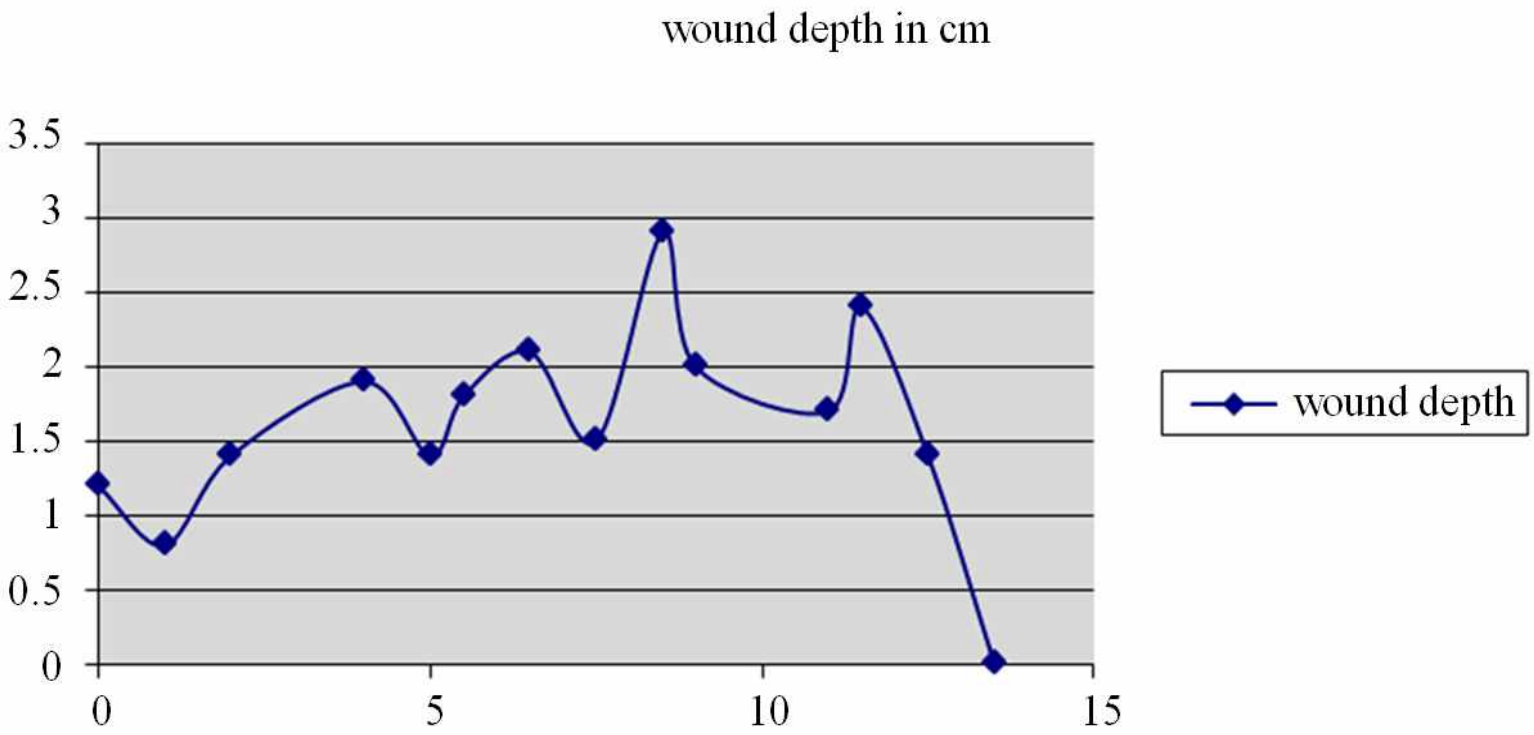
ISSN: 2158-284X Vol. 7, No. 2, February 2016

Scientific Research Publishing

International Journal of Clinical Medicine



ISSN: 2158-284X

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ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
http://www.scirp.org/journal/ijcm

International Journal of Clinical Medicine, 2016, 7, 113-175
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm

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Volume 7 Number 2 February 2016

The figure on the front cover is from the article published in International Journal of Clinical Medicine, 2016, Vol. 7, No. 2, pp. 120-126 by Jennifer D. Hastings and Sara Shapiro.

International Journal of Clinical Medicine (IJCM)

Journal Information

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International Journal of Clinical Medicine, 2016, 7, 113-119
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72012

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Impact of Low Back Pain on Quality of Life: Assessment by Patient Functionality Questionnaire and Treatment Results Using a Combination of Diclofenac plus B Vitamins or Diclofenac Monotherapy

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Received 12 November 2015; accepted 13 February 2016; published 17 February 2016

Abstract

Objective: To analyze the Patient Functionality Questionnaire (PFQ) scores of the patients treated with either Diclofenac + B vitamins (Group DB) or Diclofenac monotherapy (Group D) in order to better understand the impact of the combination of diclofenac with vitamins B_1, B_6, and B_{12} on quality of life. Research Design/Methods: We performed a post-hoc analysis of tabulated data generated during the DOLOR study (Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study), using the software GraphPad Prism 5 for Windows, v5.04. The absolute number or percentage of "True"/"False" respondents for each questionnaire item at each study visit, together with the absolute number and percentage of subjects with no change, improvement, or worsening of each PFQ item at each study visit, within and between treatment groups were arranged on contingency tables and analyzed with the Chi-squared or Fisher's Exact test. Results: At pretreatment there were no statistically significant differences between treatment groups ($p > 0.05$ for all items). At Visit 2 in both treatment groups, there were statistically significant improvements in individual question responses in each of the 12 items of the questionnaire ($p < 0.05$ for all items). At Visit 2, comparing the distribution of patients in each treatment group with "improvement", "no change", or "worsening", there was a statistically significant superiority among subjects of group DB in response to items 1, 6, 8, and 10. At Visit 3, both groups had statistically significant ($p < 0.001$) improvements in each individual item of the PFQ in relation to pre-

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How to cite this paper: Geller, M., *et al*. (2016) Impact of Low Back Pain on Quality of Life: Assessment by Patient Functionality Questionnaire and Treatment Results Using a Combination of Diclofenac plus B Vitamins or Diclofenac Monotherapy. *International Journal of Clinical Medicine*, **7**, 113-119. http://dx.doi.org/10.4236/ijcm.2016.72012

treatment values. The distribution of subjects in each treatment group presenting with "improvement", "no change", or "worsening" at Visit 3 varied significantly in favor of group DB in the responses to item 4. At Visit 4, the subjects remaining in treatment in both groups showed statistically significant improvement in PFQ responses in relation to pretreatment values ($p < 0.05$). The distribution of subjects in each treatment group presenting with "improvement" or "no change" at Visit 4 varied significantly in favor of group D in the responses to items 5, 8, and 12. Conclusion: Improvement in overall PFQ scores was observed in both treatment groups, though the specific items of the questionnaire of the subjects in group DB at Visit 2 showed greater improvement in areas related to sleep quality, mobility, ability to wash and dry, ability to walk distances, and posture comfort. These results serve to corroborate the previously published data, which indicates a benefit of combining the B vitamins with diclofenac in the treatment of patients with low back pain, yielding shorter treatment time to resolution of the lumbago in the treated patients.

Keywords

Low Back Pain, Quality Of Life, Diclofenac, Thiamine, Pyridoxine, Cyanocobalamin

1. Introduction

In a previous clinical trial, we evaluated and compared the action of the combination of diclofenac (50 mg) and vitamins B_1 (thiamine mononitrate, 50 mg), B_6 (pyridoxine hydrochloride, 50 mg), and B_{12} (cyanocobalamin, 1 mg) versus diclofenac (50 mg) monotherapy among patients presenting with acute low back pain. Among the outcome measures evaluated was the Patient Functionality Questionnaire, a 12-item questionnaire assessing the impact of low back pain on patient's quality of life in specific areas, answered by the patient at each study visit with True/False. One point was awarded for each "true" answer and the total scores of each questionnaire were reported in the previously published paper entitled "Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study" [1].

However, we chose to take a closer look at the results of the PFQ scores in each treatment group (Group DB: Diclofenac + B vitamins and Group D: Diclofenac monotherapy) and at each study visit, in order to better understand the impact of the combination of diclofenac with vitamins B_1, B_6, and B_{12} on quality of life. Study visits occurred at Visit 1—pretreatment, Visit 2—following 3 days of treatment, Visit 3—following 5 days of treatment, and Visit 4—at the end of the 7-day treatment period. The PFQ in its entirety is reproduced below; the subjects answered either "true" or "false" to each question:

Due to my back pain:

1) I do not sleep well;
2) I have to lie down more often;
3) It is difficult for me to get up from my bed or a chair;
4) I can stand only for a short while;
5) I can walk up stairs only slowly;
6) It is difficult for me to wash or dry off my whole body;
7) It is difficult for me to put on my clothes;
8) I can only walk short distances;
9) I try to avoid picking things up from the floor;
10) I have to change my posture more often;
11) I cannot carry heavy things;
12) I have to ask other people for assistance.

It is important to note that in the DOLOR study, patients presenting with significant clinical improvement at study Visits 2 and 3 were allowed to exit the study prematurely. This improvement was defined as Visual Analog Pain Scale (VAS) scores equal to or less than 20 mm on a 100 mm scale, and patient satisfaction with pain reduction. Accordingly, at Visit 2, 87 patients exited the study due to treatment success after 3 days in the DB group and 55 patients exited the study in the D group, leaving 87 patients continuing treatment in group DB and

120 patients in Group D. At Visit 3, after 5 days, a further 71 patients exited the study in group DB and 52 in group D, leaving 16 subjects continuing treatment in group DB and 68 subjects in group D.

2. Material & Methods

We performed a post-hoc analysis of previously tabulated data from the Clinical Research Forms of the DOLOR study, using the software GraphPad Prism 5 for Windows, version 5.04, Graph Pad Software, San Diego, California, USA. The absolute number or percentage of "True"/"False" respondents for each questionnaire item, at each study visit, within and between treatment groups were arranged on contingency tables and analyzed with the Chi-squared or Fisher's Exact test. Statistical significance was defined with a two-tailed p value of less than 0.05 with a confidence interval of 95%. Additionally, the absolute number and percentage of patients with no change, improvement, or worsening of each individual item of the PFQ at each study visit was determined by numerically coding "True"/"False" responses and obtaining the differences between Visits 2, 3, and 4 and pretreatment values. These results were also arranged on contingency tables and analyzed with the Chi-squared test.

3. Results

At Visit 1 (pretreatment), total mean PFQ scores were 9 and 9 in groups DB and D, respectively; there were no statistically significant differences between treatment groups in responses in any of the individual questionnaire items ($p > 0.05$ for all items). At Visit 2, mean PFQ in group DB was 4.59 while that of group D was 5.8. The responses to individual items in each group at Visits 1 and 2 can be visualized in **Figure 1(a)** and **Figure 1(b)**. The most drastic changes in PFQ responses occurred at Visit 2 in both treatment groups, with statistically significant improvements in individual question responses in each of the 12 items of the questionnaire observed in both treatment groups ($p < 0.05$ for all items).

At Visit 2, comparing the distribution of patients in each treatment group with "improvement", "no change", or "worsening", there was a statistically significant superiority among subjects of group DB in response to items 1 ($\chi^2 = 12.64$; df = 2; $p = 0.0018$); 3 ($\chi^2 = 9.54$; df = 2; $p = 0.0085$); 6 ($\chi^2 = 12.66$; df = 2; $p = 0.0018$); 8 ($\chi^2 = 6.99$; df = 2; $p = 0.03$); and 10 ($\chi^2 = 6.95$; df = 2; $p = 0.031$). None of the items responded showed statistically significant superiority in favor of group D at Visit 2 (**Figure 2**).

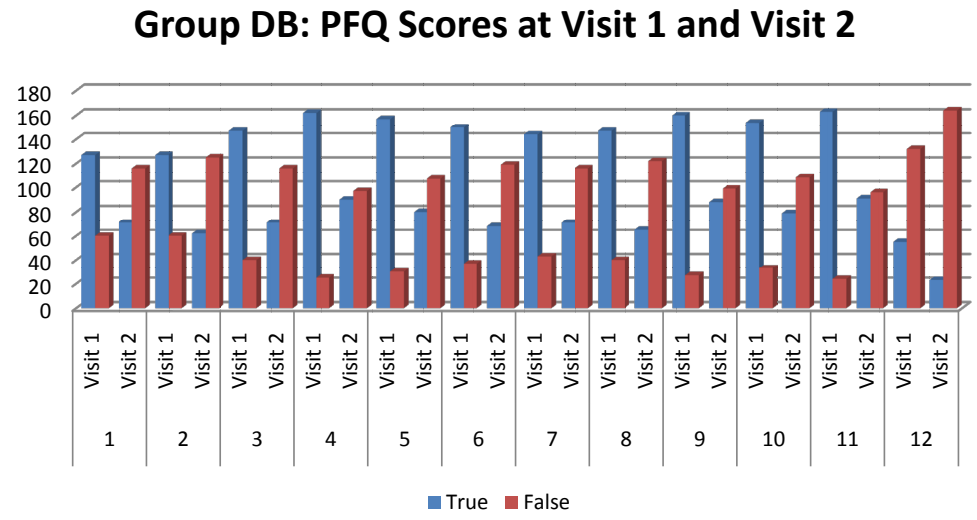
At Visit 3, among subjects of Group DB, there were statistically significant ($p < 0.001$) improvements in each individual item of the PFQ in relation to pretreatment values. The same was true among the subjects of Group D. The distribution of subjects in each treatment group presenting with "improvement", "no change", or "worsening" at Visit 3 varied significantly in favor of group DB in the responses to item 4 ($\chi^2 = 6.065$; df = 2; $p = 0.048$); no other statistically significant difference between groups was noted at Visit 3 (**Figure 3**).

At Visit 4, the subjects remaining in treatment in both groups showed statistically significant improvement in PFQ responses in relation to pretreatment values ($p < 0.05$ for all responses, in both treatment groups). There were no subjects in either treatment group presenting with "worsening" at Visit 4 in relation to pretreatment responses. The distribution of subjects in each treatment group presenting with "improvement", "no change", or "worsening" at Visit 4 varied significantly in favor of group D in the responses to items 5 ($p < 0.0001$), 8 ($p < 0.0001$) and 12 ($p = 0.042$).

4. Discussion

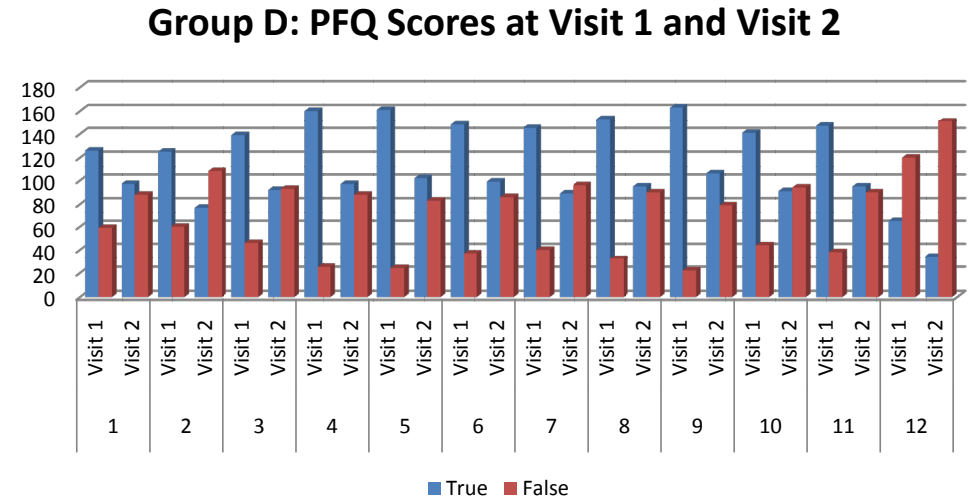
In this analysis, we investigated the individual "true"/"false" responses to the 12-item PFQ recorded during the DOLOR study, for the purpose of better understanding the impact of the addition of the B vitamins to diclofenac therapy of low back pain on the PFQ. The most prominent improvement among study participants occurred at Visit 2 among the subjects treated with the combination of diclofenac and the B vitamins, specifically in areas related to sleep quality, mobility, ability to wash and dry, ability to walk distances, and posture comfort. On the other hand, subjects treated solely with diclofenac took a longer time but showed improvements at treatment days 5 and 7 (Visits 3 and 4).

While widely used and somewhat ubiquitous, in the healthcare setting, the term quality of life is used to describe the perceived quality of an individual patient's daily life, taking into account physical, functional, emotional, and social elements. In painful conditions, evaluation of quality of life is an important part of a range of tools used in assessing treatment effectiveness of a given intervention. Quality of life is especially important



1	I do not sleep well	2	I have to lie down more often
3	It is difficult for me to get up from my bed or a chair	4	I can stand only for a short while
5	I can walk up stairs only slowly	6	It is difficult for me to wash or dry off my whole body
7	It is difficult for me to put on my clothes	8	I can only walk short distances
9	I try to avoid picking things up from the floor	10	I have to change my posture more often
11	I cannot carry heavy things	12	I have to ask other people for assistance

(a)



1	I do not sleep well	2	I have to lie down more often
3	It is difficult for me to get up from my bed or a chair	4	I can stand only for a short while
5	I can walk up stairs only slowly	6	It is difficult for me to wash or dry off my whole body
7	It is difficult for me to put on my clothes	8	I can only walk short distances
9	I try to avoid picking things up from the floor	10	I have to change my posture more often
11	I cannot carry heavy things	12	I have to ask other people for assistance

(b)

Figure 1. a): PFQ responses at Visit 1 and Visit 2 among patients in the DB treatment group; b): PFQ responses at Visit 1 and Visit 2 among patients in the D treatment group.

when discussing low back pain, both due to the prevalence of the condition and because of its influence on various areas of daily life [2]-[4].

Low back pain is an extremely common but very important health condition, affecting up to 80% of all adults at some point in time [4]. It represents the second most common reason for symptom-driven patient visits to the

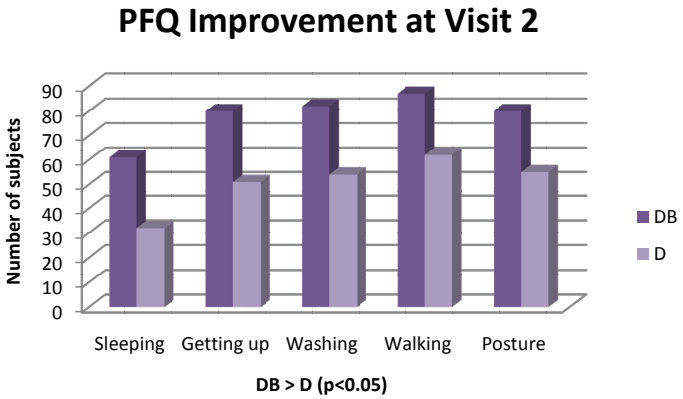
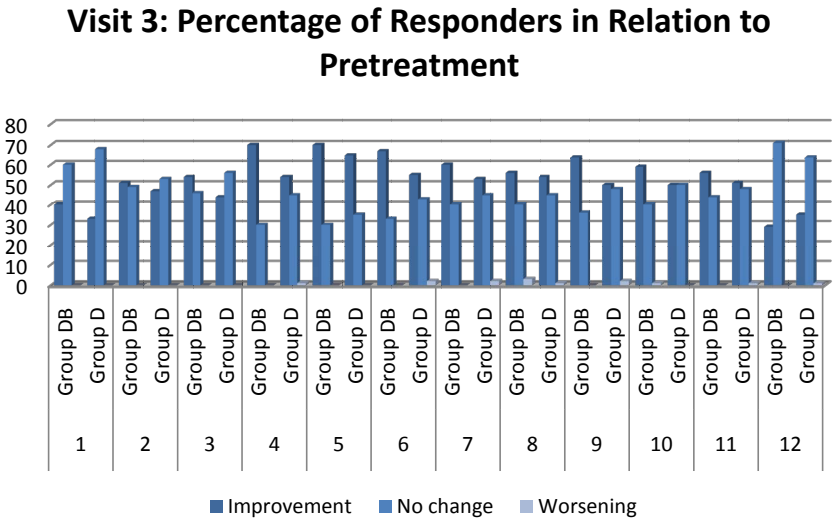


Figure 2. PFQ Responses at Visit 2 with statistically superior results in Group DB compared to Group D.



1	I do not sleep well	2	I have to lie down more often
3	It is difficult for me to get up from my bed or a chair	4	I can stand only for a short while
5	I can walk up stairs only slowly	6	It is difficult for me to wash or dry off my whole body
7	It is difficult for me to put on my clothes	8	I can only walk short distances
9	I try to avoid picking things up from the floor	10	I have to change my posture more often
11	I cannot carry heavy things	12	I have to ask other people for assistance

Figure 3. PFQ results at Visit 3 in relation to pretreatment results.

doctor's office after the common cold [5]. Low back pain carries an influence on various areas of daily life, including ability to work, exercise, and perform domestic activities. There is a considerable economic burden associated with the condition, for reasons ranging from its place as the most common cause of work-related disability and a frequent cause of missed work days, to direct costs of diagnosis and treatment [6] [7].

