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JOURNAL OF GERONTOLOGY AND GERIATRICS

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Neurological “awakening” in old age: vibration therapy as a nonpharmacological approach

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Background: Population ageing raised new health issues driving medical sciences to seek novel complementary therapies. In the elderly, a cognitive stimulation that counteracts neurological ageing could improve both reaction time (decreased fall risk) and life quality (chronic pain improvement). The principal aim of the present study was to evaluate vibrational treatment efficacy in reaction time improvement in subjects with aging-related diseases.

Methods: A Discovery and a Validation cohort of 28 and 38 subjects, with aging-related disease were prospectively enrolled at the ORPEA’s “Casamia” in Borgaro and Richelmy facility in Turin (Italy). An additional cohort of 10 age – and gender – matched subjects were included as control group. Both intervention and control group underwent vibrational treatment, and its efficacy was assessed by measuring reaction time to external stimuli before and after each single treatment session.

Results: Compared to controls, a significant improvement in reaction time was already observed after the first vibrational treatment session in subjects that underwent vibrational therapy (0.74 ± 0.46 vs 0.57 ± 0.24 s, $p = 0.134$ and 0.69 ± 0.43 vs 0.54 ± 0.24 s, $p < 0.001$, respectively). Treated subjects showed an overtime cumulative improvement of reaction time until end-of-treatment (treatment response rate: 79%). In addition, the improvement in the reaction speed obtained at the first vibrational therapy was able to predict response at end of treatment (OR = 10.83, 95% CI 1.83-64.03; $p = 0.009$). Finally, responsive subjects showed, between the first and last sessions, a progressive decline in absorbed energy compared to non-responders in whom the energy absorption was a continuum.

Conclusions: Subjects with aging-related disease may benefit from vibrational treatment showing a significant improvement in reaction time after therapy administration. Further, the possibility to promptly identify responsive subjects, may allow a cost-effective personalized therapy.

Key words: Vibrational Therapy, Gerontology, Non-pharmacological therapy, Cognitive stimulation, Active aging

INTRODUCTION

In older people, neurological slowdown and osteoarticular conditions are a priority in terms of health care and risk prevention, not only for the individuals themselves but also in the broader context of public health¹. Considering the risks deriving from falls and accidents depending either on personal factors (cognitive impairment, muscular and skeletal deficiencies, impaired visual, proprioceptive or vestibular function etc.² or

on external factors (such as dangerous obstacles in the person’s surroundings or daily activities), and the psychophysical impact of treatment and rehabilitation, make this a topic of significant importance³. In addition, falls in older people can be harmful also at a psychological level: reduction (sometimes total) of quality of life, loss of personal security, or simply the fear of falling are themselves devastating factors that can influence the functional decline of the older person, potentially leading to depression or social isolation⁴.

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Vibrational therapy is a non-pharmacological type of therapy developed in the 1990s in the USA that uses electric frequencies of pure wavelength in the audio field, which interact with the energy systems of the body. It thereby activates a process that can stabilize and correct any altered physical condition in specific parts of the body, restoring its balance⁵. On this basis, FMG Group (Turin, Italy) has developed an innovative technology consisting of a programmable oscillator controlled by a microprocessor able to generate frequencies that resonate with any cell-type of the human body. The equipment has been validated and certified by the pertinent Italian authority. The methodological approach is based on the following: use of electronic impulses at low and middle voltage; reading of electrical skin resistance as a parameter for the functional assessment of the organism; search for localized imbalances through variations in electrical skin conductance. Previously, we tested vibrational therapy efficacy in 142 subjects affected by osteoarticular diseases. After treatment, we observed an improvement of pain (VAS scale) and joint mobility (Beighton scale) in 93.6% and 76.8% of treated subjects, respectively. In another study, we tested the clinical usefulness of vibrational therapy in 48 athletes suffering from tendinitis and/or bursitis and we found that 95.8% experienced an improvement in pain scores, while 72.9% showed improved joint mobility (unpublished data). Considering the social and clinical relevance of active aging and medical science efforts in research and development of complementary therapies⁶⁻⁸, we aimed to test the clinical efficacy of vibrational therapy in older persons assessing the improvement in reaction time to immediate stimuli following treatment administration.

