: **group-A (Treatment Group)**, who received the treatment (n=8) and **group-B (Control Group)**, who were not offered (placebo) or who refused the treatment (n=8). Initially, 20 patients were recruited, however four of them were excluded due

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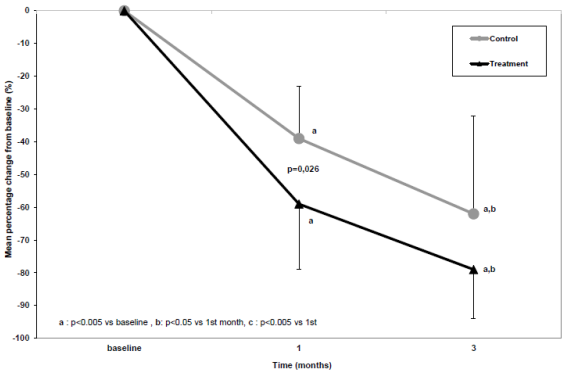

Figure 1. *Visual Analogue Scale (VAS) during the observation period*

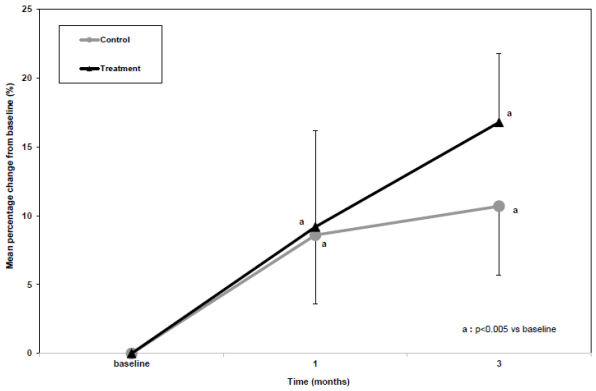

Figure 2. *The Victorian Institute of Sport Assessment-Achilles Questionnaire (VISA-A) during the observation period.*

to non-compliance with the appropriate treatment. The intake of NSAIDs, paracetamol and other painkillers, was considered as concurrent treatment(s) at the doses indicated on the product information and according to the attending physician's judgement.

Endpoint and outcome measures

This study had a duration of 10 months of which 4 months were needed to complete the enrolment. The patients' symptoms were followed over a period of 2 months, with a total of 4 visits (baseline visit, 15 days, 30 days, and 60 days). The subjective outcome was to assess the effect (30-day average change) of the treatment on pain from Achilles tendinitis measured by VAS pain (0-100 horizontal line) in subjects who received the treatment compared to who did not. The objective outcome assessed the effect (15-, 30- and 60-day average changes) of the treatment on pain from Achilles tendinitis measured by patient-reported outcomes (VISA-A questionnaire and Ankle-Hindfoot Scale) in subjects who received the treatment compared to who did not. (10-12)

Inclusion criteria

All patients were above 18 years old. The diagnosis of Achilles tendinitis was based on the presence of the clinical criteria: the subjective reporting of pain and/or pain on palpation of the tendon with a duration < 3 months either mono- or bilaterally and VAS pain when walking > 30/100

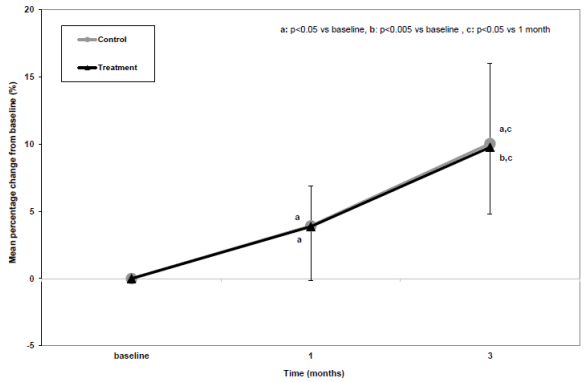

Figure 3. *The Ankle Hindfoot Score (AH) during the observation period*

Exclusion criteria

Patients with: (a) acute (<6 weeks) traumatic Achilles tendinopathy, (b) diagnosis of complete or partial rupture of the Achilles tendon, (c) diagnosis of spondyloenthesoarthritis (ankylosing spondylitis) or psoriatic arthritis, and (d) congenital or acquired deformities of the lower limbs, were excluded. Additionally, patients with (a) history of Achilles tendon surgery; (b) paratendinous injections (local anesthetics and/or corticosteroids) administered within the previous 4 weeks; (c) the administration of the same components of the treatment within the

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TABLE 1.