The correlation between sleep quality and low back pain has been investigated in studies of patients with chronic low back pain. Identified aspects of sleep negatively impacted by the presence of low back pain include: greater sleep disturbance, shorter sleep duration, reduction in sleep quality, negative impact on daytime function, increased sleep dissatisfaction and distress, and reduced ability to fall asleep [8]. The PFQ item regarding sleep was generalized, not specifying the type of impact of the low back pain on sleep in detail. Subjects simply answered with "true" or "false" to the statement "I don't sleep well". However, subjects in both treatment groups reported improvements in this category following initiation of treatment, and subjects treated with the combina-

tion of diclofenac and B vitamins showed greater improvement after 3 days of treatment as compared to subjects treated with diclofenac monotherapy. This finding may be of use to clinical practice as it indicates that reduction in pain is associated with a positive impact on other aspects of the treated subject's life.

The combination of diclofenac with vitamins B_1, B_6, and B_{12} has been reported to be beneficial in the treatment of painful conditions, including post-operative pain [9], osteoarthritis [10], and especially low back pain. Prior to the publication of the DOLOR trial, encouraging results in clinical studies of low back pain employing the combination of vitamins B_1, B_6, and B_{12} with diclofenac had been reported in the literature, especially in terms of shortened treatment time to satisfactory analgesia when compared with diclofenac monotherapy [11]-[14]. The results of the DOLOR study confirmed these findings and the results of this post-hoc analysis reinforced the benefit of adding vitamins B_1, B_6, and B_{12} to diclofenac therapy in terms of shorter treatment time to desired clinical effect.

5. Conclusion

Improvement in overall PFQ scores was observed in both treatment groups, though the specific items of the questionnaire of the subjects in group DB at Visit 2 showed greater improvement in areas related to sleep quality, mobility, ability to wash and dry, ability to walk distances, and posture comfort. These results serve to corroborate the previously published data of the DOLOR study, which indicates a benefit of combining the B vitamins with diclofenac in the treatment of patients with low back pain, yielding shorter treatment time to resolution of the lumbago in the treated patients.

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International Journal of Clinical Medicine, 2016, 7, 120-126
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72013

Healing Wounds under Mechanical Stress: A Case Example

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Received 18 January 2016; accepted 15 February 2016; published 19 February 2016

Abstract

This paper challenges the concept that the essential element in wound healing is to offload pressure. We suggest a change in approach that recognizes the integumentary system as one which, like all other body systems, adapts to the stresses put upon it. We use a clinical case example to illustrate the use of intentional mechanical stress to promote wound healing and include a review of the relevant literature. The intent of this publication is to call for a new look at clinical practice regarding wound healing and to call for future research directed at investigation of this theory.

Keywords

Wounds, Pressure Ulcer, Mechanical Stress, Electric Stimulation, Weight-Bearing

1. Introduction

Offloading pressure has been common practice in the treatment of wounds. The assumption that pressure causes wounds is nearly universal, hence the commonly used names are “pressure sore” or “pressure ulcer”. The first documented “bed sores” were found in populations who were severely debilitated, and immobile patients with acute brain injury and spinal cord injury (SCI), residing in nursing homes [1]. The wounds appeared on areas where bone was the most subcutaneous and therefore the idea that these were high points of pressure began. Response to the existence of bed sores was the mandate for turning patients on schedules to prevent buildup of pressure. More recent clinical practice guidelines address comorbid issues of malnutrition, depression, dehydration, and incontinence and consider shear as well as pressure, but pressure remains the primary focus of prevention and intervention in wounds in the SCI population [2]. With SCI the prevalence of pressure sores is high. In a recent study, 185 SCI patients who were admitted to a single facility over a six month period were reviewed, with 49.2% having at least 1 (and sometimes multiple) pressure ulcers [3]. There is also a very high incidence of

recurrence, with 20% of surgically repaired wounds recurring within 3 months of surgery [4]. The best predictor of a second pressure ulcer in the SCI population is the presence of a first pressure ulcer [5] [6].

What if we are impairing the tissue healing with off-loading?

We are aware that human tissue is adaptive to stresses put upon it. Thus, in the absence of pathology, bone will become denser with high loading or, muscles can hypertrophy in response to resistance training. Skin has self-protective measures of callous when habitual friction is encountered, and we know with certainty that female skin responds to the stressor of pregnancy with overt elongation of tissue (albeit likely influenced by hormones). Tissues respond to the physical demands of their environment by adapting to the stress. The manipulation of the physical environment can be used therapeutically to stimulate repair.

This paper reports a case where the concept that the skin must heal under the stresses that it must endure, was integral to the wound healing intervention. The second, somewhat unique, feature of this case is that the wound care interventions were provided by family and lay caregivers in the home under the instruction and monitoring by the physical therapist (PT). Houghton found that electrical stimulation (ES) could be administered safely and efficiently by lay caregivers [7] and the finding is supported by this case. Interventions included positioning, dressing changes, soft tissue mobilization, massage, progressive reseating and high volt ES (parameters and electrode placement set by PT). Institutional review board approval was received for this case review and personal permission of the individual involved was granted.

Why should ES and concomitant tissue stress and loading work? The ES is a facilitator of natural healing. The mechanism of healing with ES is not different from the normal healing process. ES attracts specific cells to the area of injury based on the polarity of the cells and their response. Current evidence shows that the specific polarity of the ES is used to draw the appropriate cells to the area of injury. Because the normal polarity of the skin without injury tends to be slightly negative and the current of injury which develops as a result of the insult, the initial treatment of electrical stimulation starts with negative (anodal) polarity.

Wolff's Law indicates that a pulsatile current creates a mechanical force that perturbs cells, causing contraction and expansion that is thought to increase collagen deposition [8]. Electrical stimulation (ES) can be considered as a mechanical stress which is a facilitator of tissue healing [9]. The mechanical perturbation changes in membrane permeability, ion movement across the cell membrane, and increased blood flow and shear force; all seem to contribute to increasing healing. Thus the addition of ES to the normal stress of loading appears to increase not only the rate of repair but the strength of the tissue that is healed.

The motivation for writing this case report is the fact that it has now been 7-year post healing and the individual has had no recurrent breakdown of this wound, nor breakdown of the surrounding tissue even in the presence of multiple challenges to health including 2 lower extremity and one upper extremity fracture which resulted in modified seated positions.

2. Case Report

At the time of wound care intervention the individual presented in this case report was a 25-year-old woman with C5 AIS A tetraplegia of 6 years with history of recurrent grade II right ischial pressure ulcer. Concomitant with systemic medical decline (aplastic anemia) the wound declared and progressed to grade IV. Strict bed rest was not possible during early phase of wound care due to need for medical appointments; bed rest was also lifted for attendance at church and for planned social activities and holiday functions. No more than 10 days of bed rest in sequence was ever experienced. Prior to PT involvement, wound care consisted of enzymatic debridement and dressing changes supervised by an outpatient wound clinic. PT promoted healing with intentional tissues stresses. Initially the tissue was stressed with high volt ES, then massage and soft tissue mobilization surrounding wound, then with daily positioning with hip and knees at 90 degrees while in supine, and finally with progressive sitting. Intentional mechanical stress was done for facilitation of healing.

Intervention

A home visiting PT did wound assessments and established wound care interventions and instructed the patient's mother in how to administer all wound care interventions. At the highest frequency PT visited daily for up to three days in a row (initially and again at week six) but for most of the duration of treatment PT visits were once a week or every other week.

Figure 1 shows the key components and timing of intervention. ES was initially done with direct technique,

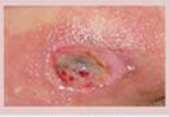
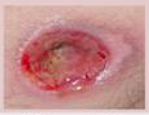
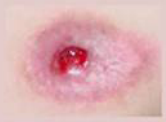
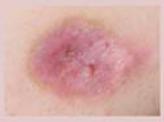
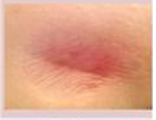
Time	ES initiates	P 6 wks	P 12 wks	P 14 wks	P 16 wks	Follow up
WOUND						
TREATMENT	Negative Polarity 100pps 50v Active in wound bed Dispersive Proximal BID 30”	Positive polarity Added **Massage** To healed skin **Tissue mobilization** P 8 Wk added **Supine 90/90 LE** Positioning 60’ daily	Indirect E Stim With saline wick BID 60 minutes Stim was after sitting session	Indirect E Stim BID 30 minutes Positive polarity	Only one E stim session between sitting 30 minutes Positive polarity	monitoring **No break down** **For 7 years** **post healing**
SITTING	Up in chair for medical appointement 4-6 hours at time	Up in chair for Church and Holiday social 2-4 hours 10 days bedrest In this 6 wks	**Intentional Loading** **two** sessions of sitting for **30 minutes** with minimum of 4 hours down time between.	continued	two @ 50 min with PR @ 30 min Progress by 10 min After 4 sessions. Progress by 15 min after 4 sessions. Progress by 30 min after reaching 2 hours. Down time=twice up time DC ad lib at 18 wks	Ad LIB 14 plus hours

Figure 1. Key aspects of intervention. pps = pulse per second, v = volts, BID = twice a day, p = post, wk (s) = week (s), LE = lower extremity, min = minutes, *Ad LIB* = without restriction.

where the active electrode was in the wound bed with saline soaked gauze as conduit. The polarity of the treating electrode was initially negative, and then changed to positive once wound appeared clean and without odor (after 4 weeks), polarity was changed back to negative for 3 days during week 7 due to a period of wound stagnation, and then held at positive for the duration of treatment. When the wound became very small at the surface but maintained significant depth the technique was changed to indirect ES (electrodes then placed peri-wound) with a saline wick. Indirect ES is when the active electrode is no longer placed in the wound bed. The dispersive is still proximal but two active electrodes are place in the wound periphery, so that the current continues to run through the wound. A saline wick is a saline soaked ¼ inch cloth dressing lightly packed into the deep wound channel. Additionally the therapist added intentional loading to the intervention plan. Two sessions of sitting for 30 minutes with minimum of 4 hours off loading in bed rest between the sitting sessions were scheduled daily. This continued for 4 weeks until wound closure. The family kept a journal and was highly compliant. Most episodes of sitting were +/− 3 minutes of the prescribed thirty minutes and there was one episode of only 3.5 hours off loading in the last week. The rationale for the intentional loading was that the wound depth was increasing due to wound contraction and therapist theorized that compression would avoid tract formation. After wound was completely closed (at 16 weeks after initiating ES) the ES treatment continued and seating was progressed intentionally with prescribed time for loading and off-loading with ES between sitting sessions. Progressing to completely *ad lib* sitting occurred over 2.5 weeks and ES continued during this time. The duration of therapy supervised wound care was 18 weeks.

3. Results

Figure 2 and **Figure 3** show the healing pattern of the wound as measured in centimeters. Volume is calculated by the measured greatest length times the perpendicular width times the depth.

Full closure was achieved and *ad lib* sitting for up to 14 hours. More significantly this individual has been followed by one author for seven years and there has not been any recurrence of this wound nor breakdown of adjacent tissues.

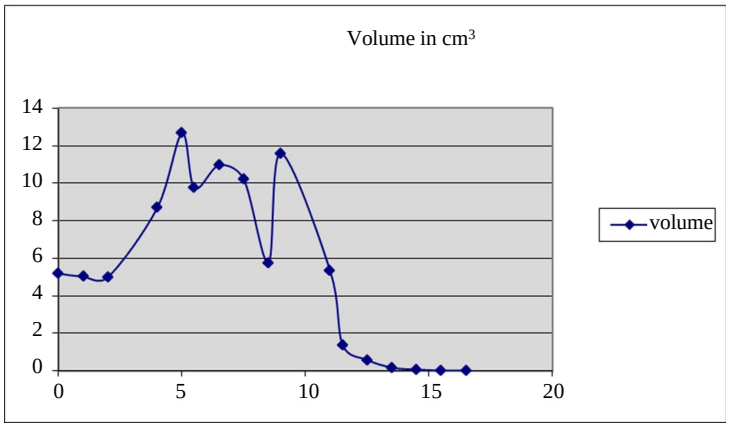


Figure 2. Wound volume over time in weeks.

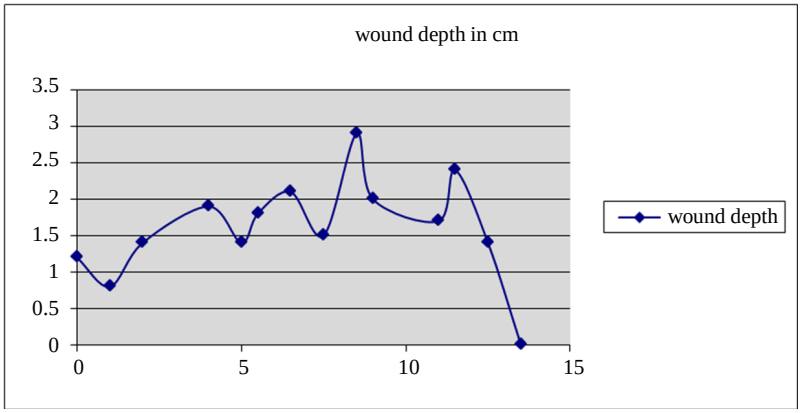


Figure 3. Wound depth over time in weeks.

4. Discussion

There is evidence that prolonged unloading can be detrimental. Reperfusion following unloading causes further buildup of damage [10]. There is a rise in damage even after the insult is removed [11]. Pietramaggiori *et al*. showed that both 4 days of continuous and similar cyclic loading showed a fourfold increase in cellular proliferation in the epidermis and a 2.8 fold increase in circulation [12].

The use of high volt ES to support wound healing has been common practice since 1960s [13]. Evidence supports this practice and the CMS approved payment for ES for wound care in 2002 [14]. Electric currents are designed to mimic the "current of injury". There is a natural and normal current which flows because of the gradient of ion concentration in the cells, each with a different electrical potential. A current of injury is generated when an injured part of a nerve, muscle, or other excitable tissue is injured. The evidence from preclinical studies [15] and clinical studies [16] indicates that healthy skin is characterized by a slightly negative current, while injured tissue is more commonly associated with a positive current. The body generates an electrical potential across these tissues. This potential is active in wound healing by promoting cellular migration. A host of events are triggered by electrical stimulation, which includes angiogenesis, granulation and re-epithelialization. Thus, the use of electrical stimulation is intended to facilitate the normal process of cell migration necessary to move the wound from the inflammatory phase forward and into the proliferation phase. Nonetheless, there is still controversy in the exact electrode configuration, polarity and even waveform offering the best outcome.

Wounds appear to require an extended period of time to heal because the body's endogenous system has been disrupted. There are quite a number of studies- both human and animal- which suggest that the ES may assist in the inflammatory phase by inhibiting inflammation and the growth of micro-organisms [17]. Electrical stimulation is believed to promote tissue healing by attracting appropriate cells to the area of the wound. At that point, the electrical stimulation facilitates altered cell membrane permeability, and an ultimate modification of endo-

genous electrical potential within the tissue. Specific cells can be attracted to the injured healing area by the addition of this electrical charge, because the cells carry a charge. Cell types such as lymphocytes, leukocytes, macrophages, and fibroblasts as well as activated neutrophils, are present when a wound is inflamed, and attracted to the negative pole [13] [16]. A number of in vivo studies have shown increases in the synthesis of adenosine triphosphate (ATP) and proteins as well [15].

In the second phase of wound healing, the proliferation of collagen production facilitates the granulation process. The application of an electric current stimulates an increase in production of DNA which is used for fibroblast synthesis [18]. The dermis, made up of primarily fibroblasts, is influenced by the electrical current as well. Studies show that fibroblasts migrate toward the anode.In wounds that were actively created and then subjected to electric stimulation, the fibroblasts actively migrated from the wound edges and closed the wound entirely in 24 hours [19] [20]. It appears that the granulation phase is promoted through an increase in collagen production and fibroplasia [21]. With the last phase of wound healing, epithelialization is assisted by electrical stimulation as well. The keratinocytes are in the majority within the cellular population. Keratinocytes are involved in re-epithelialization and migrate toward the cathode.

Why does it matter? Recurrent rates for pressure ulcers are astoundingly high. If tissue can not only be healed with an inexpensive home based intervention but healed BETTER with a stronger and more durable tissue which withstands the usual daily threats, this is a far superior outcome. The costs of this intervention were very low. At the highest frequency the PT provided daily visits, but usually once a week or every other week. There were a total of 16.5 PT hours over 27 visits. The actual interventions were being provided by the trained caregiver using parameters established by the PT. The total cost for PT services: $2,435 (this service was provided by a direct access cash based private practice under referral from a consulting MD). Charges to the family were for PT travel as well as time in home for PT services. Tele consultation via phone or email was not billed.

Typical costs for surgical repair of pressure ulcers are significantly higher. A British study found the direct medical cost of surgically treating one pressure ulcer to be €20,957 [22]. In a Canadian study authors found an average monthly cost of $4745 (CAD) with a median duration of 25 months [23] and for community acquired pressure ulcers a US study determined the cost was $124,327 with an average of 4 hospital re-admissions [24]. There are more considerations than just the cost of the surgical intervention. Surgery requires hospitalization, and for the spinal cord injured individual who is already immune compromised just being in a hospital environment is a risk. There is research to suggest that there is an increasing risk of iatrogenic infections for populations who are immunosuppressed [25]. Whereas, if the individual can stay at home where they have good social support and physical caregiving the potential for better overall health is higher. The improved psychosocial environment of the home can only be supportive to healing. Moreover, if the individual can maintain their social roles, continuing to work or be a student, this improves overall quality of life.

At a minimum, healed tissue needs to tolerate the normal daily motions of the body. It is the clinical experience of both authors to see surgical skin repair (flap procedures) dehisce, or otherwise fail. In many cases the failure will occur upon re-sitting. If you heal skin of seated surfaces in a position of hip extension it makes intuitive sense that the length of the healed tissue will not be sufficient for hip flexion. This consideration should be taken into three dimensions. The usual sliding, compression and rotational forces experienced by the skin will want to be tolerated.

The evidence supporting the approach used in this case is limited by the lack of high-quality studies, the lack of isolated electrical stimulation intervention groups, and the absence of clinical studies that included wound closure under intentional mechanical or loading stress. Further limitations of research in this area are the heterogeneity in study methodologies small sample size, limited follow up data collection and lack of follow through until complete wound closure.

5. Conclusion

Overload is a generative stimulus for every system in the human body. Bones calcify with weight bearing and muscles hypertrophy under resistance load. The cardiopulmonary system responds to overload. The nervous system is now understood to “learn” or reorganize with repetitive problem solving (stress). It should logically hold that skin will respond in the same manner to mechanical stress. We suggest if we intentionally stress the healing tissue and then supplement the healing with a facilitator (ES), this has the theoretical potential to create a more rapid and successful outcome. Research is needed to investigate this theory in larger samples of men and women with SCI.

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International Journal of Clinical Medicine, 2016, 7, 127-132
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72014

Purpose, Composition and Function of the Research Ethical Committee in the Sarah Rehabilitation's Hospital

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Received 12 January 2016; accepted 17 February 2016; published 22 February 2016

Abstract

Introduction: The Research Ethical Committee (REC) is responsible for the ethical evaluation of the projects presented by the scientific community to inform and train the members and researchers. Objective: To describe the purpose, composition and function of the REC of the Association of Social Pioneers (APS) located in the Sarah Rehabilitation's Hospital (Brasilia, Brazil). Methodology: Descriptive analysis of the REC/APS based on 2013's collected data was done. Results: The REC/APS is an independent collegiate body, which was established in 1998 in accordance with Brazilian regulation. The main objective is promoting the application of ethical principles and human rights in research involving humans. The REC was composed by chairperson and a substitute; secretary, fourteen regular members and five substitutes. We analyzed 164 projects submitted. The minimum time to a committee member who came up with the first opinion has been estimated as 14 days and the insurance of the consolidation occurred in 30 days. We approved 64 projects, of which 25 had pendencies in the first analysis, one project failed and 99 were excluded. The main problems were related to the writing of informed consent and the multicenter projects that did not include aspects such as costs, schedule and methodological limitations. We observed that the researcher could provide assistance. We considered the important role of the REC/APS to ensure trust between researchers and participants in the research. Conclusion: Despite the purpose, composition and function of the APS research ethical committee, there were encountered many obstacles in its formation, considering monitoring the progress of the research, national normative, international researches and others. The ethical committee does a vital public service with the variety of the specialized views on the meeting. We need to strike a balance and we must weigh up risks and benefits related to knowledge, in its essence, to research's participant and its relevant social participation.