MATERIALS AND METHODS

STUDY DESIGN

Between October and December 2015, a total of 28 subjects were recruited the ORPEA S.A. nursing home "Casamia" in Borgaro, Turin, for an initial observational study to test the effect of vibrational therapy on their reactivity (Discovery cohort). Subsequently, between April and June 2016, a total of 48 subjects matched for age and aging-associated illnesses both among themselves and with respect to the previous group, were recruited at ORPEA's Richelmy facility in Turin (Validation cohort). Exclusion criteria were the presence of pacemakers, joint implants or metal osteosynthesis implants, dermatitis, epilepsy, cancer, and spasticity. The volunteers signed an informed consent form. Ethical approval was not required since vibrational therapy is not considered a medical treatment by Italian Law.

VIBRATIONAL THERAPY ADMINISTRATION

Vibrational therapy was administered by means of dedicated equipment consisting of a portable delivery device, two virgin electrodes and a connecting cable, a computer with a DHCP network, an RFID card for the study participant, a programmer device to load the frequencies sequence onto the device, and a charger rack. The electrodes were placed on the distal third of each forearm after the skin had been cleansed with an alcohol solution (Figs. 1 and 2).

The frequency settings were imported from a central database. Subjects of Discovery cohort underwent a single session of vibrational therapy, whereas each study participant of Validation cohort underwent a total of six treatments at three-weekly intervals. The participant had to perform a reactivity test that consisted of pressing a button as quickly as possible after receiving a light signal at random intervals for five times (T0 test; initial reaction time). At the end of the test, a dedicated software application calculated the average reaction time and showed the individual results reported in seconds (s). When this first phase was completed, the subject underwent a vibrational therapy session for 16 minutes, after which the test was repeated (T1 test). To the control group of 10 subjects no frequency was administered, and the control subjects were not informed of the absence of treatment.

To evaluate the response to vibrational therapy, we compared the reaction times within the same group to assess progress over time and between groups to assess the efficacy of therapy with respect to the untreated group. Response to therapy was defined as an improvement of the reaction speed between the last and the first session. A centralized information system stored and managed the data of each participant, producing a graph after each session that showed the power curves and the absorbed electrical energy. The energy chart (power absorption relative to time of administration) provided the total energy delta between the first administration and the last.

The Physics basics supporting the vibrational therapy approach are listed in Figure 3.



Figure 1. PC with software for reaction speed measurement.



Figure 2. Equipment and operating procedure. **A:** Portable dispenser of vibrational therapy, two virgin electrodes, connecting cable, client card, charger rack for portable devices, configurator to load programs into the portable device **B:** Application of electrodes. Administration of vibrational therapy. Absorbed electrical energy. The energy chart (power absorption relative to time of administration) provided the total energy delta between the first administration and the last. The physics basis supporting the vibrational therapy are listed in Figure 3.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean \pm standard deviation (SD). The t-Student test were used to analyze continuous variables according to normal distribution. Data normality was checked by D’Agostino-Pearson normality test. Kinetics of reaction times were analyzed by ANOVA for repeated measures. Association between variables was analyzed by logistic regression analysis. For all analyses, a $p < 0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc software version 12.7.0.0 (MedCalc, Ostend, Belgium).