Homogeneity between groups

	Control	Treatment	p-value
Age (years)	48.80±6.92	52.18±13.05	0.474
Gender, male/female; n (%)	1(10.0)/9(90.0)	0(0)/ 11(100.0)	0.476
Height (cm)	177.00±3.02	181.00±7.40	0.122
Weight(kg)	71.20±6.20	78.73±9.40	0.045
BMI	22.68±1.33	24.01±2.26	0,124
Quinolones, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Paracetamol, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
NSAID, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Food supplement, no/yes; n (%)	9(90.0) / 1(10.0)	7(63.6)/ 4(36.4)	0.311
Metabolic syndrome, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Alcohol, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Physical exercise, amateur/prof; n (%)	8(80.0)/2(20.0)	11(100.0) / 0(0)	0.214
Lab exams, normal/abnormal; n(%)	10(100.0) / 0(0)	8(72.7)/3(27.3)	0,214
Site, right/left; n (%)	7(70.0)/ 3(30.0)	8(72.7)/3(27.3)	1.000

All values are presented as mean±SD

previous 3 months; (d) chronic (≥ 3 months) glucocorticoid therapy (≥5 mg prednisone equivalent daily); (e) cryotherapy and/or (f) ESWT performed within the previous 3 months or planned in the following 10 weeks, were also excluded.

Statistical analysis

Data were expressed as mean±standard deviation (S.D.) or median (in case of violation of normality) for quantitative variables and as frequencies, percentages for qualitative variables. The Shapiro-Wilks test was utilized for normality analysis of the parameters. The homogeneity between groups examined using the independent samples t-test and Fisher's exact test. The comparison of variables at each time point was performed using the independent samples t-test or Mann-Whitney test in case of violation of normality. One factor Repeated Measures ANOVA model was used for the comparison of different time measurement of variables for each group. Pairwise multiple comparisons were performed using the Bonferroni test.

The efficacy of the treatment during the observation period was evaluated by calculating the mean percentage changes from baseline after 1 and 3 months respectively. Comparison of percentage change from baseline of parameters during the observation period between 2 groups was analyzed using the independent samples t-test.

All tests were two-sided and statistical significance was set at $p < 0,05$. All analyses were carried out using the statistical package SPSS vr 21.00 (IBM Corporation, Somers, NY, USA).

Results

There was homogeneity between compared groups for all demographic and clinical characteristics ($p>0.05$). (**Table 1**)

At the baseline measurement of the VAS scale, (**Fig.1, Table 2**) the 2 groups had no statistically significant difference ($p=0.595$) but Treatment group presented statistically significant lower VAS

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TABLE 2.

Comparison of VAS between groups during the observation period

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	48,50±17,96	30,00±13,33 [b]	21,50±18,26 [b,c]	<0.005	-39,00±16,41	-61,89±32,31
Treatment	44,55±15,56	16,36±8,10 [b]	8,64±6,74 [b,d]	<0.005	-59,10±21,34	-79,34±15,66
p-value$_{bg}$	0,595	**0,010**	**0,042**		**0,026**	0,126

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

at 1st month (p=0.010) and 3rd month (p=0.042) respectively compared to Control group. Statistically significant differences in the percentage change of VAS from baseline to 1 month were detected between Control and Treatment groups [-39.0%±4.27 vs -59.10%±21.34; p=0.026]. For the Control group, VAS statistically significantly decreased from baseline measurement to 1 (p=0.002) and 3 (p<0.005) months respectively. Moreover, additional decrease was presented between 1st and 3rd month (p=0.009). For the Treatment group, VAS statistically significantly decreased from baseline measurement to 1 (p=0.001) and 3 (p<0.005) months respectively. Moreover, additional decrease presented between 1st and 3rd month (p=0.003).

The 2 groups had no statistically significant difference at baseline (p=0.373), 1st month (p=0.346) and 3rd month (p=0.805) respectively for VISA-A scale. (**Fig.2, Table 3**). No statistically significant differences in the percentage change of VISA from baseline to 1st month [8.58%±5.12 vs 9.19%±7.42; p=0.827] and 1st month [10.65%±5.52 vs 16.79%±11.93; p=0.146] were detected between Control and Treatment groups. For the Control group, VISA-A statistically significantly increased from baseline measurement to 1 (p<0.005) and 3 (p<0.005) months respectively. For the Treatment group, VISA-A statistically significantly increased from baseline measurement to 1 (p=0.003) and 3 (p=0.001) months respectively.