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How to cite this paper: Batista, K.T. and Seidl, E.M.F. (2016) Purpose, Composition and Function of the Research Ethical Committee in the Sarah Rehabilitation's Hospital. *International Journal of Clinical Medicine*, **7**, 127-132.
http://dx.doi.org/10.4236/ijcm.2016.72014

Keywords

Ethics Review, Research Ethical Committee, Bioethics and Research

1. Introduction

Patients who participate in research usually give an extraordinary degree of trust in researchers, institutions in which research is conducted, and the research firm as a whole, sometimes the research overlaps the best interests of patients.

Unfortunately, medical research has not always been grounded in the core ethical standards. Our modern ethical standards now have their basis in the Nuremberg Code [1]. These statements were in many documents, including the Declaration of Helsinki [2], Universal Declaration on Bioethics and Human Rights [3], Brazilian Constitution 1988 [4] and other national resolutions. In Brazil, the Research Ethic System is regulated by National Health Council [5]. We have different levels of government—local level (intern regiment), regional level and national level. In 2013, we had six hundred and eighty-four Research Ethical Committees (REC) distributed all over the country. The link used for protocol submission is www.aplicação.saude.gov.br/plataformabrasil/login.jsf [6].

The Research Ethic Committee is part of the Association of Social Pioneers (APS) Institutional Review Board, located in Brasilia, Brazil Federal Capital, designated to protect the rights, safety, dignity and well-being of human subjects and also educate researchers [7].

Association of Social Pioneers (APS) is an interdisciplinary, independent and public Research Ethic Committee in the Sarah Rehabilitation's Hospital. It was established in 1998. It receives protocols of ten public rehabilitation's hospitals in Brazil. These are the APS named Sarah Hospital in nine Brazilian regions. The primary function of the APS/REC is to safeguard human subjects by training researchers in research ethics and the best practices and by reviewing research proposals. The criteria for evaluation are documentation required by the National Regulamentation (466/12 Normative [8]), including cost, schedule, sample, methodology, interest, innovation, relevance and ethics.

Sarah Rehabilitation's Hospital (autonomous social service entity of private law and non-profit) is the name of the network of nine Brazilian hospitals, designed to care for victims of multiple trauma and locomotor problems, aiming to their rehabilitation. It is maintained by the Federal Government, although its management is up to the Association of Social Pioneers.

We are describing the experience and the purpose, composition and function of the REC of the Association of Social Pioneers (APS) based on 2013's data. The study was conducted with 2013's data to analyze the course of resolving the change of the 466/12 Brazilian Ethical Resolution, year of the creation of Resolution 466/12, and know the impact that changes in rules caused to the REC/APS.

2. Methodology

The exploratory, descriptive, retrospective study analyzed the records of the REC and of all the 164 research protocols submitted for appreciation from 1st January to 31st December, 2013. We searched the database of the REC/APS in Brazil Platform. It is an electronic system set up by the Federal Government in 2010 to systematize the receipt of research projects involving human beings Ethics Committees throughout the country.

We analyzed all studies that were registered on REC/APS on January up to December 2013. The registered records of these studies were downloaded Research Ethical Committee date in Brazil Platform and analyzed in Microsoft Excel 2007. We did descriptive and frequency analysis of the REC members, studies type and pendencies of the REC/APS based on 2013's data and we described the purpose composition and function.

3. Results

In a total of 164 protocols examined on 2013's data, we received 99 incomplete protocols, rejected and 65 were protocols with complete documentation for evaluation according to rules.

The Ethical Committee is composed by chairperson and a substitute, secretary, fourteen regular members and

five substitutes. The term of the mandate is three years. It is interdisciplinary team composed by seven masters, seven PhD and two community members. Also, it is composed by an auxiliary Scientific Committee. Our main members (60%) are doctors and nurses; the others are psychologist, statistic, physiotherapist, professor and sociologist.

In 2013, we had ten meetings, taken monthly, four hours per meeting, where six to eight protocols were studied. The protocols source was Sarah Network. We needed at least nine members to formalize a meeting. The first opinion is due fourteen days, while the last one is due thirty days. We received 164 protocols, 99 rejected due to incomplete documentation, 65 accepted and chosen to be presented on meetings. The Committee members got contact with the protocols before the meetings.

In the meeting, one member introduces each study, and then others give their views. Discussions are well-informed and decisions available to the committee are favorable ethical opinion, favorable with conditions and unfavorable ethical condition. Studies were revised basing on International and National Regulations. The research gathered fifteen thousand and four hundred participants and not a single adverse effect have been reported. The researchers are MSc and PhD Students, clinicians, surgeons and health professionals, including academic researchers (**Table 1**).

It is noteworthy that to evaluate clinical research protocols following documents are required by 466/12 normative: the research project in its completeness, authorization partakers of research (there is a model that permits must be on letterhead of the institution, signed by a responsible institutional member or signature and stamp of the institution responsible), voluntary participation and informed consent, data collection forms, information about the trial, procedures, duration, questionnaires, interviews scripts, cover document generated by Brazil Platform signed by the main researcher, detailed budget, schedule, Sponsor Declaration of responsibility, declaration concerning the purpose of the data collected. In case of use of placebo and washout, justification of non-maleficence was send. Statement on how the biological material and data, and information collected solely for the purposes specified in the protocol for the study concerned all of which will handle the material and Resolution 251/97 on complementary rules for research with new pharmaceutical products, medicines, vaccines and diagnostic tests [8].

The evaluated research projects were mainly focused on qualitative research (22%), case report (18%), case serie (18%), epidemiologic studies (18%), medical genetics (8%), trial (8%), case control (8%) and others. The protocols status has been approved with an accuracy of 61% on our first evaluation. The main obstacles regard to informed consent and methodologic aspects (67%) (**Figure 1**). Moreover, the process of ethical review in REC/APS did not hold back the large majority of the research. Only one research protocol was refused due to improper use of placebo. The final decision about the protocol should be communicated in Platform Brazil and

Table 1. Research ethic committee APS characteristics and functioning.

Aspects analysed	Results
Meetings/year	10 (montlhy/4 hour/meeting)
Protocols/meeting	6 - 8 protocols
Protocol source	Sarah Hospital
Minimum members at meeting	9
Time to first opinion	14 - 30 days
Time to final opinion	30 days
Protocols evaluated	164
Protocols approved	64
Complete protocols	65
Incomplete protocols	99
Research participants*	15.400
Report of adverse effects	0

*Research participant-individual, an informed and voluntarily, or under the clarification and authorization of his responsible legal agree to be searched.

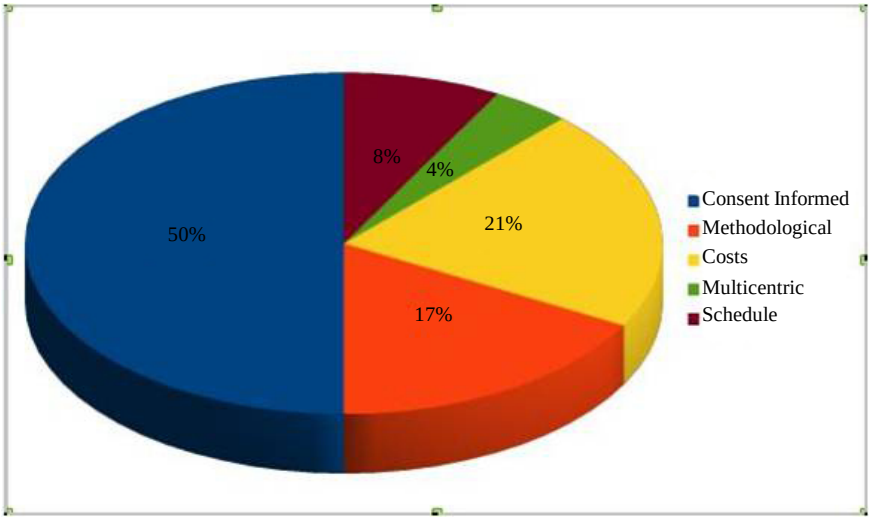

Figure 1. Pendencies distribution of research protocols of REC/APS.

include title, protocol number, researcher, date and approval or refusal decision or recommendations and suggestions for revision and procedure for having the application re-reviewed and signature of the chairperson.

The ethical standard was produced for the Bioethics, National and international normative, law, ethical and, philosophical principles of the justice, autonomy, beneficence and non-maleficence.

4. Discussion

This study aimed knowing the experience of the Research Ethical Committee (REC) of the Association of Social Pioneers activities in 2013 [1]. The study was conducted with 2013's data to scrutinize the course of resolving the change of the 466/12 Brazilian Ethical Resolution, which took place the year before the study, and know the impact that applied changes in rules caused to the REC/APS. It was observed as the negative impact of the new resolution 466/12 the amount of 99 incomplete protocols (61.5%). At 2013, when the new Brazilian Resolution (the 466/12 Resolution's) took effect, we observed that 38.5% of all projects submitted had the complete and correct documentation.

The year of 2013 was important because it was right after the new resolution, the 466/2012 and the recent electronic system (set up by the Federal Government in 2010), Brazil Platform. However, the database Brazil Platform allowed the possibility of analysis of all data and research protocols from the ethical review system in Brazilian research, but the resolution presented snags of researchers, 61.5% the protocols did not include the rules of demands.

Furthermore, Porto [9] and collaborators identified the relaxation of control standards research ethics, such as the abolition of the control of the ethical review system on international clinical trials; removal of the need for the adoption of international research by the country of origin; withdrawal of compulsive suspicion of risk by test suspension or injury; use not provided by the data or biological material protocol and remuneration of clinical trials phase of research participants 1 and bioequivalence research.

For trials protocols evaluation, in Brazil we used the Resolution 466/12 on guidelines and rules for research involving human participants that had 28 criteria for approval and Resolution 251/97 on complementary rules for research with new pharmaceutical products, medicines, vaccines and diagnostic tests. In other countries, they adopted a form of ICH-GCP (E6) that had four principles for approval [10], followed by ICH-GCP (E6) and Ministry of Health laws or guidance. Ethical Committee provides a vital independent and public service with the variety of views exposed on the meetings. We need to strike a balance and we must weigh up risks and benefits related to knowledge and its essence to participants. The review should be appropriate to the purpose of the research and all protocol is considered ethical only if its consent is informed.

Although the informed consent process is recognized as an essential requirement in research, actually it is still far from fully realizing the principle of autonomy and respect for persons [11] [12]. In this study, there were failures in the consent informed on 50% of the protocols.

Establishing bioethics committees may be a first step for States to create platforms and bodies for ethical debate, analysis and policy development. All research involving human participants should be reviewed by a competent and independent institutional research and ethics committee. We presented the interdisciplinary composition of the APS/REC and its function. Some variation of the point of view is acceptable to inquire the research protocols. However, it's not our job to assess the monetary value of the research, considering that it might be a problem if participants' time and goodwill are misused or vulnerable. For example, how to control the use or misuse of newly acquired biological and medical knowledge and biotechnologies?

According to the National Health Council [5], the Research Ethics Committee (REC) is a volunteer, interdisciplinary and independent collegiate which must exist in institutions conduct research involving humans in Brazil, created to defend interests of the research subjects in their integrity and dignity and to contribute to the development of research within ethical standards. The REC mission is to safeguard the rights and dignity of research subjects. Moreover, REC contributes to the quality of research and for studying the role of discussion in institutional development and social development of the community. It contributes to the enhancement of the researcher who receives recognition that its proposal is ethically appropriate.

At the present time, we need to develop a critical frame of mind and a system of values that prepare us to judge each new research. Here, it is also important to point out that the committee members have been elected to establish the Association of Social Pioneers (APS), located in the Sarah Rehabilitation's Hospital Committee. Despite the implementation of Resolution 466/12 and international regulatory standards, there still are some ethical issues, especially in regards of the methodologic aspects, use of placebo, informed consent and the participation of people under vulnerability in developing countries. We need continuous training and update members. However, the distance of contact between Regional Committees and National Commission of Ethics in Research is a difficulty faced by the REC/APS. Other problems presented are related to Brazil-based data platform and difficulty in monitoring the progress of research. Furthermore, Research Ethical Committees are important on refining research participant protection, adding legitimacy to the research, improving the quality of an intervention being investigated and it can even help mitigate harm [13].

5. Conclusions

This article assesses the purpose, composition and functions of the REC/APS and identifies incomplete protocols and pending issues among research protocols presented at 2013. Attention to the normative 466/12 and researcher training could make a difference. However, it is also important to consider the participation of committee members in the preparation of resolutions. Moreover, it is worth mentioning the importance of training committee members in bioethics, appropriate expertise and representation, qualified chair, members, separation of conflict interests from ethics review function, and knowing what the researchers and committee members think about the normative.

Despite the purpose, composition and function of the APS Research Ethical Committee, many hurdles were encountered in its formation, considering monitoring the progress of the research, with the 466/12, national and international ethical and others issues.

The ethical committee does a vital public service with the variety of the specialized views on the meeting. We need to strike a balance and we must weigh up risks and benefits related to knowledge, in its essence, to research's participant and its relevant social participation.

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International Journal of Clinical Medicine, 2016, 7, 133-143
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72015

Membrane Lipid Replacement: Clinical Studies Using a Natural Medicine Approach to Restoring Membrane Function and Improving Health

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Received 5 January 2016; accepted 17 February 2016; published 22 February 2016

Abstract

Functional oral supplements containing cell membrane glycerolphospholipids and antioxidants have been used to safely replace damaged membrane lipids that accumulate during aging and in various clinical conditions. This approach differs from other dietary and intravenous interventions in the composition of phospholipids and the presence of fructooligosaccharides that protect the phospholipids against oxidation and bile and enzymatic damage. Various chronic clinical conditions are characterized by membrane phospholipid oxidative damage, resulting in loss of cellular function. Recent clinical trials have shown the benefits of Membrane Lipid Replacement in replenishing damaged membrane lipids and restoring mitochondrial function, resulting in reductions in fatigue in aged subjects and patients with a variety of clinical diagnoses. Recent *in vitro* experiments with nonphysiological concentrations of phospholipids did not result in enhancement of mitochondrial electron transport enzyme activities. This can be explained by the use of the wrong phospholipid fatty acids, over-dilution of membrane constituents and mitochondrial swelling. A similar phenomenon was seen when human sperm were incubated *in vitro* with high concentrations of glycerolphospholipids and their motility was assessed. Only lower, more physiological concentrations of glycerolphospholipids stimulated sperm motility. Additional studies are needed to determine the functional effects of Membrane Lipid Replacement on other cellular membranes, such as the plasma membrane and other intracellular membranes of various cells and tissues.

Keywords

Membrane Phospholipids, Lipid Oxidation, Mitochondrial Function, Fatigue, Clinical Trials, Membrane Lipid Replacement

How to cite this paper: Nicolson, G.L. (2016) Membrane Lipid Replacement: Clinical Studies Using a Natural Medicine Approach to Restoring Membrane Function and Improving Health. *International Journal of Clinical Medicine*, **7**, 133-143.
http://dx.doi.org/10.4236/ijcm.2016.72015

1. Introduction

Oral supplementation of membrane glycerolphospholipids provides patients with important cellular constituents that are damaged during chronic illnesses and aging [1]-[3]. These membrane phospholipids fulfill at least four major requirements for cell and tissue health [2] [3]. They are used as: 1) the matrix for all cellular membranes, enabling separation of enzymatic and chemical reactions into discrete cellular compartments; 2) an important energy storage reservoir; 3) bioactive molecules in certain signal transduction and molecular recognition pathways; and 4) important functional molecules that undergo interactions with other cellular constituents, such as proteins and glycoproteins that provide enzymatic function [3] [4].

Dietary sources often cannot provide enough essential lipids for maintenance of health, and in particular, for individuals with chronic illnesses [2] [3] [5]. Therefore, membrane glycerolphospholipids [1] [3] [6] or certain bioactive lipids [2] [5] at high concentrations have been used as supporting treatments or for health maintenance. Essential lipids, such as glycerolphospholipids, and fatty acids, are efficiently absorbed in the upper small intestine, almost all within hours of ingestion [3] [7] [8]. From there glycerolphospholipids and fatty acids are transported to every cell in a human to insure a source for the natural replacement of damaged membrane lipid components [3] [4] [9].

During aging (and in most if not all acute and chronic illnesses) cellular membranes are damaged by free radicals [3] [9]-[11]. When the production of reactive oxygen species (ROS), such as superoxide anion radicals, hydroxyl radicals and hydrogen peroxide, and reactive nitrogen species (RNS), such as peroxynitrite anion, are in excess of a cell's ability to neutralize these free radicals using natural antioxidants, damage to cellular structures occurs [3] [9]-[11]. Membrane lipids are especially sensitive to oxidative damage by ROS and RNS [3] [10] [11]. Thus oral supplementation of membrane lipids as membrane lipid replacement (MLR) molecules for cellular membranes and other structures, or as natural or synthetic bioactive lipids that can act as effector molecules in signaling and other cellular processes, can be used to restore cellular homostatasis [1] [3] [5] [9].

There is a rich history of using various lipid supplements to promote health. Readers are directed to various contributions, mainly reviews of the literature, for historical perspective [1]-[3] [5] [6] [9] [10].

2. No Safety Issues

There are no known safety issues with MLR. High doses of membrane phospholipids have been given to animals and humans with no apparent acute or chronic toxicity [3] [8] [12]. In phase I/II clinical trials on patients with cardiovascular disease, phosphatidylinositol was given at doses over 5 g per day with only positive effects. This membrane phospholipid was shown to increase plasma high-density lipoprotein cholesterol and apolipoprotein A1 levels and reduce triglyceride levels without any evidence of toxicity [13]. Long-term administration of relatively high oral doses of replacement membrane lipids has improved cardiovascular blood markers. For example, older subjects (average age = 60.7) received over 2 g per day oral glycerolphospholipids (NTFactor®, **Table 1**) for over 6 months and showed no evidence of adverse effects of the phospholipids. In fact, their cardiovascular blood marker levels, such as homocysteine, improved significantly during the trial ($p < 0.001$) [14]. Reviews of clinical studies on the use of MLR in the long-term treatment of cardiovascular and other diseases concluded that there was no evidence of any toxicity from glycerolphospholipids [3] [15].

The U.S. Federal Drug Administration (FDA) has classified membrane phospholipids used in MLR in the category of "Generally Recognized as Safe" (GRAS) [16].

3. Membrane Lipid Replacement

MLR supplements for membrane repair and replacement of damaged lipids have been developed that contain mixtures of the common membrane glycerolphospholipids, along with unsaturated fatty acids and other lipid components [2] [3] [6]. Of the commercially available oral MLR supplements, most are lecithin preparations that lack protection from oxidation and enzymatic destruction. There are oral MLR supplements, such as NTFactor® and NTFactor Lipids® (**Table 1**) that fulfill the requirements for convenience, efficacy, safety and protection against oxidation and degradation [1] [3]. They contain antioxidants and fructooligosaccharides to protect the glycerolphospholipids from oxidation, high or low temperature, and bile and enzymatic destruction [17]. These supplements contain suggested daily amounts of 1.8 to over 4 g of glycerolphospholipids with mostly unsaturated fatty acids (**Table 1**). Some NTFactor-containing supplements also contain probiotic bacteria, various

Table 1. Lipid composition of NTFactor®[a].

Name	Abbreviation	Percent [w/w]
Glycerolphospholipids		
Phosphatidylcholine	PC	31.62
Phosphatidylinositol	PI	24.87
Phosphatidylethanolamine	PE	18.86
Phosphatidic acid	PA	13.88
Digalactosyldiacylglycerol	DGDG	5.88
Phosphatidylglycerol	PG	2.37
Lysophosphatidylcholine	LPC	0.98
Lysophosphatidyethanolamine	LPE	0.70
Phosphatidylserine	PS	0.48
Monoglactosyldiacylglycerol	MGDG	0.31
Fatty Acids		
Linoleic acid	18:2Δ9,12 (n − 6)	58.41
Palmitic acid	16:0	19.39
Oleic acid	18:1Δ9 (n − 9)	9.68
Linolenic acid	18:3Δ9,12,15 (n − 3)	5.87
Stearic acid	18:0	3.90

[a]NTFactor® is a patented product produced by Nutritional Therapeutics, Inc. of Hauppuage, NY.

vitamins and minerals and other ingredients. For example, a specific supplement for mitochondrial support, ATP Fuel®, contains 2 g per serving or 4 g per day of NTFactor® and also NADH, Coenzyme-Q10, vitamin E, alpha-ketoglutaric acid, L-carnitine, and other ingredients [18]. Other oral MLR products, such as those containing purified phosphatidylserine (PS), are also available [19].