RESULTS

DISCOVERY COHORT

Administration of vibrational therapy to the 28 subjects

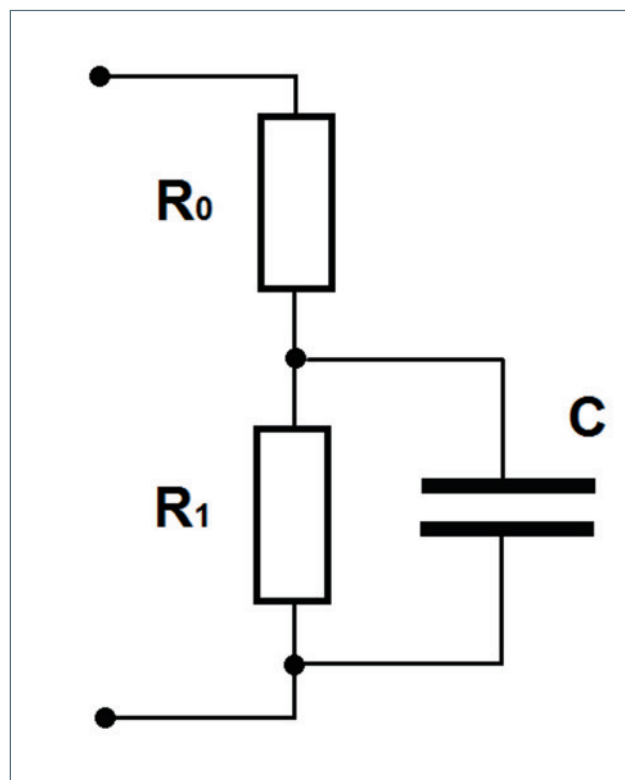


Figure 3. Electrotechnical theory. R_0 is the residual resistance part or minimum value below which it is not physically possible to go underneath; R_1 is in parallel resistance to the capacitive part of the human body; C is the capacitive part and its counterpart in resistance named reactance X_C . X_C is inversely proportional to frequency and capacitance, so higher frequency values lead to lower X_C values, consequently generating higher current, power and energy absorption values. For all three components R_0 , R_1 , C (X_C) it is not known how they change with temperature, body hydration, mood and physical states or other physiological parameters. The whole of the three components is called Z-impedance, and with these assumptions, being not a magnitude constant in time even at the same frequency, it is certainly possible that it increases in some sessions then decreases and increases again. Increasing Z leads to lower absorbed power and therefore to lower absorbed energies, inversely a decrease in Z leads to an increase in power and absorbed energy.

(minimum age of 60 years, 17 males and 11 females) of Discovery cohort demonstrated a measurable improvement of the reaction speed after administration of a single series of therapeutic sequences (pre-treatment: 1.72 ± 0.85 s vs post-treatment: 0.97 ± 0.49 s; $p < 0.001$).

VALIDATION COHORT

The study participants included in Validation cohort were men and women with a minimum age of 60 years and intact cognitive abilities who were randomized into

Table I. Reaction time and adsorbed energy according to vibrational treatment session in intervention and control group.

Study participants	Session	T0 (s)	T1 (s)	E (J)	p
Cases	1	0.69 ± 0.43	0.54 ± 0.24	18.14 ± 4.95	< 0.001
	2	0.54 ± 0.30	0.49 ± 0.22	18.17 ± 4.70	0.053
	3	0.52 ± 0.29	0.49 ± 0.23	17.62 ± 5.00	0.197
	4	0.49 ± 0.16	0.52 ± 0.31	18.10 ± 5.60	0.545
	5	0.49 ± 0.20	0.46 ± 0.21	18.83 ± 6.14	0.068
	6	0.53 ± 0.26	0.45 ± 0.13	16.18 ± 5.81	0.026
Controls	1	0.74 ± 0.46	0.57 ± 0.24		0.134

The p value was calculated by means of Student's t-test for paired data and refers to the comparison between T0 and T1.

two groups: an intervention group (38 subjects; 24 women, 14 men) and a control group (10 subjects). Intervention and control group were comparable in terms of demographic and clinical characteristics.