The 2 groups had no statistically significant difference at baseline (p=0.067), 1st month (p=0.100) and 3rd month (p=0.189) respectively for AH score. (**Fig.3, Table 4**) No statistically significant differences in the percentage change of AH from baseline to 1st month [3.92%±3.66 vs 3.87%±4.38; p=0.977] and 1st month [10.05%±6.32 vs 9.78%±5.54; p=0.918] were detected between Control and Treatment groups. For the Control group, AH statistically significantly increased from baseline measurement to 1 (p=0.002) and 3 (p=0.003) months respectively. Moreover, additional increase presented between 1st and 3rd month (p=0.055).For the Treatment group, AH statistically significantly increased from baseline measurement to 1 (p=0.033) and 3 (p<0.005) months respectively. Moreover, additional increase presented between 1st and 3rd month (p=0.014).

Discussion

Achilles tendon pathology is a very common disease with a rising incidence due to sport activities, life expectancy, environmental and dietary factors, some drug therapies and systemic disorders. Not only athletes, but also the general and elder populations suffer from post-traumatic, overuse, inflammatory or degenerative tendinopathies. It seems that the combination of anatomical (tendon quality) and functional (mechanical overuse) factors leads to the development of the Achilles pathology. (1,3)

Histological studies have evaluated the disturbed matrix metabolism in Achilles tendinopathies. An imbalanced MMP/TIMP expression and highly increased collagen expression, seems to be the

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TABLE 3.

Comparison of VISA between groups during the observation period of 3 months

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	73.00±10.77	79.00±10.83 [b]	80.60±11.88 [b]	<0.005	8.58±5.12	10.65±5.52
Treatment	68.73±10.69	74.64±9.87 [b]	79.45±9.05 [b]	<0.005	9.19±7.42	16.79±11.93
p-value$_{bg}$	0,373	0,346	0,805		0,827	0,146

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

TABLE 4.

Comparison of AH between groups during the observation period of 3 months

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	78.00±5.42	81.10±6.79 [a]	85.90±8.58 [a,c]	<0.005	3.92±3.66	10.05±6.32
Treatment	82.64±5.48	85.73±4.92 [a]	90.73±7.64 [b,c]	<0.005	3.87±4.38	9.78±5.54
p-valuebg	0,067	0,100	0,189		0,977	0,918

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

most important characteristic in tendinopathy and chronic ruptured tendons. On the other hand, in acute rupture cases, other mechanisms such as inflammation and innervation as indicated by CD45 and CD68 positive cells and the expression of inflammatory cytokines and nerve markers, seem to play a more important role. (13)

Targeting the disturbed matrix metabolism or - event better - preventing the inflammatory cascade seems to be a very attractive therapeutic approach for Achilles tendon pathologies. (**Table 5**) Recently, the use of oral supplements has been proposed to support the physiological turnover of tendon tissue, in order to prevent inflammation and degeneration. Such oral supplements, also mentioned as *nutraceuticals*, involve glucosamine and chondroitin sulphate (GlcN-CS), vitamin C (vit C), hydrolysed type 1 collagen (Col 1), L-arginine alpha-keto-glutarate (AAKG), curcumin, boswellic acid (BA), methylsulfonylmethane (MSM), and bromelain. Increasing the concentration of these compounds in tendon context may help to preserve, or even repair, the damaged tendons. As food supplements, these are not subjected to rigorous controls and licensing processes as drugs; even if some of these products received permissions to be commercialized as drugs in many countries. An amount of pre-clinical studies and randomized controlled trials (RCTs) have been conducted to assess the effectiveness of oral supplements in the management of tendinopathies. (14)

Sandqvist et al, compared Glc-Nor indomethacin

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TABLE 5.

Overview of principal nutraceutical and their properties (14)

Nutraceutical	Biological effect
Glucosamine and chondroitin sulphate (GlcN-CS)	Increase collagen synthesis, ameliorate mechanical properties, organization of collagen bundles and resistance to fatigue, helpful in the management of pain.
Vitamin C (Vit C)	Stimulate hydroxyproline synthesis of procollagen, enhance angiogenesis and maturation of Col III to Col I fibers, anti-inflammatory and antioxidant effect.
Collagen I (Col I)	Increase mechanical properties, beneficial effects on collagen-rich tissues.
L-arginine-α-keto-glutarate	Substrate of NOS, increase NO levels and collagen synthesis.
Curcumin	Neo-angiogenesis and apoptosis inhibitor, antioxidant effect, stimulate tenocytes survival.
Boswellic acid	Elastase and 5-LO activity inhibition, reduce TNFα, IL-1, IL-2, IL-4, IL- 6 e INFγ levels.
Methilsulfonilmethane (MSM)	Analgesic, anti-inflammatory and antioxidant effects, reduce MDA and GSSG levels.
Bromelain	Decrease lymphocytes rolling, anti-edema, antioxidant and immunosuppressive effects, reduce MDA levels.