An intravenous-delivered MLR mixture of glycerolphospholipids ("Essential phospholipids") can deliver high phospholipid concentrations without the need for inhibiting intestinal disruption [6]. However, this product is still susceptible to enzymatic and oxidative damage, and daily intravenous delivery comes with some risk for adverse events, such as infection, blood vessel damage, thrombosis, pruritus, dyspnoea, urticaria, among other potential problems.

4. Clinical Uses of Membrane Lipid Replacement—Fatigue

Until recently MLR was used primarily to treat fatigue [1] [3] [20]. Fatigue is the most common complaint of patients seeking general medical care [21] [22], and it is associated with most if not all chronic medical conditions as well as natural aging [21]. Fatigue is considered a complex, multidimensional sensation that is not well understood but is perceived to be a loss of overall energy, mental or physical tiredness, a feeling of exhaustion or diminished endurance, and an inability to perform even simple tasks without exertion [21]-[23]. At the cellular level moderate to severe fatigue has been related to loss of mitochondrial function and diminished production or leakage of ATP from mitochondria [20] [23] [24].

Fatigue develops during aging and chronic diseases due to a variety of additive and synergistic causes [20]-[25]. An important contributor to fatigue is oxidative damage to mitochondrial membrane lipids. This increases inner membrane leakiness and lowers trans-membrane potential of the inner mitochondrial membrane (MIM), thus impairing mitochondrial function and production of ATP, resulting in reduced physical and mental performance with aging and disease [20] [24]-[26]. For example, chronic fatigue syndrome patients present with evidence of oxidative damage to DNA and lipids [26] [27], such as oxidized blood markers and oxidized membrane lipids that are indicative of excess oxidative stress [27] [28]. These patients also have sustained, elevated levels of peroxynitrite due to excess nitric oxide, which can also result in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production [29].

MLR has been used in several clinical studies to treat moderate to severe chronic fatigue patients in order to reduce their fatigue levels [30]-[37] (**Table 2**). Although most of the clinical studies presented in **Table 2** contained fewer than 50 patients and were open-label, there were significant outcomes in terms of fatigue reduction. For example, the effect of NTFactor® glycerolphospholipids on fatigue in moderately fatigued subjects was examined to see if mitochondrial function improved with oral administration of the MLR supplement [31]. In this cross-over clinical trial there was good correspondence between reductions in fatigue and gains in mitochondrial function. After 8 weeks of MLR with 3.9 g per day NTFactor®, mitochondrial function was significantly improved, and after 12 weeks of NTFactor® supplementation, mitochondrial function was found to be similar to that found in young healthy adults (26.8% increase, $p < 0.0001$), while fatigue was reduced 35.5% ($p < 0.001$) [31]. After 12 weeks of supplement use, subjects were placed on placebo without their knowledge for an additional 12 weeks, and their fatigue and mitochondrial function were again measured. After the 12-week placebo period, fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on the supplement [31]. Similar results on the effects of NTFactor® on fatigue were found in patients with chronic fatigue syndrome (CFS/ME) and/or fibromyalgia syndrome, Gulf War illness and chronic Lyme disease (reductions from 26% - 43%, **Table 2**). Taken together, these clinical data indicate that MLR can be successfully employed to reduce fatigue in different chronic conditions.

Loss of mitochondrial function is not always related exclusively to membrane lipid damage [20]. Thus supplements containing Coenzyme Q10, L-carnitine, alpha-lipoic acid, NADH along with membrane glycerolphospholipids have has also been used in combination mitochondrial supplement studies (for example, ATP Fuel®) to treat long-term chronic illness patients with intractable fatigue [36] [37]. The patients in these clinical studies had been ill with moderate to severe intractable fatigue for an average of over 17 years, had been seen by many physicians (>15), and had taken an average of over 35 supplements or drugs with no effect on their fatigue [36] [37]. Although the numbers of patients enrolled in the studies were limited, they responded with significant reductions in fatigue within 60 days ($p < 0.0001$). Regression analysis of the data indicated that the reductions in fatigue were gradual, consistent, and occurred with a high degree of confidence ($R^2 = 0.960$ - 0.998). The combination supplement proved to be a safe and effective method to significantly reduce fatigue in patients with long-term intractable fatigue [36] [37].

In addition to fatigue in chronic illnesses, fatigue is also one of the most common symptoms of cancer. It occurs in cancer patients from the earliest forms of cancer to the most progressed forms of metastatic disease [35]. Cancer-associated fatigue is not well understood, but it is thought to be due to a combination of the effects of cancer itself plus the effects of cancer treatments [35] [38] [39]. MLR has been used to treat cancer-associated fatigue and the fatigue-effects of cancer therapy [35] [40]. For example, NTFactor® in a vitamin-mineral formulation (Propax™) was used to reduce some of the adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting, malaise, diarrhea, headaches and other side effects [39]. In advanced metastatic colon, pancreatic and rectal cancer patients this supplement reduced the adverse effects of chemotherapy, resulting in significantly fewer episodes of fatigue, nausea, diarrhea, constipation, skin changes, insomnia and

Table 2. Some clinical effects of dietary MLR supplement NTFactor® on fatigue scores.[a]

Subjects/patients	n	Av age on MLR	Time on MLR	Fatigue scale reduction (%)[b]	Reference
Chronic fatigue[c]	34	50.3	8 wks	40.5**	Ellithorpe *et al.* [30]
Aging, chronic fatigue[d]	22	68.9	12 wks	35.5*	Agadjanyan *et al.* [31]
Chronic fatigue syndrome[d]	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe [32]
Obesity, fatigue[e]	35	42	8 wks	23.9*	Ellithrope *et al.* [33]
Aging, chronic fatigue[f]	67	57.3	1 wk	36.8**	Nicolson *et al.* [34]
Cancer, fatigue[c]	35	50.7	8 wks	30.1*	Nicolson [35]
Chronic fatigue syndrome[g, h]	30	55.0	8 wks	30.7**	Nicolson *et al.* [36]
Lyme disease, fatigue[g, h]	17	52.4	8 wks	26*	Nicolson *et al.* [37]
Gulf War Illness, fatigue[g, h]	16	42.2	8 wks	34.6*	Nicolson *et al.* [36]

[a]Modified from Nicolson and Ash [3], [b]Piper Fatigue Scale [38], [c]Propax™ with NTFactor®, [d]NTFactor®, [e]Healthy Curb™ with NTFactor®, [f]Advanced Physician's Formula™ with NTFactor®, [g]ATP Fuel® with NTFactor®, [h]Intractable fatigue (>17.1 years), **$p < 0.0001$, *$p < 0.001$ compared to without NTFactor determined by t-test®.

other effects as assessed by nurses and separately by the patients themselves. Eighty-one percent of the patients on chemotherapy that used Propax™ experienced an overall improvement in quality of life parameters. In a subsequent double-blind, placebo-controlled cross-over trial 36 patients on chemotherapy plus Propax™ showed fewer adverse effects, resulting in improvements in fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators [40].

5. Other Clinical Uses of Membrane Lipid Replacement

In other clinical studies, MLR may modify metabolism through body mass reduction and appetite restraint [33]. In this study 30 normal obese subjects used oral HealthyCurb®, an NTFactor® and alpha-amylase inhibitor formulation, 30 min before each meal. Subjects gradually lost weight, with significant reductions in waist and hip circumferences, along with reductions in body mass index (BMI) and basal metabolic rate (BMR) ($p < 0.001$). Overall hunger was reduced 44.5% ($p < 0.001$), with reduced cravings for sweets and fats, and there was a 23.9% reduction in fatigue ($p < 0.009$). Along with fatigue reduction there was a 26.8% perceived improvement in cognition and ability to concentrate, remember and think clearly ($p < 0.004$) [33].

Mental clarity has been examined in a preliminary study using NTFactor Lipids® [41]. A group of 29 subjects were given 0.6 g of NTFactor Lipids® in a drink, and fatigue and mental focus were surveyed after three hours. At this time a self-reported survey instrument was given to the participants. A majority of subjects responded within one hour, and by three hours they reported perceived improvements in cognition function, mental clarity and focus along with fatigue reductions [41].

Specific glycerolphospholipids, such as oral phosphatidylserine (PS), have been used in clinical studies to assess improvements in memory loss and cognition. In 30 male and female subjects (aged 50 - 90 years old, average 74.6 years old) with memory impairments unrelated to neurological disease, stroke, diabetes, infections or inflammatory processes, a 12-week study was initiated to determine if 300 mg PS per day modified outcomes in 6 different tests of memory and cognition [42]. At the end of the trial participants showed significant improvements in memory recognition ($p = 0.004$) and recall ($p = 0.006$), total learning ($p = 0.013$), executive functions ($p = 0.004$), metal flexibility, and visual spatial learning. There were no adverse events during the trial, and interestingly both mean systolic and diastolic blood pressure values were reduced at 12 weeks in comparison to baseline values [42]. Kato-Kataoka *et al*. [43] conducted a similar double-blind, randomized study on 78 subjects (50 - 69 years old) to determine if 100 - 300 mg oral PS per day versus placebo affected memory scores. They found that PS significantly improved behavioral memory functions, especially short-term memory and cognitive function in low-scoring (delayed word recall) participants ($p < 0.01$) [43].

Oral MLR preparations have been used to treat memory loss in aged subjects and in Alzheimer's disease (AD). AD patients supplemented with 300 mg per day bovine PS for 6 months showed cognitive improvement relative to placebo controls [44]; however, this was not seen in another study on elderly subjects with age-associated memory impairment that received 300 - 600 mg soy PS daily for 12 weeks [19]. In these and other studies the PS was found to be completely safe [45].

6. Membrane Lipid Replacement—Studies on Mitochondrial Function

Since mitochondrial function is related to symptoms like fatigue, it is appropriate to ask whether this is a silent relationship. In fact, fatigue in general, and fatiguing illnesses in particular, are characterized by losses in mitochondrial function [20] [23] [24] [46] [47]. Filler *et al*. [23] have reviewed the literature on fatigue and the association of mitochondrial dysfunction and its possible causes. In addition, they examined the association of the levels of various mitochondrial metabolites, such as acylcarnitine and coenzyme Q10, with fatigue in selected publications [23].

Although some clinical conditions associated with fatigue are clearly related to mitochondrial dysfunction, such as chronic fatigue syndrome (CFS/ME), fibromyalgia syndrome, cancer, among other conditions, others are less clearly associated with loss of mitochondrial function. Various mental disorders, such as schizophrenia, bipolar disease, and others, may be associated with mitochondrial dysfunction, but the links are less clear [23]. These patients are also often characterized with moderate to severe depression. Depression is a commonly found comorbidity in cancer, mental disorders and other conditions, where it shows physical, cognitive and emotional overlap with fatigue in individual patients [48].

Various mitochondrial supplements have been used to treat mitochondrial dysfunction and alleviate or more

commonly reduce fatigue [1] [3] [20] [23] [39] [49]. However, in only a few studies were the losses of mitochondrial function directly related to fatigue scores. A cross-over trial discussed in the previous section directly related loses or gains in mitochondrial function in individual patients to their fatigue scores [31]. In this case the oral use of NTFactor® glycerolphospholipids resulted in significant improvements in mitochondrial function in patients with various diagnoses plus chronic fatigue [31]. I have listed the studies that have used MLR, specifically NTFactor®, to reduce fatigue in **Table 2**.

MLR can also have negative consequences, if the wrong membrane lipids are used. For example, feeding rodents a rapeseed oil-rich diet was found to alter hepatic mitochondrial membrane lipid composition and reduce mitochondrial function [50]. In this animal study hepatic mitochondria were examined after rats were fed the rapeseed oil diet for 22 days, after which they were found to express differences in the relative proportions of glycerolphospholipid classes (increase in PC to PE ratio and differences in cardiolipins) and ratios of saturated to unsaturated fatty acids in their mitochondrial membranes. These mitochondrial membrane lipid alterations paralleled the negative changes in mitochondrial energetics [50].

7. Membrane Lipid Replacement—*In Vitro* Studies

There has been a tendency in recent years to reduce the complexity of living systems down to studying cell organelles and even single molecules [51]. In this regard experiments designed to test the role of certain phospholipids on function have utilized isolated organelles, such as mitochondria, and to these isolates have been added specific glycerolphospholipids to test the effects of MLR. For example, Shaikh *et al*. [52] prepared small PC vesicles or PC/cardiolipin vesicles and incubated these with isolated, suspended rat heart mitochondria *in vitro*. The vesicles were observed to fuse with the mitochondria, resulting in reductions in electron transport enzymatic activities. Thus the authors concluded that increasing mitochondrial membrane phospholipid content lowers electron transport enzymatic activities [52]. There are a number of problems with this approach, including the misinterpretation that this *in vitro* experiment is the same as MLR. The authors used only one glycerolphospholipid (PC) with one fatty acid (oleic) with or without cardiolipin at non-physiological concentrations, and they did not account for dilution of the mitochondrial membrane components in order to incorporate the excess phospholipids [52].

MLR is the natural *in vivo* replacement of damaged membrane phospholipids, not the *in vitro* excess packing of phospholipids into isolated organelles or organelle membranes. In the case of mitochondria, the relative amounts and ratios of membrane phospholipids-to-electron transport complexes are important for functional activity [53]. Mitochondrial membranes also contain more than just PC and cardiolipin, and in the case of the mitochondrial inner membrane, phosphotidylethanolamine (PE) is functionally important in the stabilities, interactions and activities of membrane respiratory chain complexes [54]. PE depletion results in decreased transmembrane potential across the inner mitochondrial membrane, and this results in impaired mitochondrial function [54]. In addition, PE has been shown to be important in regulating membrane fluidity [55]. Fusion of phospholipid vesicles with organelles like mitochondria results in organelle swelling and dilution of membrane components that are normally compacted into dense super complex structures for maximal interactions [56].

A similar *in vitro* phenonmenon was seen when intact spermatozoa were incubated with glycerolphospholipid vesicles generated from NTFactor Lipids® [57]. At lower glycerolphospholipid concentrations vesicle fusion with sperm resulted in enhanced motility [57], which is directly related to mitochondrial activity [58]. However, this was not seen at higher concentrations of the vesicles where membrane swelling due to incorporation of excess membrane glycerolphospholipids occurred [57]. Thus it is important to maintain the compact nature of cellular membranes to retain biological activity [58]-[60]. The fusion of high, nonphysiological concentrations of glycerolphospholipids into mitochondrial membranes *in vitro* cannot be expected to mimic natural *in vivo* MLR.

8. Conclusions

Using oral MLR supplements in clinical trials has shown that MLR is a safe and effective method to replace damaged membrane glycerolphospholipids in order to restore membrane function. Replacing damaged membrane phospholipids has a positive effect on cellular functions, such as mitochondrial function, but MLR is not limited to a single organelle. The positive effects of MLR also occur in other membrane compartments, such as the plasma membrane, and future studies will undoubtedly concentrate on the functional effects of MLR on the

plasma membranes of epithelial cells, nerve cells, and other cells as well as on various intracellular membranes. Since MLR natural supplements are not drugs, the usual drug safety issues are not applicable. Extremely high doses of MLR glycerolphospholipids have been given to animals and humans over long periods of time without any toxic or adverse effects [3] [16]. Thus MLR glycerolphospholipids are extremely safe to use as a daily dietary supplement or for treatment of specific membrane deficits, such as loss of mitochondrial MIM function.

It should be clear from this contribution that additional clinical studies are needed to further examine the role of MLR supplements in enhancing mitochondrial function *in vivo* and reducing symptoms like fatigue. With two exceptions [31] [40], the MLR studies reviewed in this contribution were open label, not blinded, placebo-controlled studies. In the cross-over trial by Agadjanyan *et al*. [31], a variety of patients with various diagnoses that had moderate to severe chronic fatigue were studied. The trial could have been improved if patients were enrolled that presented with one primary diagnosis where fatigue was a major symptom, such as chronic fatigue syndrome. Also, with one exception [34], the clinical studies in **Table 2** utilized less than 50 patients. Thus, more robust, blinded, placebo-controlled studies with more uniform cohorts of patients would be an improvement for studying the relationship between fatigue, mitochondrial function and the effects of MLR supplements.

The potential uses of MLR supplements to improve health and treat various clinical conditions are numerous and widespread [2] [3] [5] [61]. In fact, this review has presented some limited data on the potential uses of MLR supplements to improve mitochondrial function, but the future uses of MLR are much broader than mitochondria and are extended to many aspects of membrane health and function. New formulations of MLR supplements directed primarily at restoring damage in plasma membranes, nuclear membranes and other intracellular membranes will likely be important in future studies.

Acknowledgements

This contribution was supported by grants and contracts to the Institute for Molecular Medicine, a non-profit, tax-exempt research organization under section 501 (c) (3) of the U.S. tax code. Professor emeritus Garth Nicolson is a part-time consultant to the following: Nutritional Therapeutics, Inc. of Hauppuage, NY; Resarched Nutritionals of Los Olivos, CA and Naturally Plus USA of Las Vegas, NV.

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Abbreviations

ATP: adenosinetriphosphate;
CFS: chronic fatigue syndrome;
CL: cardiolipin;
DHA: docosahexaenoic acid;
EPA: eicosapentaenoic acid;
ETC: electron transport chain;
FA: fatty acid;
FDA: US Federal Drug Administration;
GRAS: generally recognized as safe;
MDA: malondialdehyde;
ME: myalgic encephalomyelitis;
MIM: mitochondrial inner membrane;
MLR: membrane lipid replacement;
PC: phosphatidylcholine;
PE: phosphatidylethanolamine;
PG: phosphatidylglycerol;
PI: phosphatidylinositol;
PS: phosphatidylserine;
RNS: reactive nitrogen species;
ROS: reactive oxygen species.

International Journal of Clinical Medicine, 2016, 7, 144-168
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72016

Assessment of Risk of Malnutrition in Elderly Hypertensive Patients with or without Associated Cardiovascular Risk Factors Living at Home (West Algeria) Sidi-Bel-Abbès

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Received 12 January 2016; accepted 24 February 2016; published 29 February 2016

Abstract

Undernutrition is frequently underestimated in the elderly, because clinical manifestations are non-specific. For the francophone Club geriatrics and nutrition, poly medication is one of the warning signs to be the possibility of malnutrition in an elderly person. To do this, it is particularly interesting to verify what the profiles of hypertensive patients who are at risk of malnutrition are. This component remains very little explored and studies are lacking. The authors conducted a descriptive cross-sectional study whose objective is to evaluate the prevalence of undernutrition in hypertensive patients with or without associated cardiovascular risk factors, in a population of consultants of liberal medical offices, determine the profiles of hypertensive patients who are at risk of undernutrition and describe their eating habits and their anthropometric parameters as well as the link between the number of supported antihypertensives and risk of undernutrition. 1144 patients with an average age of 65 years old have been collected during the period of recruitment. The data collection was done using a questionnaire: the MNA. Sensitive and specific, it is validated method which has international sacle. The percentage of the risk of malnutrition was estimated at 36.7%. Thus the number of associated cardiovascular risk factors becomes larger, and the risk of malnutrition is increased. The risk of malnutrition was three times higher in patients who take more than three medications per day compared with those who consumed less (75.8% vs. 24.2%). As a monotherapy, an increased risk of malnutrition is associated with diuretics. For these older hypertensives, the risk of malnutrition was linked to the type of used dual. The percentage of hypertension risk of malnutrition treated with free dual was significantly higher

How to cite this paper: Merad-Boudia, H.N. and Bereksi-Reguig, K. (2016) Assessment of Risk of Malnutrition in Elderly Hypertensive Patients with or without Associated Cardiovascular Risk Factors Living at Home (West Algeria) Sidi-Bel-Abbès. *International Journal of Clinical Medicine*, **7**, 144-168. http://dx.doi.org/10.4236/ijcm.2016.72016

compared to hypertensive treated dual handset. Some associations have proved to be more favorable than others in terms of nutritional risk. Finally, a third of hypertension patients who were treated with quadruple therapy were at risk of malnutrition. This work was also designed to present an argument to a doctor to detect the risk of undernutrition in elderly hypertensives. The use of the MNA is a simple, effective and quick way for pressure balance rhymes with nutritional balance.

Keywords

Risk of Malnutrition, Cardiovascular, Risk Poly Medication, Older Hypertensive Mini Nutritional Assessment

1. Introduction

Under the term "malnutrition", it is possible to encompass very different situations and reading the medical literature contains a large number of examples.

For the ANAES, undernutrition is the result of an imbalance between contributions and the protein-energy requirements of the body.

This imbalance leads to tissue loss with deleterious functional consequences. It's a different strictly involuntary tissue loss of weight loss which may be voluntary or not [1].

It can be global, and is called protein-energy malnutrition, or part, and in this case, it affects preferentially one or more nutrients, especially micronutrients.