Among Validation cohort, a significant improvement in reaction time was already observed after the first vibrational treatment session in subjects that underwent vibrational therapy (0.69 ± 0.43 vs 0.54 ± 0.24 s; $p < 0.001$), whereas no significant improvement was observed in control group (0.74 ± 0.46 vs 0.57 ± 0.24 s; $p = 0.134$) (Tab. I). Moreover, treated subjects showed an overtime cumulative improvement of reaction time until end-of-treatment (ANOVA for repeated measures, $p < 0.001$). Overall, 30 out of 38 (79%) treated subjects showed reaction time improvement. In addition, response to first treatment session seems able to predict end-of-treatment response (univariate logistic regression, OR = 10.83, 95% CI 1.83-64.03; $p = 0.009$). The mean value of absorbed energy at the first treatment was 18.14 ± 4.95 J, while the median value at the end of the vibrational therapy was 16.18 ± 5.81 J ($p < 0.001$). In addition, the energy absorbed during the first treatment (> 18.5 J) was associated with an improved reaction to the stimulus (OR = 9.00, 95% CI 2.13-37.98; $p = 0.003$).

Of the 38 members of the intervention group, 30 (79%) were responsive to vibrational therapy. No significant differences were observed in demographic and clinical features between responders and non-responders. Analyzing the kinetics of the reaction time before treatment (T0; Fig. 4) and after treatment (T1; Fig. 5), we observed significant variation in the kinetics of the reaction times at T0 ($p < 0.001$) but not in that at T1 ($p = 0.185$). In addition, the two kinetics were significantly different from each other ($p = 0.036$) (Fig. 6). The improvement in the reaction speed obtained at the first vibrational therapy session was significant in predicting the response at the end of treatment, which in this study was set at the sixth session (OR = 10.83, 95% CI 1.83-64.03; $p = 0.009$).

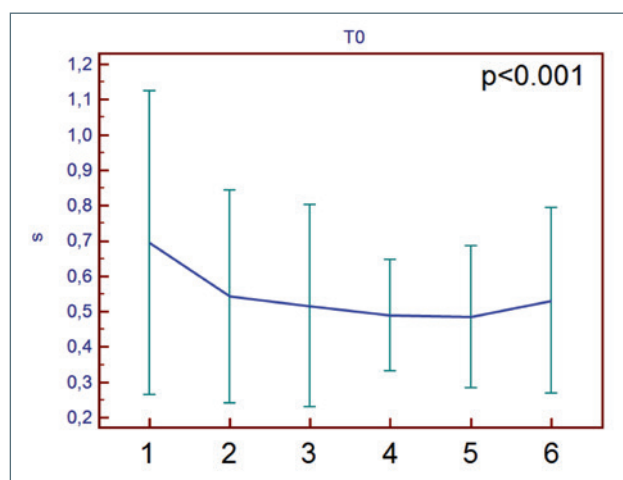


Figure 4. Average reaction times before each treatment (T0) in the course of 6 sessions.

With regard to energy absorption, responsive subjects show a progressive decline in absorbed energy between the first and last sessions and consequently further administration of vibrational treatment sessions does not alter the general tendency towards decline (Fig. 7A). In contrast, subjects not responding or relapsing, show the energy absorption is the same or even higher than the previous one (Fig. 7B). This is the consequence of a Z impedance decline among first and last session.

DISCUSSION

In the present study we analyzed the efficacy of vibrational therapy among older persons and we observed a significant improvement in reaction time in both Discovery and Validation cohort. Among the latter, 30 participants (79%) were responsive to the treatment, with significant changes in kinetics of the reaction times and also between the first and the last session. In addition, the improvement in the reaction speed obtained at the first vibrational therapy session was able to predict

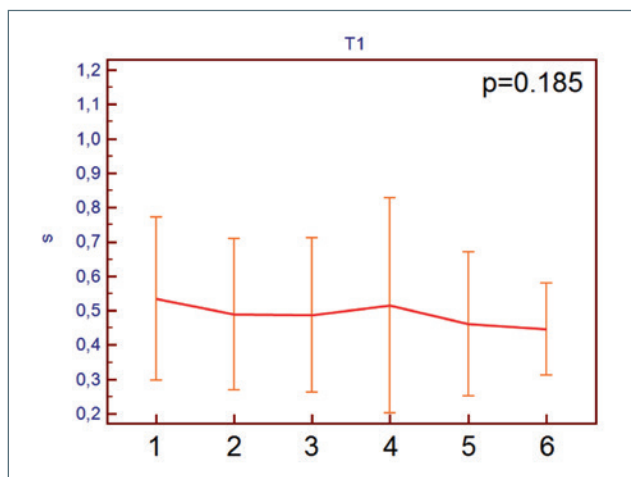


Figure 5. Average reaction times after vibrational therapy (T1) during the 6 sessions.