* *Glc-N-CS: glucosamine and chondroitin sulphate; vit C: vitamin C; Col I: collagen type 1; Col III collagen type 3; AAKG: L-arginine-α-keto-glutarate; NOS: nitric oxide synthase; NO: nitric oxide; 5-LO: 5-lipoxygenase; TNFa: tumor necrosis factor a; IL-1/2/4/6: interleukin 1/2/4/6; IFNγ: interferon γ; MSM: methilsulfonil methane; MDA: malonyldialdehyde; GSSG: oxidized glutathione).*

administration in the management of Achilles peritendinitis showed that Glc-N had a better overall therapeutic effect on 2/3 of the patients compared to 1/3 of the patients treated with Indomethacin. Especially in those patients who endure a persistent pain, Glc-N proved to be more effective than indomethacin. Also non-responders to Indomethacin showed a little/moderate benefit from Glc-N therapy on pain level. (15)

Notarnicola et al, tested the effect of nutraceutical supplementation (L-arginine-α-cheto-glutarate, vinitrox™ (a polyphenolic compound), MSM, bromelain, type 1 collagen, and vitamin C) and extracorporeal shockwave therapy in patients with insertional Achilles tendinopathy. The authors reported that the combined treatment lead to a lower level of pain and better results at Ankle-Hindfoot scale, and Roles/Maudsley score than extracorporeal shockwave therapy alone. (9)

Arquer et al, valuated a commercial available dietary supplement containing mucopolisaccharides, type 1 collagen, and vitamin C in the management of Achilles, patellar, and common extensor tendons tendinopathies. The overall showed an improvement of symptoms and structural evolution of injured tendons. Patients treated with the oral supplementation for 90 days showed a reduction of pain and a functional improvement already after 10 days. At 90 days they demonstrated a significant improvement of functional scales: 38% for Achilles, 46% for patellar and 77% for common extensor tendons, and also a reduction of tendon thickness from 10 to 20%, depending on the anatomical region. (16)

Merolla et al, assessed the analgesic effect of Tendisulfur (GlcN-CS, vitamin C, type 1 collagen, L-arginine-α-keto-glutarate, BA, curcumin, and MSM) in patients with a full-thickness supraspinatus tendon rupture treated arthroscopically. Patients were randomly assigned to dietary supplement or placebo for 2 months. After 1 week, treatment group showed significantly lower level of VAS, night pain and pain after activity. Constant-Murley score and simple shoulder test (SST) did not differ between the 2 groups. Patients also reported a good global assessment and no adverse effects. However, after 2 weeks all scores presented no significant differences, even if pain values were lower. The authors

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concluded that Tendisulfur alleviated short and partially mid-term pain, but did not affect long term pain. To solve this limitation, they suggested to increase dosage over the first 4 weeks and by extending treatment by 1 or 2 months. (17)

In our study, the use of Tendisulfur Forte (Methylsulfonilmethane, Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin and Myrrh.) in recreational and professional athletes with acute Achilles tendinitis showed satisfactory results regarding pain and function of the tendon. The subjective VAS pain score was significantly improved in both groups from baseline to 1 month when the treatment ended. The score continue improving for both groups up to 3 months when the observation period ended. However, The VAS score was statistically significantly better for the Treatment group at 1 month and significantly better for the Treatment group at 3 months. These data suggest that Tendisulfur Forte alleviates pain rapidly at the short term period and continues offer relief even after the end of its administration. Regarding the objective outcomes, the VISA-A questionnaire score was improved in both groups at 1 and 3 months. However, the Treatment group demonstrated much better results at 3 months when compared to Control group. It is the authors' impression that extending the treatment beyond one month, we would have had statistically significant better VISA-A scores when compared to Control group. Finally, the Ankle-Hindfoot scale was significantly increased in both groups but with no differences between the groups. All above findings suggest that Tendisulfur forte contributes strongly to pain relief and mildly to function of the affected Achilles tendon. A longer period of treatment would probably offer better functional results and enhance the rehabilitation of the patient. Since such nutraceuticals are not doing any harm, patients suffering from Achilles tendinitis or tendinopathy would benefit by taking supplements such as Tendisulfur Forte during the period of rehabilitation and additionally to any other conservative or surgical intervention.

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