In the study Euronut-Seneca conducted in 1005 elderly at 74 - 79 years old, living at home, 23.9% of men and 46.8% of women had food inadequate intake in one or more of the following micro-nutrients: calcium, iron, retinol, beta-carotene, vitamin B1, B6 or (c). [2]

The prevalence of undernutrition depends on the tools used for diagnosis and the whereabouts of the people studied.

In developing countries, it is likely to be higher, between 15% and 30%, but studies currently are lack [3], especailly in the main group at risk of malnutrition, the elderly.

The analysis of these studies used to assess the extent of the phenomenon and its consequences in terms of morbidity and mortality is done.

In the elderly, undernutrition contributes to the occurrence of sometimes serious pathologies. It helped destabilize the balance of chronic diseases such as heart, kidney or respiratory failure.

Malnutrition weakens people and makes them more vulnerable: the risk of infections is therefore greatly increased, in the case of operation healing is difficult and long. Undernutrition is also responsible for muscle wasting; it is even responsible for an increase in the risk of falls.

This state also contributes to the accelerated aging and reduction of autonomy.

Malnutrition in the elderly is therefore a serious condition which weakens considerably these already vulnerable people.

Several studies have identified situations at risk of malnutrition among the elderly already considered themselves as a group at risk. Alibhai *et al*. [4] have done a review of the most common causes of weight loss in the elderly among them: the HTA.

According to steps wise on NCD conducted in 2003 in Algeria with 4156 people, the prevalence of hypertension was 26% [5].

Hypertension was also the most frequent morbid conditions found in 16.23% of those aged 35 to 70 years old of Tahina survey, conducted in 2005 in 4818 households [6].

Nutritional diagnosis is too often overlooked in diagnostic procedures in daily clinical practice. This is related to the lack of time or lack of knowledge of nutritional problems and their impact on the health of patients by the medical staff. Nutritional disorders are being seen as secondary to the disease causing hospitalization [7].

According to the American Society for Parenteral and Enteral Nutrition (ASPEN) [8], it is important to detect malnutrition among people aged aggressively.

The collection of clinical and biological components easily accessible and the use of simple composite indices

provide a nutritional diagnosis satisfying to consider therapeutic step [9].

For cela experts of the national Programme nutrition santé (PNNS), as well as the European Society for Parenteral and Enteral Nutrition (ESPEN) recommend the use of the MNA test in the elderly [10] [11].

The introduction of early and appropriate nutritional support is indeed the pledge of a decrease of co-morbidities of the duration of hospital stays and hospitalization costs related to malnutrition [12].

2. Subjects and Methods

The main objective was to assess the prevalence of undernutrition in hypertensive patients with or without risk factors cardiovascular Associates, aged 50 years and over within the population of patients seen in medicine of city.

The survey was conducted in the town of sidi bel abbes; 01 March 2014 to 31 October 2014.

The recruitment of patients was done with medical specialists in cardiology and internal medicine.

The number of patients included in the investigation corresponds to those having consulted during this period.

2.1. Secondary Objectives

Determine the profiles of hypertensive patients who are a risk of undernutrition.

Describe their eating habits and their anthropometric parameters as well as the link between the number' caught antihypertensives and risk of undernutrition.

2.2. Inclusion Criteria

Age over 50 years for both sexes.

Hypertensive known and treated with the same therapy for at least three months.

Presence or not of one or more associated cardiovascular risk factors (diabetes or Dyslipidemia treated...).

2.3. Exclusion Criteria

Edemes, some either their origins, for example: If lowering of the oncotic pressure: during a cirrhosis, in case of malnutrition in a kwashiorkor, during a nephrotic syndrome by renal loss of proteins, dialysis patients and there is the drug causes: blockers, steroids and NSAIDs, causing water retention.

Patients with ascites.

Patients dehydrated.

Patients who have undergone surgery in the past 12 months.

2.4. The Preliminary Survey

Any investigation inevitably alters the behavior of the observer, so before you begin, the Protocol that was developed was the subject of a test on the field in order to verify that the subjects are actually available, that medical records are accessible, that questionnaires are usable and are not too long to complete, that response rates to obtain the necessary staff etc.

Improbably, this led to revise some aspects of the original Protocol (including questionnaires). Changes to the questionnaire are summed up to the replacement of the number of meals in question No 10.

How real meal the patient take per day?

Score 0 = 2 meals, 1 = 3 meals, 2 = 4 meals.

Instead of:

Score 0 = 1 meal, 1 = 2 meals, 2 = 3 meals.

The interest of this preliminary survey was also to treat a new dimension of the subject based on other works and readings.

By targeting appropriate patient profiles, key concepts and notions have been recorded in order to explore them and to deepen.

The mode of administration of the questionnaire was standardized for more accuracy and consistency inspired by the manual of the Mini Nutritional Assessment MNA issued by the NNI [13]. A final Protocol was then prepared.

2.5. Definition of Concepts

2.5.1. The MNA

The data collection was done using a questionnaire: the MNA.

The MNA ® was translated into over 20 languages and used in different elderly populations in several countries: hospitalized populations, preoperative, convalescing in house retirement or at home [14].

It is a method of evaluation of I' nutritional status of the elderly at risk of malnutrition, which is month expensive. fast, simple non-invasive and validated international, way, if necessary, a nutrition intervention or a correction of the diet [15].

The MNA consists of 18 items and can be done in 10 minutes or less.

II includes:

An overall assessment; an food investigation; anthropometric measures, provides information on the consumption of drugs and also subjectively evaluates the condition of health.

The Dem can be used in the form of quantitative or qualitative variable.

To meet the objectives, this scale was routinely administered in its entirety. Insofar as the MNA was viewed as a quantitative variable.

The extent of the variation of the score to the MNA was apprehended to compare scores with each other, appreciate the relationship with the possible factors of malnutrition and seize the heterogeneity of the problems.

The thresholds for risk of malnutrition were considered as qualitative variable to describe our population and establish profiles of hypertensive patients at risk of malnutrition.

The MNA is:

-More sensitive than serum albumin in the detection of those at risk of malnutrition;

-Predictive of mortality at 3 months.

Furthermore, using clinical examination as reference, the sensitivity and specificity of the MNA ® were 96% and 98%.

The diagnosis of malnutrition is based on anthropometric and biological criteria or the MNA score. One of these criteria is sufficient to make the diagnosis of malnutrition in the elderly

Weight loss involuntary > 5% in 3 months or > 10% in 6 months.

A BMI < 21), l' albumin < 35 g/l and (DEM < 17) [16].

2.5.2. Undernutrition

The definition of malnutrition varies according to the sources.

The Working Group of the Directorate of hospitalization and care organization (DHOS), the national programme nutrition health (PNNS) [17], as well as the European Society for Parenteral and Enteral Nutrition (ESPEN) recommend the use of the MNA ® test for the detection of malnutrition in the elderly [18].

The ASPEN recommends (151), among other searching for Comorbidities, all patients, regardless of the place (home, hospital, another place of care) [19].

In accordance with the classification of the MNA, hypertensive elderly patients were split into three groups: a group having a correct nutritional status (MNA ≥ 24), a group with a risk of malnutrition (17 < MNA < 24) and a group with poor nutritional status (MNA ≤ 17).

Then the risk group and the group with poor nutritional status were considered as one group 'at risk'. The hypertensive were therefore split into two groups:

A group having a correct nutritional status (MNA ≥ 24) and a group with a risk of malnutrition (MNA < 24).

This grouping can be found in the literature [20] [21].

2.5.3. Weight

The weight measurement is essential.

It was measured with a minimum of clothing using an electronic scale (NEC France).

The latter was broad, stable and appropriate to the degree of autonomy so that the elderly can keep standing. [1].

Regular calibration of the balance was necessary, accuracy of ± 50 g [22].

Patients with ascites or edema artificially increasing body weight were systematically excluded under the exclusion criteria.

To complete question 2 of the Dem on the recent weight loss, l es earlier variations found in the records of patients were particularly interesting.

More than the weight itself measured the day of the survey, this weight loss was an early sign of malnutrition [1].

2.5.4. The Size

To assess the risk of malnutrition, it is not necessary to get the size of as strictly for resuscitation [23].

The problem is that its decline with age.

The size was measured in an upright position without shoes and heels with a measuring rod.

Failing BMI was calculated from the size found on the ID card [23].

2.5.5. BMI

Regarding BMI, the categories defined by who were used [24] see **Table 1**. BMI was calculated as weight (kg) divided by the square of the height.

2.6. Statistical Analyses

The statistical analysis was performed on Epi info version 7. Provided several parametric tests reserved for large samples were used, inter alia, the comparison between two percentage when it comes to qualitative characters, comparison between two averages for quantitative traits.

The test of KHIDEUX of PEARSON was used after check the normality of the distribution and operating conditions.

When the latter were not met, we have processes to either of the two methods, either the grouping of classes or the correction of YATES.

Several variants of the KHIDEUX test have been used as, KHIDEUX of uniformity, the test of khideux of independence.

The FISCHER test-SNEDECOR was aimed to check the overall homogeneity of the various profiles in our sample for this:

The report of dispersal inter-groups and dispersal intra groups was calculated (to compare several averages of a quantitative trait). Simple correlation analysis was used to measure the intensity and linearity in the case of its existence between two quantitative variables (independent explanatory variable and dependent variable explained).

The p significance threshold ≤ 0.05 is considered for all statistical analyses.

2.7. Confidentiality, Information from Persons and Legal Provisions

The survey received a favorable opinion on the part of participating doctors.

The anonymous questionnaires were administered with a serial number and the initials for names and first names.

It was explained to each patient who responded to the questionnaire was included as part of the history of routine in order to improve their support.

Table 1. WHO according to BMI classification [24].

BMI ($kg \cdot m^2$)	Interpretation
	The classes
less than 16.5	undernutrition or famine
16.5 to 18.5	thinness
18.5 to 25	normal body
25 to 30	overweight
30 - 35	obesity moderate
35 to 40	severe obesity
more than 40	morbid or massive obesity

Also some issues as well as some anthropometrics settings were already respect for medical confidentiality was of course guaranteed.

3. Results

Thus 1144 patients have been collected during the period of recruitment. The characteristics are represented to the **Table 2**, **Table 3**.

3.1. Individual Morbidity

3.1.1. Frequency of Diabetes

Almost half of the 50 years, included hypertensives in this study, was known and treated for diabetes (regardless of the type of diabetes), this frequency was higher among women 66.66 percent men 33.33% (**Figure 1**).

3.1.2. Frequency of Dyslipidemia

Amongst the hypertensive constituting our sample, almost two patients on five were dyslipidemic (37.76%) (**Table 4**), sex, this frequency was nearly two times more increased among women (72.22%) compared to men (27.77%) (**Figure 2**).

Table 2. Characteristics of the study population.

	Men	Women	Total	Statistical parameters
	(440)	(704)	(1144)	
Sex ratio				
(f/h) East of 1.6	38.5%	61.5%		
Age	65.88 ± 9.65	65.49 ± 9.88	65.26 ± 9.93	Ɛc = 1.16
Weight	75.44 ± 12.51	75.30 ± 12.58	75.33 ± 12.62	Ɛc = 0.18 CV = 0.16
The size	168.8 ± 6.58	168.1 ± 7.14	168.1 ± 7.18	Ɛc = 1.69 CV = 0.04
IMC	26.62 ± 4.12	25.64 ± 4.27	25.64 ± 4.27	Ɛc = 0.08
Brachial circumference				
CB < 21	8	12	20	$Chi^2 = 0.36$
	1.81%	1.7%	1.7%	DDL = 2
21 ≤ CB ≤ 22	24	36	60	p = 0.38
	5.45%	5.11%	5.24%	CV = 0.16
CB > 22	408	656	656	
	92.72%	93,18%	93%	
Calf circumference				
CM < 31	60	72	132	$Chi^2 = 2.91$
	13.63%	10.22%	11.53%	DDL = 1
CM ≥ 31	380	632	1012	p = 0.41
	86.36%	89.77%	88.46%	

Table 3. Frequency of diabetes.

Disease state	Men		Women		Total	
	n	%	n	%	n	%
Diabetic	200	33.33	400	66.66	600	52.44
Non-diabetic	240	44.11	304	55.88	544	47.55
Total	440		704		1144	100%

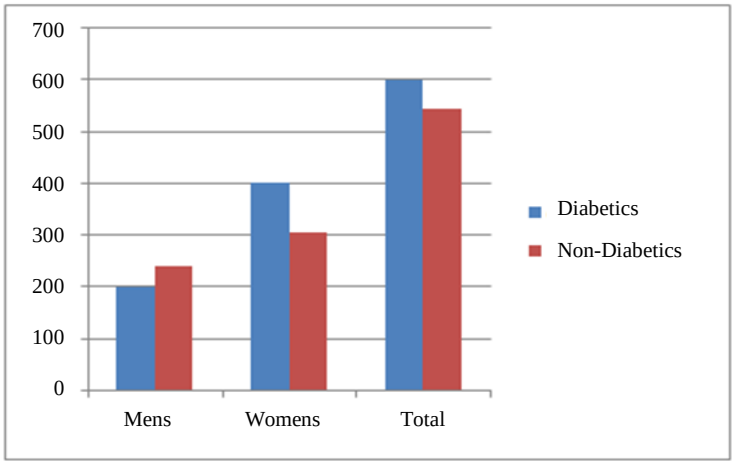

Figure 1. Frequency of diabetes.

Table 4. Frequency of dyslipidemia.

Disease state	Men		Women		Total	
	n	%	n	%	n	%
Dys lipidemique	120	27.77	312	72.22	432	37.76
Not dyslipidemique	320	44.94	392	55.05	712	62.23
Total	440		704		1144	100%

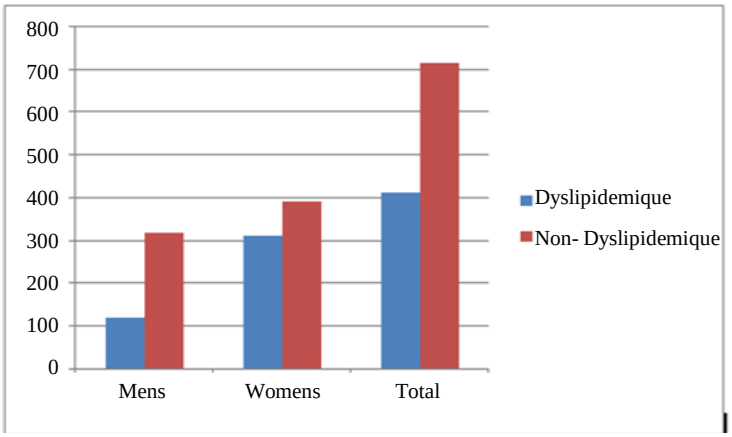

Figure 2. Frequency of dyslipidemia.

3.2. Distribution of Patients According to Anti Hypertensive Therapy

The distribution of patients was significantly different according to antihypertensive therapy, (Chi^2 = 26.85, ddl = 4) (**Table 5**), almost 2 patients on five were treated by one (41%) or two antihypertensive drugs (42.65%). Furthermore, 12.93% of the patients were treated by three antihypertensives and only 3.5% by a four.

It was also quite interesting to see what items the hypertensive elderly lost points in the MNA (**Table 6**).

Firstly, the rather positive items to their nutritional status.

Mean BMI was 25.64 ± 4.27 corresponding to a "normal" said index, at the limit of overweight.

In other words, the majority of hypertensive elderly presents a quite correct body and does not seem thin (even as table above).

The hypertensive elderly in our sample appear to have proper food consumption, since 66.1% consume, at least once a day, dairy products, 1 - 2 times per week, eggs or legumes and 73.1% consume, at least twice a day,

Table 5. Distribution of patients according to the anti hypertensive therapy.

Anti hypertensive therapy		Men		Women		Total	
		n	%	n	%	n	%
Monotherapy		180	41	288	41	468	41
Dual therapy total (488)	BI-free	128	29	128	18.18	256	22.37
	BI-combinee	64	14.54	168	23.86	232	20.27
Triple therapy		52	11.81	96	13.63	148	12.93
Four		16	3.63	24	3.4	40	3.5

Table 6. The positive items for their nutritional status to the MNA.

BMI greater than or equal a 23	84.26%
BMI between 21 and 23	8.74%
BMI between 19 and 21	3.84%
BMI less than 19	3.14%
Brachial circumference greater than 22 centimeters	93.00%
Circumference of the calf longer than 31 cm	88.46%
No weight loss over the last three months	71.4%
Showed no disease acute or psychological stress during the last three months	61.88%
Do not have pressure sores or skin wounds	90.90%

fruit and vegetables.

Moreover, it seems that this is not dependence for feeding that average is associated with loss of points to the MNA.

In fact, only 1.9% need assistance for food. 2.8% feed alone, but with difficulties and 95.3% feed only without difficulty.

De plus, 72.3% consider themselves without specific nutritional problems.

All the other items that make lose points in the MNA, entirely due to the weaknesses related to the pathology poly.

First of all, 86.7% of they consume more than three drugs per day.

Only 52.1% are four meals a day, 35.4% take three meals a day, 8.2% two meals and only 4.3% one meal per day. Moreover 11.8% take more than 5 glasses of drink per day.

These items are fairly characteristic of the population consuming a large number of medicines that tends a little hydrated and take less meals, including one for the night.

Furthermore, nearly 60% of hypertensive elderly presented recent loss of appetite, which may be associated with a high consumption of drugs, but also has other factors: problems digestive difficulty chewing or swallowing, recent surgery.

Thus 1144 patients have been collected during the period of recruitment. The characteristics of the patients are given in the table.

The percentage of the risk of malnutrition was estimated a 36.7% which corresponds to a 21.2 average DEM 2.32 ± which varies between a minimum of 11.5 (severe malnutrition) and a maximum of 23.5 malnutrition threshold selected scale MNA.

The average age of the hypertensive risk of malnutrition is of 67.95 ± 6.22 Males 68.54 ± 6.38 and women 67.66 ± 6.19 ($\mathcal{E}$ = 1.35, p = 0.18 > 0.05).

No significant difference (p > 0.05) were observed between the age of women and men with age values centered around the average for both sexes (C.V men = 0.093 and C.V women = 0.091)

Thus, half of the men at risk of malnutrition have an age between 59 and 77 years old and half of women at risk of malnutrition have an age between 60 and 74 years (**Figure 3**).

Figure 3. Age of hypertension at risk of malnutrition.

The average MNA of men at risk of malnutrition is 21.26 ± 2.28 Women's equal average MNA has 21.18 ± 2.32.

The risk of malnutrition was significantly related to sex (Chi-square = 7.67, ddl = 1, p = 0.003); higher among women 39.77% Vs 31.81% for men.

ANM score going in the women at risk of malnutrition of 19.5 in the first quintile to 23 in the last and among men by 19 in the first quintile was 23.5 last ($p < 0.001$).

The MNA allowed screening for hypertension a risk of malnutrition before even the decline in BMI, brachial circumference, the circumference of the calf and without same there is weight loss (**Figure 4**).

Thus, among the 36.7% of hypertensive has risk of malnutrition: 85.71% have upper brachial circumference was 22 and 78.09% have a circumference greater than or equal calves has 31. Through elsewhere, weight loss were observed for 23.8% during the previous three months.

According to the classification who, 100% of patients who have a BMI less than 18.5, thinness and extreme thinness stage are also tracked by the MNA.

For a BMI greater than or equal a 18.5 (normal or more) more than 97.14% are considered at risk of malnutrition by the MNA.

Finally, for 71.4% was not there a weight loss over the last three months.

The percentage of hypertension risk of malnutrition with a circumference brachial inferior to 21 was very high: 80%.

In addition, found hypertension risk of malnutrition, 100% of them who had the most mediocre MNA (equal to 11.5) had among other a circumference brachial inferior to 21 (**Figure 5**).

The risk of malnutrition was five times higher in hypertensives that have a circumference brachial inferior has 22 Odds ratio OR 5.86, CI 95% = [3.48, 9.88].

The percentage of hypertension risk of malnutrition with a circumference of calves less than 31 was two times higher compared with those who had a circumference of the calf greater than or equal to the same value (**Figure 6**).

The risk of malnutrition was more than four times higher in hypertensives who have a lower calf circumference a 31 Odds ratio = OR = 4.79, 95% CI % = [3.23, 7.11].

Correlation analysis showed that the risk of malnutrition and the age range in the same direction (cov (risk age) = 4.48) but the correlation coefficient was low (r = 0.14) then it seems that several confounding factors can interact:

At a very advanced age of hypertensive treated monotherapy may be neither diabetic nor dyslipidemic, while older hypertensive of 65 for example can be treated with an anti hypertensive therapy; Therefore it is difficult to interpret these results.