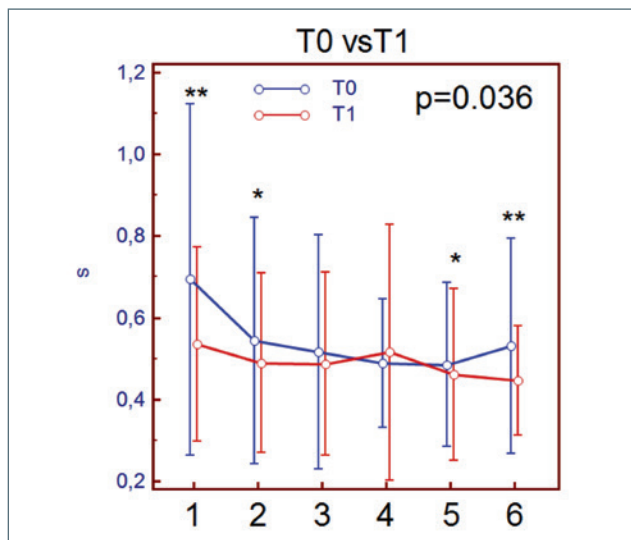


Figure 6. Comparison of the reaction times before and after vibrational therapy (T0 vs T1) during the 6 sessions.

response at the end of treatment (OR = 10.83), implying relevant clinical and economic implications. Regarding non-responders subjects, no differences were observed in demographic and clinical features compared to those who responded to vibrational therapy. To date, we are unable to identify potential variables affecting treatment outcome. Indeed, considering the system oscillator-human body as an electrical circuit, Z impedance could be affected by several physiological parameters including body temperature, body hydration and mood, electrodes efficiency (use condition) thus conditioning treatment efficacy. The latter variable may be easily controlled by the operator himself, by reading

the electrodes manufacturer recommendation about the maximum number of times to be used before their electrical conductivity is widely deteriorated.

Regarding kinetics of reaction time, we observed significant variation in the kinetics of the reaction times at T0 ($p < 0.001$) but not in that at T1 ($p = 0.185$); moreover the two kinetics were significantly different ($p = 0.036$). This can be explained by the fact that subjects undergoing vibrational therapy showed improved reaction speed already after the first session; the improvement was durable and tended to accumulate in the course of subsequent sessions. With regard to the kinetics at T1, the absence of any significant variation over time might be due to the attainment of the physiological reaction limit of the study participants. It is likely that, with a number of sessions greater than six, as shown in previous studies, the two kinetics will tend to overlap, indicating the moment the vibrational therapy can be ended.

Finally, responder subjects showed a progressive decrease in absorbed energy, while no significant variations was reported in the controls. This feature suggests a correlation between the absorbed energy and functional status, allowing to establish objectively that the treatment has reached its goal and can therefore be ended. Indeed, the reduction of energy absorption, constantly visible to the monitor, was significantly associated with both symptomatic improvement and mobility improvement. It is possible to affirm, with the evidence-based results, that there is a correlation

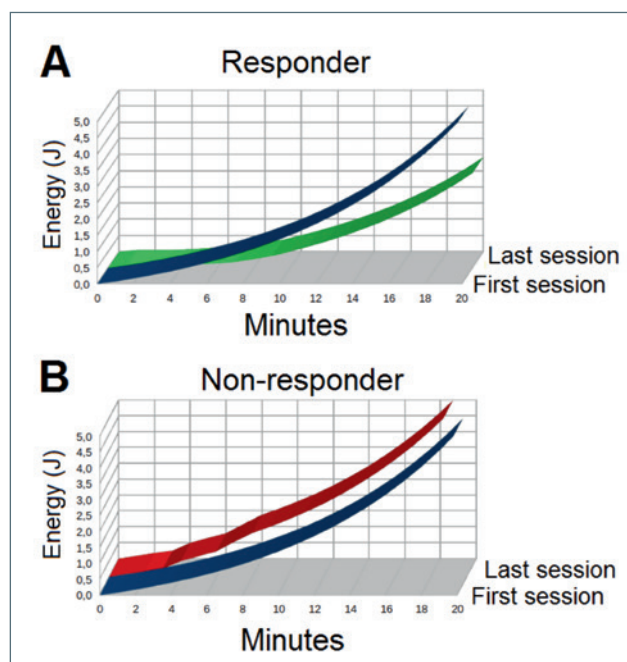


Figure 7. Cumulative dispersion chart of absorbed energy (on screen image) of responsive (A) and non-responsive subjects (B).

between the absorbed energy and the state of functionality. This allows to objectively evaluate the level of malfunction and to quantitatively evaluate the state of efficiency of the biological system. In contrast, in non-responsive subjects, a continuum of energy absorption was observed.

Compared with the currently available electrical stimulation-based practices, this new method has the advantage of not being administered to separate districts of the body but to produce a transfer of energy from the device to the whole body, creating a dynamic and modifiable electric field depending on the frequencies and voltage used, the application time, and the biological characteristics of the subject. At the same time it enables the operator to graphically monitor any changes taking place. The present study may be limited by the low number of subjects enrolled. However, to our knowledge, this is the first study investigating the efficacy of vibrational therapy as non-pharmacological approach for cognitive stimulation in subjects with neurological ageing. The results obtained foster further studies on larger cohort of subjects with aging-related diseases to better define vibrational treatment protocols.

CONCLUSIONS

These results indicate that, if vibrational therapy will be more widely adopted and applied to a substantial number of people, it might provide obvious socioeconomic benefits (given the lower vibrational therapy costs compared with the currently used pharmacological and physical therapies) in addition to the documented physical and mental well-being⁹.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ORIGINAL INVESTIGATION

The engagement in Healthy Ageing Promotion Scale: development and validation

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Purpose of the study: This article reports the development and Italian validation of a new self-report instrument (The Engagement in Healthy Ageing Promotion Scale) that assesses older people engagement in healthy ageing promotion and is grounded on an ecological operational definition of this phenomenon.

Methods: 14 items were developed basing on a previously conducted qualitative study exploring older adults' experiences and meanings of engagement in health promotion. Analyses were conducted on an Italian sample of 540 adults aged 60 years and older, randomly split into an exploratory (n = 308) and a confirmatory (n = 232) group. A final scale of 8 items was validated with confirmatory factor analyses. Concurrent and criterion validity of the final items were evaluated with measures of patient activation, readiness to change lifestyle and wellbeing.

Results: Both exploratory and confirmatory factor analyses confirmed the one-factor structure of the eight-items scale, with a variance explained of 44% and an eigenvalue equal to 3.5. The fit values of the final model indicated a good model fit. Internal consistency of the scale was good, with a Cronbach's Alpha equal to 0.81. Finally, concurrent and criterion validity revealed significant relationships with the patient activation construct ($r = .401$; $p = .000$), with the readiness to change lifestyle ($r = .211$; $p = .000$), and with older people's wellbeing ($r = .205$; $p = .000$).

Implications: The developed instrument can represent a useful tool to estimate the extent to which older citizens are engaged in health promotion activities, as well as to develop and evaluate interventions aimed to improve wellbeing and preventive behaviours of older citizens.

Key words: Health promotion, Scale validation, Health engagement, Older people

INTRODUCTION

Worldwide societies are becoming older and older. For the first time in history, the majority of people can expect to live 60 years or over. Indeed, in the last 50 years, life expectancy has increased by about 10 years in Europe ¹, and projections show a steady and continuous increase in the upcoming decades ². This is surely a public health success, but social and economic challenges of managing the health of an increasing older

population are consistent. Keeping older adults healthy is becoming a necessary condition to prevent disease conditions which can substantially lower the quality of life and reduce the autonomy of older adults, and which can represent an unsustainable burden for healthcare systems. Considering these assumptions, a global health priority is now allowing older adults ageing successfully and strengthening their individual and social resources in order to help them maintaining a good health status as long as they can ³.