On the practical level, to work around this problem and meet the objective main risk of malnutrition was appreciated on several components:

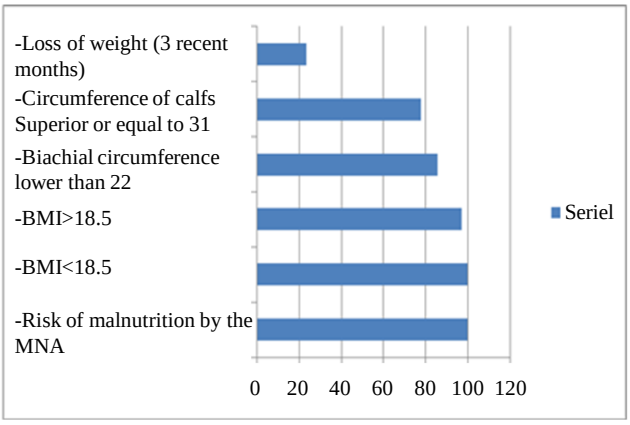

Figure 4. Sensitivity of the MNA compared with anthropometric parameters (as a percentage).

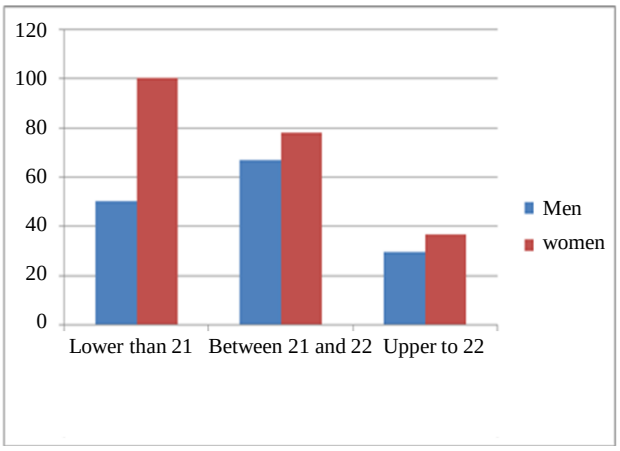

Figure 5. Risk of malnutrition and brachial circumference (in percentage).

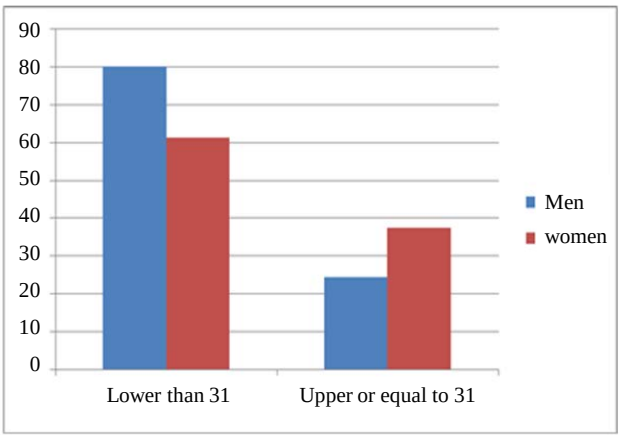

Figure 6. Risk of malnutrition and circumference of the calf (in percentage).

Assess the relationship between the number of drugs taken by day and risk of malnutrition and poly medication (Item 8 of the MNA questionnaire).

Evaluate the risk of malnutrition according to each strategy anti hypertensive (monotherapy, dual, triple, and

four), and finally evaluate cardiovascular risk.

Thus more cardiovascular risk factors there, more risk of malnutrition is increased (**Table 7**) (**Figure 7**).

The presence of diabetes and hypertension at the same time is very common. The PROCAM study the prevalence of hypertension in diabetics is 50% [84].

3.3. Poly Medication and Risk of Malnutrition

The risk of malnutrition was not the same in both groups (Ɛc = 3.9).

According to **Figure 8**, it was three times higher in patients who take more than three medications per day compared with those who consumed less. (75.8% Vs 24.2%) OR = 3.00, 95% CI % = [2.26, 3.99].

3.4. Risk of Malnutrition and Anti Hypertensive Therapy

3.4.1. Monotherapy

The average age of the hypertensive risk of malnutrition treated in monotherapy was 67.64 years ± 10.24 (67 years and 8 months) with an average dem of 21.40 ± 1.93. (MNA min = 16, MNA max = 23.5).

Table 7. Risk of malnutrition and cardiovascular risk.

	Dyslipidemiques non diabétics	diabétics non dyslipidemiques	Diabétics and dyslipidemiques
Risque of malnutrition	24 (5.71%)	88 (20.95%)	132 (31.42%)

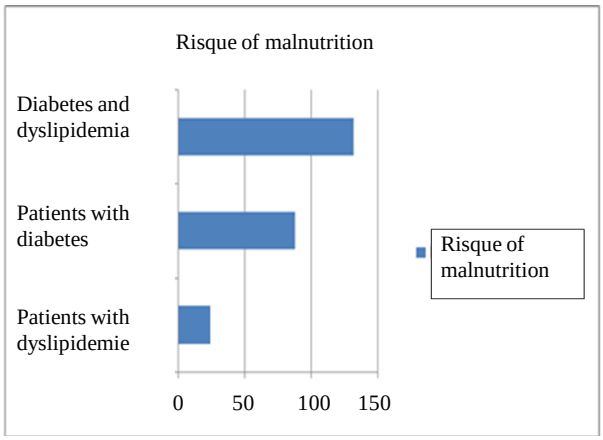

Figure 7. Analysis of correlation between age and the risk of malnutrition.

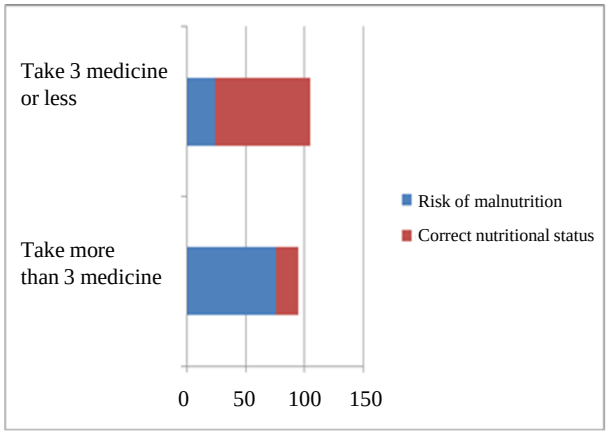

Figure 8. Risk of malnutrition and poly medication.

The risk of malnutrition in hypertensives treated monotherapy was significantly different between the five classes of antihypertensive agents recovered (Chi-square = 19.02, ddl = 4).

Hypertension treated with a diuretic monotherapy, 60% of them were at risk of malnutrition with an average score of the most mediocre MNA of 19.95 ± 0.69 (Nam min = 19 max = 21 MNA) and little variation in the same group (CV = 0.034) (**Figure 9**).

Concerning the distribution of patients at risk of malnutrition in monotherapy according to age and score average MNA:

In the group treated with a beta-BLOCKER monotherapy, the risk of malnutrition was lower: 28.57% with a score average MNA of 20.95 ± 1.74.

On the other hand, with a risk of malnutrition by 33%, hypertension treated with an ANGIOTENSIN 2 receptor ANTAGONIST appeared to have an average dem approaching the correct nutritional status with 22.21 more ± 1.11 (DEM 20 min and a max of 23.5 DEM) (**Table 8**) and less significant variations compared to the Group of hypertensive patients under beta BLOCKER:

(CV = 0.049 for the ANTAGONIST of RECEPTORS of the ANGIOTENSIN 2 Vs CV = 0.083 to the beta-BLOCKER).

3.4.2. Risk of Malnutrition and Total Dual: (Free Dual + Dual Combined Therapy)

The average age of treated dual hypertension risk of malnutrition was 67.66 years ± 10.20 (67 years and 7 months) with an average 21.13 DEM ± 2.32. (MNA min = 11.5, MNA max = 23.5) (**Figure 10**).

The risk of malnutrition was linked to the type of combination therapy used.

The percentage of hypertension risk of malnutrition in free combination therapy was significantly different compared to hypertensive treated combined dual: (39% vs. 32.7%). (Chi-square = 4.14, ddl = 1).

Free Dual

Analysis of the risk of malnutrition in hypertensives treated dual in each of the two strategies has seemed us particularly interesting.

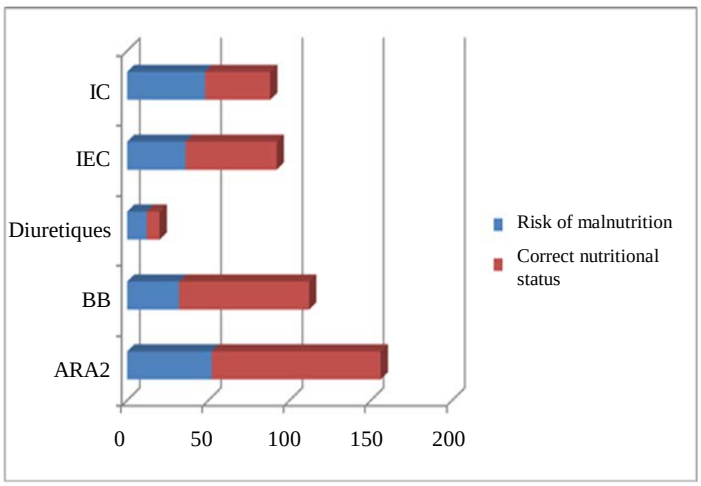

Figure 9. Risk of malnutrition and anti hypertensive therapy.

Table 8. The distribution of patients at risk of malnutrition as monotherapy according to the age and the average dem score.

Classes	MNA average	S.D	MNA min	MNA Max	C.V
ARA2	22.21	1.11	20	23.5	0.049
BB	20.95	1.74	16.5	23.5	0.083
Diuretics	19.95	0.69	19	21	0.034
IEC	20.58	1.31	17.5	22.5	0.063
IC	21.07	1.87	16	23.5	0.088

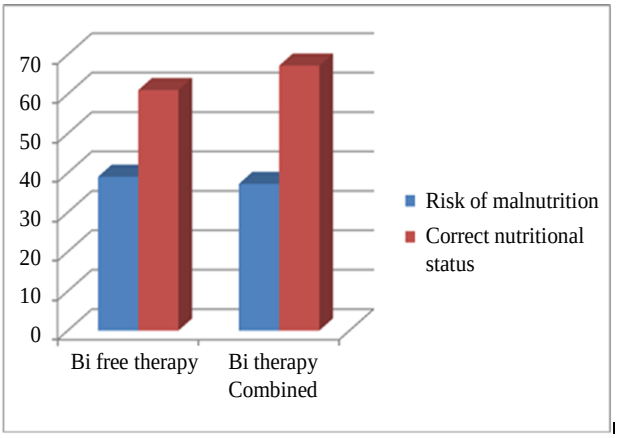

Figure 10. Risk of malnutrition and total dual: (free dual + combined dual).

In the management of hypertension in boat form, the authors compared the association IC and others with diuretics and other associations: it seems that the way of the IC (shown in blue in the figure below) is better because the percentage of other hypertension risk of malnutrition under association IC does not exceed the 50% unlike the associations with diuretics.

For hypertension treated with a diuretic (having the highest risk of malnutrition in monotherapy and the poorer MNA) associated with an IC, an INHIBITOR of the converting ENZYME, an ANTAGONIST of RECEPTORS of the ANGIOTENSIN 2 or beta-BLOCKER risk of malnutrition was greater than or equal to 50% (**Figure 11**).

Furthermore, in terms of percentage the two associations: INHIBITOR of the ENZYME from converting/IC (represented in red) and ARA/beta-BLOCKER are equal with 25% of hypertensive risk of malnutrition each, but the latter is not recommended by the Haute Autorité de santé.

In the group or they are associated one another, beta BLOCKER and diuretic, the risk of malnutrition was max (a 100%) with an average dem = 19 ± 0.00.

Conversely for hypertension treated with a beta-BLOCKER (with a risk of the lowest malnutrition monotherapy) associated to the other classes of antihypertensive drugs risk was strictly less than a 50% Free, free dual beta-BLOCKER and diuretic-treated groups are all at risk of malnutrition below 30% (represented in red in the boat **Figure 12**).

Combined Dual

In the group treated the percentage of hypertension free dual risk of malnutrition as antagonist of angiotensin 2/diuretic (shown in blue) was almost twice and a half higher has that handled dual combined by the same association 75% Vs 31%) Odds ratio OR = 6.69, CI 95% = [2.06, 21.73] (**Figure 13**).

Similarly, the percentage of hypertension a risk of malnutrition treated by the association INHIBITOR of the ENZYME of CONVERSION/diuretic (shown in blue in **Figure 11**) free dual was three times higher than treated dual combined by the same association (60% Vs 20%) **(Figure 14)** Odds ratio OR = 6, CI 95% = [1.45, 24.68].

Conversely, the percentage of hypertension a risk of malnutrition treated by the association (represented in red, **Figure 15**) ICA/ANGIOTENSIN receptor ANTAGONIST2 free dual seems less has the group treated by the same association combined dual (29.4% vs. 45.5%) but this hypothesis remains to be confirmed because the Ods ratio was not for a true association between uses it has a dual free or combined and a possible risk of malnutrition (**Figure 16**) Odds ratio OR = 1.1, CI 95% = [0.53, 2.26].

3.4.3. Triple Therapy

Among the hypertensive patients who were treated by a triple (average age of 68 ± 10.24). 35.13% were at risk of malnutrition with an average dem = 21.13 ± 2.12 (DEM min14 and DEM max = 23.5).

92 patients (62.16%) among those under antihypertensive therapy, showed a combination recommended by the HAS: IC with converting ENZYME INHIBITOR or ARBS or beta BLOCKER + thiazide diuretic (Which are respectively 5.4%, 56.75% and 0% with the beta BLOCKER).

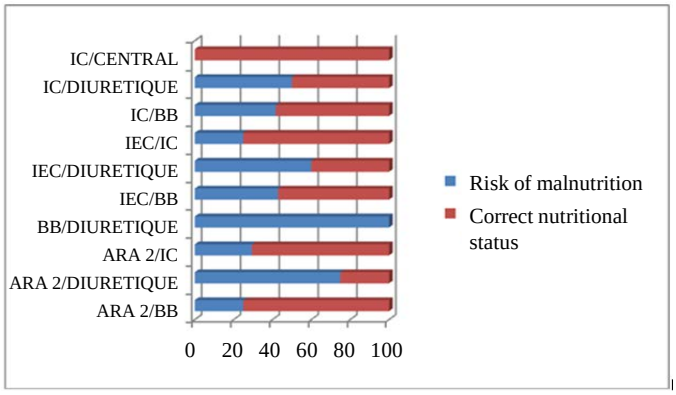

Figure 11. Risk of malnutrition and free dual.

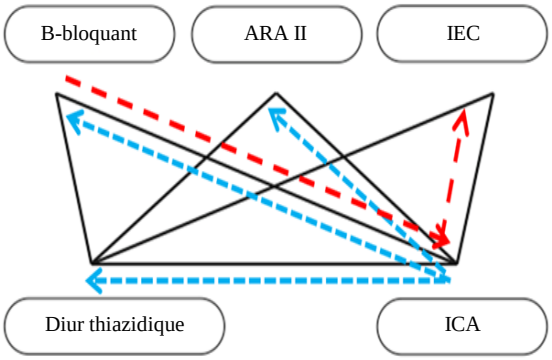

Figure 12. The possible combinations of antihypertensives which has the risk of the lowest malnutrition in the elderly hypertensive.

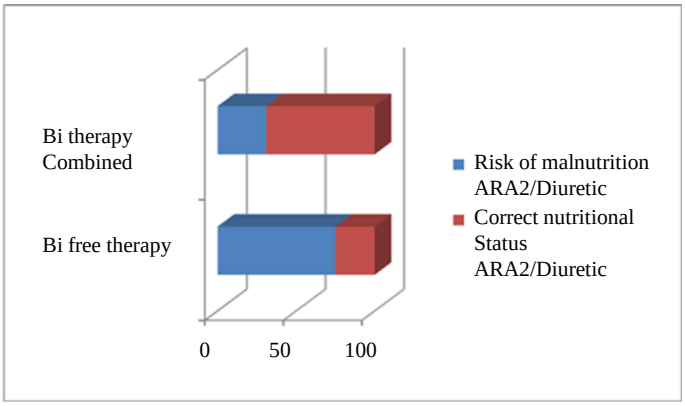

Figure 13. Risk of malnutrition and combined bitherapy (ARA2/ diuretic).

The percentage of hypertension risk of malnutrition for the first combination (INHIBITOR of CONVERSION the of ENZYME/IC/DIURETIC) was zero, but the number of patients was insufficient to infer a any conclusion (0.7% of all patients in the study).

In the second combination (ARA DIURETIC-IC-2) the percentage of malnutrition was of 33.33%.

Less while the triple: (ARA 2/BETA-BLOCKER/DIURETIC) which was 50% or even triple therapy (ARA 2/IC/*β*-BLOCKER) which was 66.7%.

Finally, it seems to us that the combination recommended by the HAS (diuretics thiazide and inhibitor calcium) basket 2 including 2 of basket 1 ANGIOTENSIN receptor ANTAGONIST was also the best in terms of

risk of malnutrition with an average dem which is close to the application of more than one nutritional state correct (see table below), and that the abandonment of the thiazide diuretics or calcium inhibitor increases see double the percentage of hypertension a risk of malnutrition.

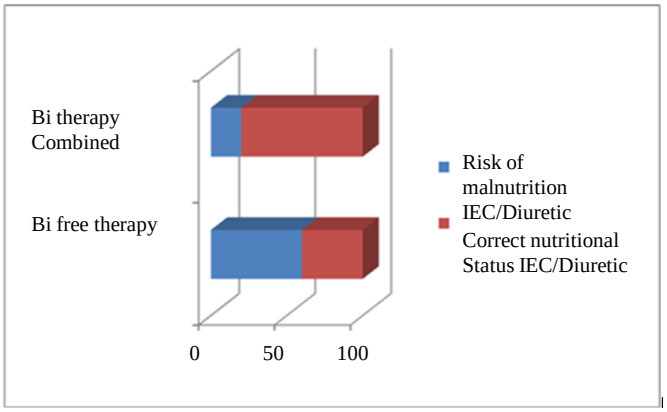

Figure 14. Risk of malnutrition and combined bitherapy (conversion/diuretic enzyme inhibitor).

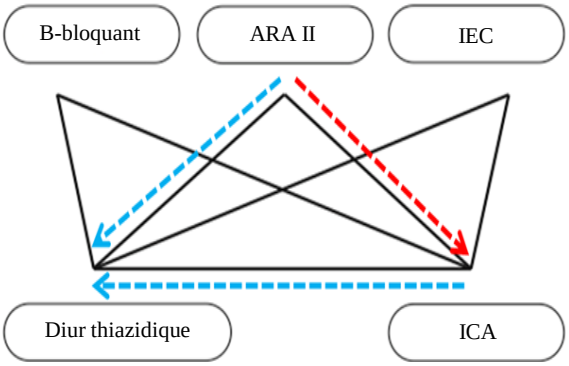

Figure 15. The possible combinations of antihypertensives which has the risk of the lowest malnutrition in hypertensive elderly subjects (combined dual vs free dual).

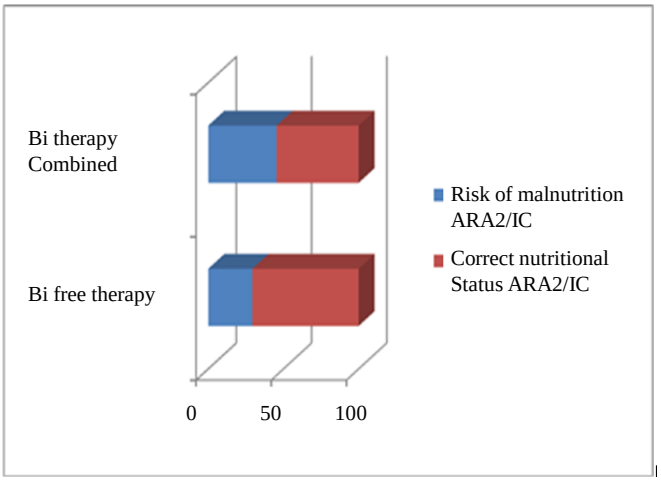

Figure 16. Risk of malnutrition and combined bitherapy (ARA2/blocker).

3.4.4. Four Therapy

30% of hypertension who were treated by a four therapy were at risk of malnutrition with an average DEM = 22.03 ± 1.26 (MNA min19 = and MNA max = 23.5).

In this same group 33.33% of them had less than 55 years with all a Dem of 23.5.

While 66.66% of them had over 70 years with an average dem of 20.58 ± 0.72 (The lowest MNA: 21.40 average DEM ± 1.93 monotherapy, an average 21.13 MNA ± 2.32 in combination therapy, and an average dem = 21.13 ± 2.12 in triple therapy).

What got us arrested, it is that all these hypertensives treated with a four that were a risk of malnutrition had diabetes or Dyslipidemia, the presence of a resistant hypertension, or other risk factors and the increase in arterial stiffness with age which justify the use has other additional antihypertensive agents for controlling these patients is probably a tipping their nutritional status.