With this goal, different labels (e.g., active ageing,

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successful ageing, healthy ageing, optimal ageing) advocate for a new vision of ageing as a source of opportunities which – if properly sustained – can improve the quality of life and the health status of older citizens⁴. As literature demonstrated, health-promoting behaviors during old age can delate age-related physical, mental, and functional problems^{5,6}. For this reason, there is a growth of policies and interventions specifically devoted to promote the active healthy ageing of older citizens⁷⁻⁹. However, these generally lack to consider older people's needs, expectations, and desires to play an active role in their health promotion^{8,10}. Even though older citizen's disposition and attitude to be engaged in health efforts might be an important factor able to explain health promoting behaviours^{11,12}, this has been rarely explored and measured in literature. Indeed, it is possible to advise in literature kindred concepts and measures of adults' engagement in health promotion, such as salutogenic wellness promotion¹³, perceived control in healthcare¹⁴, health promoting lifestyle¹⁵, perceived wellness¹⁶, readiness to change health behaviors¹⁷, or self-efficacy for health behaviors¹⁸. All these concepts cover important aspects of health promoting efforts. However, they focus on health behavioral attempts (i.e., health promoting lifestyle, readiness to change), on perceived health components (i.e., perceived wellness, salutogenic wellness promotion), or on intrapsychic psychological variables (i.e., self-efficacy, perceived control) which can impact on health behaviors. They lack to consider the disposition and attitude of citizens to engage in health promoting behaviors, and do not focus on specific population targets such as older citizens. There are also other concepts and measures within the healthcare domain (i.e., patient activation, patient engagement, self-management of chronic diseases, patient empowerment, shared decision-making), which however do cover control only with healthcare conditions and target chronically ill patients¹⁹⁻²³, or focus on population from different age ranges²⁴.

Consequently, the need arises for a valid measure of older people engagement in healthy ageing promotion that is specifically attuned to older citizens' experiences, that covers health promotion domains, and that specifically addresses the "engagement" construct. Indeed, a qualitative study exploring older adults' experiences of engagement towards health promotion and health management revealed that this concept is grounded in older adults' experiences, can be operationalized, and deserves a different operationalization from that ones of patient engagement or patient activation²⁵.

With this study, we aim to report the development and validation process of a new instrument specifically measuring older people engagement in healthy ageing

promotion (*The Engagement in Healthy Ageing Promotion Scale*, EHAP-S). The instrument grounded on an ecological operational definition of the phenomenon of older people engagement in healthy ageing promotion and resulted from a taxonomy of health engagement experiences co-constructed with older citizens in a previously conducted qualitative study²⁵.

DESIGN AND METHODS

ETHICS PROCEDURES

Ethical approval was obtained by the Ethical Committee of the Catholic University of Milan before starting the study. Written consent to treat data for research purposes was obtained from all participants who consented to be involved in the study.

SCALE DEVELOPMENT

The items of the scale were developed basing on a qualitative study exploring the older Italian adults experiences of engagement – and disengagement – in health promotion²⁵. 25 semi-structured repeated interviews with Q-sorting tasks designed according to the Ethnoscience method were conducted with a group of older adults aged 65 years and over to deeply understand the phenomenon of health engagement and depict a shared vocabulary and taxonomy of experiences. A first taxonomy of meanings and experiences of the phenomenon of older people health engagement comprised 45 units of analysis. The second interviews round allowed a final taxonomy to be participatory selected and depicted, comprising four main semantic areas (e.g., physical care, soul care, daily lifestyle, contact with ageing) and a set of experiential domains graduated into three positions of engagement (i.e., locked position; awakening position; climbing position). Basing on this taxonomy and on interviewees' feedbacks which suggested to group items on emotional, cognitive, and behavioral dimensions, an initial set of 14 items was developed (see Tab. I). The last (the "higher") engagement position (i.e., the climbing position) was chosen for the items to represent the phenomenon, and a 5-points Likert scale ranging from strongly disagree through strongly agree was adopted.