3.5. Risk of Malnutrition and Protein Consumption

28.3% of hypertensive patients who consumed the three categories of foods recommended were at risk of malnutrition versus 67.3% who had a correct nutritional status.

This percentage increases in hypertensives who consumed less than three categories of foods: 37.8% and 39.1% for those who consumed one or two categories of foods) but it has not put in evidence a statistically significant link between the quality of food consumed and the risk of malnutrition. Odds ratio Odds ratio OR = 1.24, 95% CI % = [0.91; 1.69].

3.6. Risk of Malnutrition and Consumption of Fruits and Vegetables

The percentage of hypertension risk of malnutrition was twice more in hypertensives who did not eat at least twice per day of fruits or vegetables compared with those who consumed Odds ratio Odds ratio OR = 3.23, 95% CI % = [2.46; 4.23].

The average MNA of hypertension who ate no fruit and vegetables and who were a risk of malnutrition was 21.18 ± 2.33, it varies little in the same group (CV = 0.11) (Min = 11.5 and MNA max = 23.5).

While the average MNA of hypertension who ate fruits and vegetables and who were risk of malnutrition was 21.25 ± 2.01, it varies little in the same group (CV = 0.09) (MNA min = 15 and MNA max = 23.5).

Moreover, there in Group consumer of fruit and vegetables at risk of malnutrition, about three times less hypertensives to poor MNA ≤ 18 (6.55% in consumer Vs 20.45% in the non-consumer group).

3.7. Consumption of Drinks

The percentage of hypertension risk of malnutrition that consumed less than three glasses a day (average dem 21.18 ± 2.33) was once and a half higher than hypertension risk of malnutrition that consumed more than five glasses (Average dem 21.25 ± 2.13).

But it was difficult to establish a link between the amount of drinks consumed daily and risked malnutrition. Odds ratio Odds ratio OR = 1.07, 95% CI % = [0.73, 1.55].

On the other hand, the percentage of hypertension has risk of malnutrition to poor MNA ≤ 18 (severe undernutrition) past of 13.72% among those who consumed less than three glasses was 11.90% among those who consumed between three and five glasses then has 8.33% among those who consumed more than five glasses a day.

The average dem found varied little within the three groups.

CV = 0.11 for those who consumed less than three glasses a day.

CV = 0.08 for those consuming between three and five glasses per day.

CV = 0.10 for those consuming more than five drinks per day.

4. Discussion

Protein-energy malnutrition is frequently underestimated in the elderly, because clinical manifestations are non-specific. However all systematic studies had its high frequency in geriatrics, whatever the context of care and place of life.

The literature gives a frequency of the risk of malnutrition which can reach 25% - 30% [27] [28] until same

58% [29] from 10.8% (between 60 and 69 years) to 22% (between 70 and 79 years) p our population aged cardiovascular risk.

The survey shows that 3.14% of elderly hypertension a risk cvs are malnourished and 36.7% of them are a risk of undernutrition.

Large epidemiological studies European (Euronut-SENECA) [25] Or American (NHANES) show that approximately 4% of seniors living at home are undernourished [26].

The prevalence of undernutrition is variable depending on the populations studied (the elderly living at home, institutionalized or hospitalized) and used tools (Anthropometry, the weight loss recent, or composite tools such as the Mini Nutritional Assessment).

However, large scale studies with a valid tool (MNA) in populations older hypertendue in medicine of city are still rare.

Although the factors related to the patient such as addiction [30] [31].

The decline of appetite [30] is known to be associated with malnutrition, much less is known about the impact of chronic diseases such as hypertension and poly medication on malnutrition.

Thus adult component sample of the TAHINA study carried out in 2005 in Algeria, 25.87% chronic pathologies are represented by high blood pressure. Then come the diabetes (12.89%), asthma (8.30%), and rheumatism (8.28%).

Furthermore, the sample consists of patients followed for chronic diseases in medicine of city, thus it is not possible to report them to the general population, or to calculate prevalence.

With regard to a first survey of its kind, there is no reference in Algeria or elsewhere to assess the extent of the problem.

However, it appears clearly in the light of the results that undernutrition is a major problem in the hypertensive population of Sidi Bel Abbes.

The thresholds used to define the population of elderly ranged [18] [32] [33].

Recruited patients were over 50 years old with an average age of 65. Several authors worked on the same age group [34]-[36].

The most important mortality, cardiovascular mortality and hypertension risk factor is age. The risk of developing an HTA at age 65 is more than 90% in the Framingham study [37].

Women are the most vulnerable; the risk of malnutrition beyond 50 years is about 40%.

This very high risk could be estimated because of the higher life expectancy of women compared to men. those ci are over-represented in the population.

In the study of suominen the study population was composed of 19.3 per cent men and 80.7% of women [38].

In de Ventose R, latter equaled 173 recruits on a total of 250 [39].

Large-scale epidemiological studies propose the BMI for the estimation of the cardiovascular risk [40].

This report is also selected as one of the criteria diagnostic of malnutrition in the elderly by several learned societies the ESPEN [41], the francophone Club geriatrics and nutrition [33] the Anaes [1] and also in studies of mortality and morbidity related to undernutrition [42] [43].

For a BMI greater than or equal a 18.5 (normal or more) more than nine hypertensive ten are considered at risk of malnutrition by the MNA.

This last was recognized more sensitive than the use of BMI and serum albumin for the detection of persons at risk of bad nutrition [44].

Poly pathology is one of the most common causes of unintentional weight in elderly loss: [4].

The results show that there are more (diabetes, Dyslipidemia) associated cardiovascular risk factors, the risk of malnutrition is increased.

The pathology poly leads to a poly medication.

The drug abuse concerns not only the number of drugs but also their dosages [45]. This component has not been addressed in the MNA.

These patients are the main victims of the drug supply: it is very frequent and severe, as responsible for a sizeable hospitalization rate %), with a morbidity, mortality and consequences in terms of loss of autonomy [46].

The risk of malnutrition was multiplied by three for the hyeprtendus who took three prescription drugs or more (reasonable indication for the presence of co-morbidity).

For the francophone Club geriatrics and nutrition [47].

Poly medication, is also one of the 12 warning signs to be the possibility of undernutrition.

Despite this, the HYVET study [48] the largest study ever conducted on elderly patients and hypertensive demonstrates for the first time the beneficial effect of antihypertensive treatment even after 80 years to reduce total mortality and cardiovascular events.

The purpose of the treatment of arterial hypertension in the elderly patient is not only to bring back to normal blood pressure figures. It is important also to avoid a deterioration of the nutritional status.

In the journal of Alibhai *et al*. [4] these treatments appear as one of the most common causes of unintentional weight loss, in accordance with the recommendations of the ESPEN [41].

It thus proposes to search for possible disorders endocrine and pathologies cardiovascular to detect the risk of malnutrition the elderly [56].

A cohort of 4 714 people over 65 living at home (Cardiovascular Health Study) was monitored for 3 years [49]. Among men, 16.2% have lost more than 5% of their body weight during the 3 years of follow-up, and 4.1% have lost more than 10%.

Among women, 18.7% have lost more than 5% and 6.3% have lost more than 10%.

Compared to those who have maintained a stable weight, those who lost weight were older, more often had such pathologies.

What coronary artery disease, diabetes... and took more drugs.

Meta-analysis of Staessen *et al*. Published in 2000 [50] includes 8 test results (SHEP, Syst-Eur, Syst-China, EWPHE, HEP, STOP and MRC1, MRC2). It covers more than 15,000 patients 60 years of age and more and finds that a reduction in no 10 mm Hg would allow a reduction of 26% of deaths all-cause mortality, 22% of the risk of stroke and 7% of coronary events.

This amounts to reduce the risk of a possible unintentional weight loss directly related to the risk of malnutrition [4] [41].

So it is particularly interesting to check what are the patterns of hypertensive patients who are at risk of malnutrition? This component remains very little explored and studies are lacking.

According to the latest recommendations of the French society of Hypertension blood pressure should focus on five classes of antihypertensive agents that demonstrated a prevention of cardiovascular complications in hypertensives.

Although Co morbidities often lead to guide the choices, in order of seniority, it comes of thiazide diuretics, beta blockers, calcium channel blockers, inhibitor (INHIBITOR of the ENZYME DE CONVERSION)-converting enzyme and angiotensin 2 receptor antagonists (ANGIOTENSIN 2 receptor ANTAGONIST).

(Co morbidity the antihypertensive choice)

Diabetes, renal INHIBITOR of converting ENZYME, receptor ANTAGONIST of ANGIOTENSIN 2 heart failure, diuretic, INHIBITOR of the ENZYME of CONVERSION, beta blocker.

Coronary artery disease-converting ENZYME, β-blocker blockers Atrial Fibrillation INHIBITOR) [51].

At the same time, The risk of malnutrition in hypertensives treated monotherapy was significantly different between five classes.

Ascending, beta-BLOCKERS, ANGIOTENSIN 2, converting ENZYME INHIBITOR, CI receptor ANTAGONIST.

Finally an increased risk of malnutrition is associated with diuretics, (Approximately three hypertensive on five treaties in a diuretic monotherapy, were at risk of malnutrition with an average score of the most mediocre MNA) Crogan and al had found similar results.

Among 266 residents over age 65 living in a retirement home, was one of the factors associated with undernutrition la taken diuretics ($p = 0.004$) [52].

In the group treated with a beta-BLOCKER monotherapy, the risk of malnutrition was so low.

On the other hand, with a risk of malnutrition more or less identical, hypertension treated by an ANTAGONIST of RECEPTORS of the ANGIOTENSIN 2 seemed an average dem approaching the more than one nutritional state correct with less significant variations compared to the Group of hypertensive patients under beta BLOCKER.

In terms of cardiovascular risk The LIFE study [53] (2002), therapeutic randomized double-blind, has been shown in patients aged 55 to 80 years with LVH (mean age 70 years) and after about 5 years of follow-up, a greater reduction in cardiovascular events and including stroke, with a receptor ANTAGONIST of ANGIOTENSIN 2, as with beta blockers and this for a same drop in PA.

SCOPE study found a significant reduction in the cerebrovascular events in hypertensive patients aged over

70 years treated by angiotensin receptor antagonist 2 [54] [55].

As in several testing superiority [54] [55], the ALLHAT study [56] published in 2002 found that a calcium channel blocker or a converting ENZYME INHIBITOR had the same effect on cardiovascular events in the subgroup of patients over 65 years of age.

The risk of malnutrition turned out to be less with converting enzyme inhibitors.

The probability to control hypertensive elderly patient with monotherapy is about 30%. Most often it is useful to use the dual therapy to achieve pressure [57].

In 2006, the ENNS 2006 study showed that the pressure control was obtained by monotherapy in only a quarter of the population of treated hypertensives [58].

So SHEP (aged hypertensive subjects monitored for more than 4 years) indicates that 75% of patients should receive a combination of two drugs antihypertensives to achieve the objective of processing [59]. In the study HOT, 74% of patients in the group whose pressure is on average 140/80 mm Hg are treated with a combination of antihypertensive drugs [60].

For these older hypertensives, the risk of malnutrition was linked to the type of used dual.

The percentage of hypertension risk of malnutrition treated with free dual was significantly higher compared to hypertensive treated combined dual.

This trend is found in the recommendations of the ESC/ESH advocating the fixed-dose combinations in the treatment of hypertension because they" simplify treatment and promote compliance [61].

The choice of combinations of antihypertensive drugs is function of the associations known to be synergistic, additive.

It is recommended to start with a drug of the basket 2 (thiazide diuretics or calcium channel blocker). In case of need for a dual therapy, one can add a basket 1 drug (or ARBS or beta blocker-converting ENZYME INHIBITOR) [62].

The ARBS and converting ENZYME INHIBITOR association: to avoid because the ONTARGET study [63] [64] showed no superiority Anti hypertensive latter compared to converting ENZYME INHIBITOR alone, but more than kidney side effects. Moreover, no old hypertensive the did.

In the basket 1, and on comparing each association including converting ENZYME INHIBITOR for each association including the ANGIOTENSIN 2 receptor ANTAGONIST.

Converting ENZYME INHIBITOR proved to be more protective even though quite a few of them are incriminated in the foul which is much more common and potentially irreversible in aged hypertensives [65].

For hypertension treated with a beta-BLOCKER (with a risk of the lowest malnutrition monotherapy) associated with other classes of antihypertensives risk was strictly less than 50%.

Furthermore, the converting enzyme inhibitor bitherapy and calcium channel blocker: ACCOMPLISH showed the superiority of this association versus the INHIBITOR of the ENZYME for CONVERSION and diuretic combination [66].

Test study in France, concluded that practitioners associate preferentially an ICA rather than a diuretic, using renal impairment as a determinant of choice in patients at cardiovascular risk [67].

Although several studies (Syst-Eur [68] and STOP [69] recommend the use of the Intercity or diuretics for the treatment of hypertension in the elderly, in the basket 2, it seems that the way of the IC is better because the percentage of hypertension a risk of malnutrition under association including an IC does not exceed the 50% unlike associations including a diuretic).

The HOT [70] and the Syst-Eur study [68] provide reassuring arguments screw blockers, they are now present in all the major recommendations. Recently amlodipine has demonstrated its interest in the ALLHAT study.

Finally, in the diabetic subject and the elderly, the superiority of the association INHIBITOR of the ENZYME for CONVERSION and thiazide diuretic versus placebo demonstrated by studies ADVANCE [71] and HYVET is discordant with the results found in the risk of malnutrition [48].

This association is among those that have the highest percentages of risk of malnutrition.

For hypertension treated with a diuretic (having the highest risk of malnutrition in monotherapy and the poorer MNA) associated with an IC, an INHIBITOR of the converting ENZYME, an ANTAGONIST of RECEPTORS of the ANGIOTENSIN 2 or beta-BLOCKER risk of malnutrition was greater than or equal to 50%.

It seems, in view of the results that this class of antihypertensive agent should be handled with caution so that the pressure balance is synonymous with nutritional balance.

The Working Group HAS, in situations of the long treatment courses by diuretics, the risk of malnutrition in

the elderly is not negligible [72].

Compliance can be defined as the degree of concordance between the conduct of an individual (in terms of making drug, followed by diet and lifestyle change) and the requirements or medical recommendations [73], or more simply the ability of a person to take a treatment according to a given prescription.

In literature, this term can be replaced by adhe difference, concordance or compliance [74].

In the group free dual the percentage of hypertension risk of malnutrition as antagonist of angiotensin 2/diuretic was almost twice and a half higher than treated dual combined by the same association.

Clinical studies have shown that the association AAII + diuretic is significantly more effective than each of the components taken separately [75]-[77].

Similarly, the percentage of hypertension risk of malnutrition treated by the INHIBITOR of the ENZYME of CONVERSION/diuretic association free dual was three times higher than treated dual combined by the same association.

This association is very well tolerated clinically.

All studies show that the INHIBITOR of the ENZYME CONVERSION + diuretic association is significantly more efficient in terms of decrease in the readings that each of the components taken separately [78]-[81].

Conversely, the percentage of hypertension a risk of malnutrition treated by the association receptor ANTAGONIST of ANGIOTENSIN 2/IC free dual seems less has the group treated by the same association combined dual (29.4% vs. 45.5%) but this hypothesis remains to be confirmed because the Ods ratio was not for a true association between uses it has a dual free or combined and a possible risk of malnutrition.

The first therapeutic trials with this new fixed combination demonstrate some efficacy and good tolerability.

Contraindications to this new association are those related to each molecule taken separately [82].

In the case of triple therapy, rule HAS plans to associate the two drugs of the 2 (Diurétique thiazidique et inhibiteur calcique) basket and basket 1 drug (or ARBS or beta blocker-converting ENZYME INHIBITOR) and this outside specific situations such as co-morbidities cardiovascular (heart disease, disorders of rhythm, angina or heart failure), diabetes and violations of kidney, and particularly frequent iatrogenic risk in the elderly where the choice of treatment should be adapted [51].

In this context, the percentage of hypertension risk of malnutrition for the combination (INHIBITOR of CONVERSION the of ENZYME/IC/DIURETIC) was zero, but the number of patients was insufficient to infer a any conclusion (0.7% of all patients in the study).

On the other hand, i l seems the combination recommended by the HAS (diuretics thiazide and inhibitor calcium) basket 2 including 2 of basket 1 ANGIOTENSIN receptor ANTAGONIST was also the best in terms of risk of malnutrition with an average dem which is closest to correct nutritional status, and that the abandonment of the thiazide diuretics or calcium inhibitor increases see double the percentage of hypertension a risk of malnutrition.

Finally, one third of hypertension who were treated by a four were at risk of malnutrition, and more than half of them were over 70 years old with a low average dem (compared to monotherapy, dual and triple therapy).

What is particularly interested, is that all these hypertensives treated with a four that were risk of malnutrition had diabetes or Dyslipidemia.

The BEST study talks about the gap that exists between the recommendations of scientific bodies in cardiovascular prevention and what actually happens on the ground in high blood pressure and Dyslipidemia [83].

This finding is reinforced by the fact that the presence of a resistant hypertension, which justify the use of other additional antihypertensive agents for controlling these patients is probably a tipping their nutritional status.

5. Conclusions

The survey clearly shows that there is a risk of malnutrition in elderly patients of Sidi Bel Abbès; the latter is likely under estimated in hypertensives.

So the clinician must be more attentive to malnutrition because screening is not only easy but also a tool that we can act today on risk factors so that blood pressure can control rhymes with nutritional balance.

This is one of the particular challenges in the field of cardiovascular prevention.

In our country, the current period can be considered as a period in which public authorities should develop offensive strategies of prevention and struggle for control of the future nutritional situation.

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Abbreviations

quadrithérapie = quadruple therapy

BB: beta blockers

IEC or Inhibitor of the enzyme of conversion: ACE inhibitor

ARA 2, or angiotensin 2 receptor antagonists: receptor antagonists of angiotensinogen 2

IC or CI: calcium channel blockers

International Journal of Clinical Medicine, 2016, 7, 169-175
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.72017

Scientific Research Publishing

NEM® Brand Eggshell Membrane Effective in the Treatment of Pain and Stiffness Associated with Osteoarthritis of the Knee in an Italian Study Population

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Received 19 January 2016; accepted 24 February 2016; published 29 February 2016

Abstract

A single-center, open-label clinical study was conducted to evaluate the efficacy and safety of NEM® as a natural treatment for pain and stiffness associated with osteoarthritis of the knee in an Italian population. NEM® brand eggshell membrane is a unique dietary supplement that contains naturally occurring glycosaminoglycans and proteins essential for maintaining healthy joints and connective tissues. Twenty-five subjects received oral NEM®, 500 mg once daily for four weeks. The primary outcome measure was to evaluate the mean effectiveness of NEM® in relieving general pain associated with moderate osteoarthritis of the knee at 10 and 30 days utilizing a 10-question, abbreviated questionnaire based on the WOMAC osteoarthritis questionnaire. Supplementation with NEM® produced a significant treatment response from baseline at both 10 days and 30 days for composite pain (40.6% reduction, $p < 0.001$; 66.4% reduction, $p < 0.001$, respectively). There was also a statistically significant concurrent reduction in analgesic use during the 30-day study period. Additionally, a significant treatment response from baseline was also observed for composite stiffness at both 10 days and 30 days (22.2% reduction, $p = 0.009$; 59.7% reduction, $p < 0.001$, respectively). There were no adverse events or serious adverse events reported during the study and the treatment was reported to be well tolerated by study participants. NEM® is an effective and safe natural therapeutic option for the treatment of both pain and stiffness associated with osteoarthritis of the knee. Supplementation with NEM®, 500 mg taken once daily, significantly reduced both pain and stiffness rapidly (10 days) and this effect continued to improve through 30 days. There was also a meaningful reduction in the amount of analgesic consumed on a weekly basis, which further enhanced patients' safety.

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How to cite this paper: Brunello, E. and Masini, A. (2016) NEM® Brand Eggshell Membrane Effective in the Treatment of Pain and Stiffness Associated with Osteoarthritis of the Knee in an Italian Study Population. *International Journal of Clinical Medicine*, **7**, 169-175. http://dx.doi.org/10.4236/ijcm.2016.72017

Keywords

Knee, Osteoarthritis, Supplement, Egg Shell Membrane, Glycosaminoglycans

1. Introduction

Osteoarthritis (OA) is a degenerative disease primarily affecting the cartilage of articular joints and is frequently accompanied by varying degrees of joint pain and stiffness in afflicted subjects. OA is one of the most common causes of chronic pain in adults 65 and older and often leads to disability as the disease progresses [1]. Estimates of the prevalence of OA in European populations vary widely, however, two recent studies conducted in Italy found the prevalence of knee OA to be 29.8% [2] and 36.7% [3]. The pain associated with these maladies can be quite debilitating and few treatment options exist outside of easing symptoms. This usually involves the use of analgesics (e.g. acetaminophen, hydrocodone) or non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen, celecoxib, etc.), alone or in combination. Most of these treatments have shown limited effectiveness in randomized controlled clinical trials (RCTs) [4]-[6] or are known to have significant and sometimes severe side effects [7] [8]. NEM® brand eggshell membrane has previously demonstrated good efficacy in relieving joint pain and stiffness in multiple clinical trials in the U.S. [9] [10] and recently in a German population [11].

Eggshell membrane is primarily composed of fibrous proteins such as Collagen Type I [12]. However, eggshell membranes have also been shown to contain other bioactive components, namely glycosaminoglycans (*i.e.* dermatan sulfate [13], chondroitin sulfate [13], hyaluronic acid [14], etc). ESM Technologies, LLC (Carthage, MO, USA) has developed methods to efficiently and effectively separate eggshell membrane from eggshells on a commercial metric-ton scale. The isolated membrane is then partially hydrolyzed using a proprietary process and dry-blended to produce NEM® brand eggshell membrane. Compositional analysis of NEM® conducted by ESM Technologies has identified a high content of protein and moderate quantities of glucosamine (up to 1% by dry weight), chondroitin sulfate (up to 1%), hyaluronic acid (up to 2%), and collagen (Type I, up to 5%).

The single-center trial reported here was designed to evaluate the efficacy of this natural arthritis treatment in an Italian population and to confirm the results found previously in the U.S. and Germany. Therefore, a 1-month open-label study was conducted at a single clinical site in Italy to evaluate the efficacy and tolerability of NEM® for the relief of the pain and discomfort associated with osteoarthritis of the knee.

2. Patients and Methods

2.1. Study Design

The study was conducted according to a prospective, single-center, open-label design and was conducted in Italy in accordance with the International Conference on Harmonization guideline for the principles of Good Clinical Practice (ICH E6) and the Declaration of Helsinki. Patients provided their written informed consent to participate. The clinical investigators were not blinded to treatment (open-label). Treatment consisted once daily orally of 500 mg of NEM® in vegetarian capsules that were stored in closed containers at ambient temperature. Clinic visits were scheduled for subjects at study initiation and at 10 days and 30 days following the onset of treatment. Treatment compliance was checked at clinic visits by patient interview and by counting the number of unused doses of the study medications. Analgesics (*i.e.* acetaminophen) were allowed for pain relief, as needed. Subjects recorded the time and amount of analgesic taken in patient diaries.

2.2. Patients

All subjects 18 years of age or older who were seeking relief of mild to moderate pain due to osteoarthritis of the knee were considered for enrollment in the study. In order to be eligible, subjects must have had moderate persistent pain in the knee associated with osteoarthritis and must have had baseline scores within the range of 4 - 7 on questions 1, 2, & 5 dealing with joint pain. Subjects that were currently taking analgesic medications daily, currently taking glucosamine, chondroitin sulfate, MSM, or collagen were ineligible to participate in the study. Patients were excluded if they were currently receiving remission-inducing drugs such as methotrexate or im-

munosuppressive medications or had received them within the past 3 months. Other exclusionary criteria were: a known allergy to eggs or egg products, or pregnant or breastfeeding women. Subjects participating in any other research study involving an investigational product (drug, device, or biologic) or a new application of an approved product, within 30 days of screening were also excluded from participating in the trial.

2.3. Location of Patients

The majority of patients were enrolled in an area of 50 km around the city of Verona, the capital of the homonymous province, where the Medical center REGENESIS is located, others patients come from different provinces, in particular Trento, Vicenza, Padova and Pordenone. The map below shows the different origins of the patients.

2.4. Treatment Response

The primary outcome measure of this study was to evaluate the mean effectiveness of NEM® in relieving general pain associated with moderate osteoarthritis of the knee (composite score of Questions 1 - 8). A composite score was calculated as the sum of the questions of interest. Additional outcome measures were to evaluate general stiffness (composite score of Questions 9 & 10), analgesic use during the study, and non-composite mean results for all 10 individual questions. The primary treatment response endpoints were the 10-and 30-day patient assessments utilizing a 10-question short-form questionnaire (see **Figure 1**) derived from the Western Ontario & McMasters Universities Osteoarthritis Index (WOMAC) questionnaire. Each question included a zero to 10 analog Likert-scale, with zero equating to no pain (or no stiffness) and 10 equating to most severe pain (or most severe stiffness). Patients were asked to mark a number corresponding to the perceived pain (or stiffness) from the affected treatment joint (s). Endpoints were then compared to pretreatment assessments.

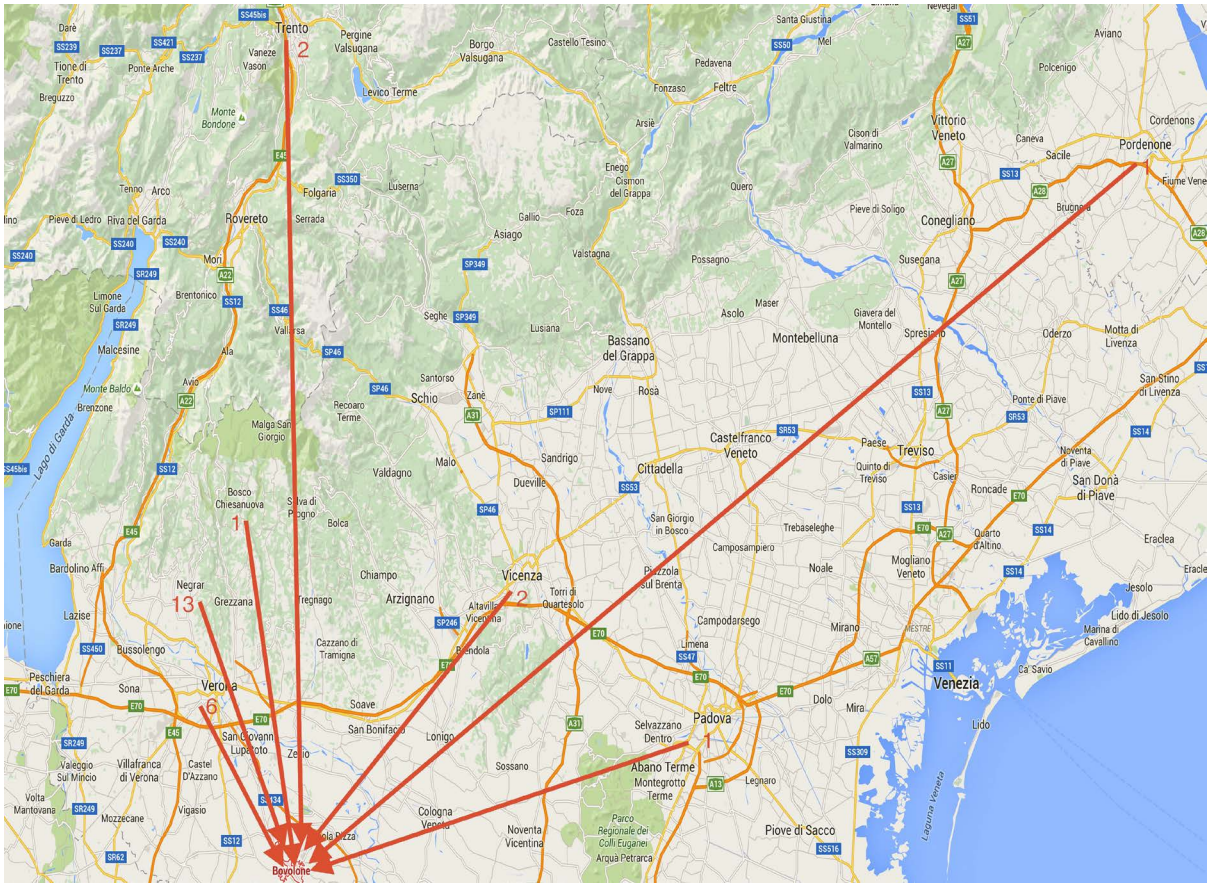

Figure 1. Questions used in the short-form questionnaire completed by study participants.

Question 1: *Pain when walking on level ground*?
Question 2: *Pain when going up or down stairs*?
Question 3: *Pain while at rest* (*i.e. sitting, lying down, etc.*)?
Question 4: *Pain when sitting with legs bent for an extended period of time* (*i.e. in a car, at a theater, etc.*)?
Question 5: *Pain when getting up from a seated position*?
Question 6: *Pain when getting in and out of a car, a bathtub, etc.*?
Question 7: *Pain when bending, stooping, or kneeling*?
Question 8: *Pain when putting on socks or pantyhose*?
Question 9: *Stiffness when first getting up from bed in the morning*?
Question 10: *Stiffness when sitting, laying, or resting later in the day*?

2.5. Adverse Events

A secondary objective of this study was to evaluate tolerability and any adverse reactions associated with supplementation with NEM®. The subjects' self-assessment diaries were reviewed and any discomfort or other adverse events were recorded and reported in accordance with applicable ICH Guidelines. Adverse events and serious adverse events were assessed by the clinical investigator at each study visit and followed until resolution, as necessary. Serious adverse events were required to be reported to the clinical investigator immediately.

2.6. Statistical Analysis

As this was an open-label study, a simple single-group sample size estimate [15] was performed for statistical power determination for a continuous variable. In the similar trial with NEM® conducted in Germany [11], the mean standard deviation for the study subjects for pain was 1.55 points. We hoped to be able to detect a 1.5 point difference from baseline within the 10-point Likert scale. Therefore a minimum of 18 subjects would need to be enrolled to have a 95% likelihood of detecting the expected improvement with a statistical power of 80%. Post-baseline statistical analyses were done as repeated measures Analysis of Variance (rm-ANOVA). Items found to have statistical significance with rm-ANOVA were then compared using a Wilcoxon test for dependent samples. Statistical significance was accepted at $p < 0.05$. Analysis of the primary outcome measure (the change from baseline in general pain levels) was conducted in the per protocol population. SPSS Statistics V19.0 was used for all statistical analyses [16].

3. Results

Patient recruitment began in May 2014 at a single clinical site in Italy and the final follow-up was conducted in July 2014. A total of twenty-five subjects between the ages of 43 and 81 were enrolled with osteoarthritis of the knee. Of these subjects, twenty (80%) were female and five (20%) were male. Of the twenty-five subjects with knee OA, 10 (40.0%) had bilateral incidence. Patient demographics are reported in **Table 1**. All twenty-five

Table 1. Patient demographics.[a]

Age, yrs	69.4 ± 9.6
Sex	
Male (%)	5 (20)
Female (%)	20 (80)
Height, cm	165.8 ± 7.0
Weight, kg	71.0 ± 10.5
Body-mass Index	25.8 ± 3.2
Affected Joint	
Knee (l, r, bilateral)	25 (5, 10, 10)

a. Except where indicated otherwise, values are reported as mean ± standard deviation (SD) (n = 25). BMI was determined as weight in kilograms divided by height in meters squared.

subjects completed the one month study per the protocol. Compliance with the study treatment regimen was good.

A clinical comparison of valid subjects was carried out to obtain mean baseline scores for each of the ten questions from the subject questionnaire, as well as the 10-day and 30-day endpoints. Statistical analysis of the primary outcome measure revealed that supplementation with NEM® produced a significant treatment response from baseline at both 10 days and 30 days for composite pain (40.6% reduction, $p < 0.001$; 66.4% reduction, $p < 0.001$, respectively) (see **Figure 2(a)**). There was also a statistically significant concurrent reduction in analgesic use during the 30-day study period. At baseline, subjects consumed analgesic slightly less than one day per week on average, and this dropped 78.3% ($p = 0.017$) to 0.2 days through the 10-day endpoint. All 25 subjects consumed no analgesic through the final 3 weeks of the study ($p = 0.003$) (see **Figure 2(b)**). A significant treatment response from baseline was also observed for composite stiffness at both 10 days and 30 days (22.2% reduction, $p = 0.009$; 59.7% reduction, $p < 0.001$, respectively) (see **Figure 2(c)**). Supplementation with NEM® also produced a significant treatment response from baseline after 10 days when replying to Questions 1 - 5 & 7 - 8 (30.2% to 50.0% improvement) and at 30 days for all eight pain-related questions evaluated (50.9% to 78.9% improvement) (see **Table 2**). Treatment response fell shy of statistical significance for Question 6 at 10 days ($p = 0.190$). Similarly, a significant treatment response for stiffness was found at 10 days (Question 9) (27.7% improvement) but fell just shy of significance for Question 10 (15.4% improvement, $p = 0.069$). There was also a significant treatment response at 30 days for both stiffness-related questions (Q9 & Q10) (53.2% & 69.2%, respectively). There were no adverse events or serious adverse events reported during the study and the treatment was reported to be well tolerated by study participants.

4. Discussion

Osteoarthritis is very common in Italy with about one-third of the population having some form of the disease [2] [3]. This has a large impact on the quality of life of those afflicted with OA [17]. This open-label clinical trial was designed to evaluate the efficacy of NEM® as a natural arthritis treatment in an Italian population and to further validate the extension of the body of clinical evidence for NEM® from the United States to the general European population. The study demonstrated that NEM® is effective and safe for treating both pain and stiffness associated with osteoarthritis of the knee and results in the use of less analgesic medication.

Study subjects experienced relatively rapid (10 days) responses for both composite pain (40.6% improvement) and composite stiffness (22.2% improvement). By the end of the follow-up period (30 days) the mean response for composite pain and stiffness had increased substantially (66.4% improvement & 59.7% improvement, respectively). These results are quite similar to results from previous clinical studies of NEM® that were conducted in the U.S. [9] [10] and is a somewhat larger effect than what was found recently in a German population [11]. This difference may be a result of a small difference in mean pain at baseline between the two study populations (4.6 compared to 4.9 in Germany). Both studies showed statistically significant treatment effects at 10

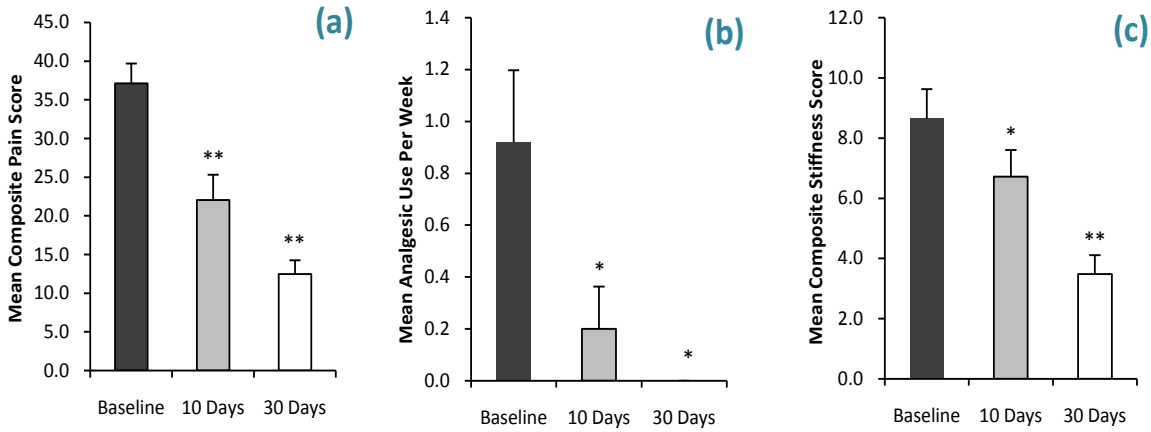

Figure 2. Mean composite pain score (**a**), mean analgesic user per week (**b**), and mean composite stiffness score (**c**) at baseline and 10 & 30 days of supplementation. Values are reported as means ± standard deviation (SD) (n = 25). *$p > 0.05$, **$p < 0.001$

Table 2. Mean values by question in an NEM-supplemented treatment group at baseline and 10 & 30 days post-treatment.

	Days Post-Treatment	Mean ± SD	Percent Improvement	*P*-value[a]		Days Post-Treatment	Mean ± SD	Percent Improvement	*P*-value[a]
Question 1	Baseline (n = 25)	5.1 ± 0.3	-	-	Question 6	Baseline (n = 25)	2.9 ± 0.6	-	-
	10 (n = 25)	3.1 ± 0.5	39.2%	<0.001**		10 (n = 25)	2.2 ± 0.6	24.1%	0.190
	30 (n = 25)	2.0 ± 0.5	60.8%	<0.001**		30 (n = 25)	0.9 ± 0.2	69.0%	0.002*
Question 2	Baseline (n = 25)	5.6 ± 0.4	-	-	Question 7	Baseline (n = 25)	5.3 ± 0.6	-	-
	10 (n = 25)	3.1 ± 0.6	44.6%	<0.001**		10 (n = 25)	3.7 ± 0.5	30.2%	0.005*
	30 (n = 25)	1.7 ± 0.4	69.6%	<0.001**		30 (n = 25)	2.6 ± 0.3	50.9%	<0.001**
Question 3	Baseline (n = 25)	3.2 ± 0.6	-	-	Question 8	Baseline (n = 25)	3.8 ± 0.6	-	-
	10 (n = 25)	1.6 ± 0.5	50.0%	0.031**		10 (n = 25)	1.9 ± 0.5	50.0%	0.006*
	30 (n = 25)	0.8 ± 0.3	75.0%	<0.001**		30 (n = 25)	0.8 ± 0.3	78.9%	<0.001**
Question 4	Baseline (n = 25)	5.6 ± 0.4	-	-	Question 9	Baseline (n = 25)	4.7 ± 0.6	-	-
	10 (n = 25)	3.5 ± 0.4	37.5%	<0.001**		10 (n = 25)	3.4 ± 0.5	27.7%	0.018*
	30 (n = 25)	1.9 ± 0.3	66.1%	<0.001**		30 (n = 25)	2.2 ± 0.4	53.2%	<0.001**
Question 5	Baseline (n = 25)	5.6 ± 0.3	-	-	Question 10	Baseline (n = 25)	3.9 ± 0.5	-	-
	10 (n = 25)	3.0 ± 0.5	46.4%	<0.001**		10 (n = 25)	3.3 ± 0.5	15.4%	0.069
	30 (n = 25)	1.8 ± 0.4	67.9%	<0.001**		30 (n = 25)	1.2 ± 0.3	69.2%	<0.001**

a. *P*-values were determined by Wilcoxon test for dependent samples following a statistically significant difference as determined by rm-ANOVA, and represent treatment versus baseline. *****$p < 0.05$, ** $p < 0.001$.

days, so this is not too concerning. Study subjects also experienced large improvements in particular aspects of pain when reviewing the individual questions from the short-form questionnaire. For example, at 30 days there was a 75% improvement in pain while at rest (Question 3) and a 79% improvement in pain when putting on socks or pantyhose (Question 8). Likewise, pain when going up and down stairs (Question 2) and pain when getting in and out of a car, bathtub, etc. (Question 6) were both improved by nearly 70%. This broad treatment effect relating to numerous activities of daily living should have a profound impact on the subjects overall quality of life. This should also help them to remain active as they age, which is also important to other aspects of health (*i.e.* cardiovascular disease, neurodegenerative disease, etc.).

The safety profile for NEM® was again found to be excellent as there were no reports of adverse events or serious adverse events associated with treatment. This was comparable to the clinical trials conducted with NEM® previously [9]-[11]. No side effects from consuming NEM® have so far been identified, excluding the obvious egg allergy concern. This is very important in a disease like osteoarthritis that requires long-term treatment. The analgesics and NSAIDs normally used to treat such conditions are known to lead to gastric [7] and cardiovascular [8] complications which can considerably increase mortality in an elderly population.

The trial had a limited enrollment (25 subjects), however no subjects withdrew from the study and there was good treatment compliance. As the trial was also open-label, there is the obvious issue of the placebo effect. The inclusion of a placebo control would have provided greater clinical clarity, however it would have required a substantially larger study population. These limitations are minor when considering the totality of the available clinical evidence for the use of NEM® in joint and connective tissue disorders.

5. Conclusion

It is important for patients to have treatment options that are both safe and effective in managing chronic diseases such as osteoarthritis, especially in Italy where about one-third of the population is affected. The reporting of the results from this single-center, open-label clinical study demonstrates that NEM® brand eggshell membrane is a viable natural treatment option for the management of osteoarthritis of the knee. In this clinical study, NEM®, 500 mg taken once daily, significantly reduced both composite pain and stiffness rapidly (10 days) and this effect continued to improve through 30 days. There was also a meaningful reduction in the amount of analgesic consumed on a weekly basis, which further enhanced patients' safety.

Acknowledgements

The study was sponsored by Phytonaturesas. Dr. Emy Brunello and Dr. Antonio Masini are employed by the sponsor. The authors would like to acknowledge ESM Technologies, LLC for providing the NEM® study material for this trial.

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ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
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