SET OF INCLUDED MEASURES

Basing on the results of the previously conducted qualitative study²⁵, a set of validated questionnaires was defined to explore construct and concurrent validity. More in details, for construct validity, the Italian translation²⁶ of the 13-items Patient Activation Measure (PAM)²⁴ and the 4-items stage of change questionnaire adapted for

Table 1. Initial set of items (english translation).

Item 1-I	I include in my daily life activities that positively impact on my health
Item 2-I	I listen to my body to consequently adapt my lifestyle
Item 3-I	I am able to understand what it is good for my health and what it is not
Item 4-I	I am happy when I manage my health
Item 5-I	I take care of my health because I love myself
Item 6-I	I am satisfied with how I am managing my health
Item 7-I	Over years I improved my way of managing my health
Item 8-I	I have life plans that make me feel good
Item 9-I	The way I am managing my health reflects what I think it should be done
Item 10-I	My health is in my hands
Item 11-I	Thinking on what I can do to feel better is a daily habit
Item 12-I	I ask help to others to promote and manage at best my health
Item 13-I	I have enough information to follow a healthy lifestyle
Item 14-I	I encourage the people I care to lead a healthy lifestyle

lifestyle's change assessment¹⁷ were adopted. The Italian multidimensional Wellbeing and Cognitive Abilities in Older Adults (BEN-SSC) questionnaire of the Wellbeing and Cognitive Abilities (BAC) portfolio was chosen for concurrent validity so to have an ecological measure of wellbeing specifically constructed for the older Italian population²⁷. The questionnaire is a validated 32-items on a 4-point Likert scale that provides a total wellbeing score featured by three main factors: personal life satisfaction (for the past, the present, and the future life), coping strategies (as ability to deal with daily problems, self-efficacy, and perception of autonomy), and emotional competence (as awareness of own feelings and social satisfaction). Finally, clinical (self-reported type and number of chronic illnesses) and socio-demographical (age, gender, marital status, educational level, place of residence) questions were introduced to characterize the sample of participants.

DATA COLLECTION

A cross-sectional survey was conducted between January 2014 and January 2016 to collect data among a non-representative sample of Italian adults aged equal or over 60 years. A minimum sample size of 300 participants – also considering potential missing values and drop-out rates – was defined before starting recruitment. Participants were recruited through different senior centers (e.g., community centers, aggregative centers, recreation associations), which were contacted by telephone and invited to take part in the study. Most of participants were recruited by a national senior

association (ANCeSCAO, Associazione Nazionale Centri Sociali, Comitati Anziani e Orti), which disseminated the questionnaire in the senior centers distributed along the Italian territory. The anonymous questionnaire included a cover letter explaining the length (about 10 minutes) and the aim of the study, providing contact information, and informing participants about the possibility to refuse in every moment to participate. The informed consent was collected at this moment. Participants were free to participate and no incentive was given to them to participate.

DATA ANALYSIS

The first goal of the study was to obtain a scale comprising a low number of items measuring the latent construct of interest. The initial scale comprised 14 items. In order to calibrate the scale and to reduce the number of items, several analyses were conducted. Descriptive analyses were performed on each item of the developed scale to observe distributions, kurtosis, asymmetry, eventual ceiling and floor effects and missing values. Thereafter, a Partial Credit Rasch Model was performed to check unidimensionality and the fit of each item to the construct of interest. In particular, to check whether the items fitted to the expected model, a Chi square test and two item fit mean square (MNSQ) statistics (infit and outfit) were computed. MNSQ determines how well each item contributes to defining a single underlying construct. Infit is more sensitive to misfitting responses to items closest to the person's ability level, while outfit is more sensitive to misfitting items that are farther away. If the data fit to the Rasch model, the fit statistics should be between 0.6 and 1.4²⁸. Analyses of difficulty and step parameters were conducted to guarantee a sufficient ranking of the different categories of response and to respect the monotonic order. The conjoint use of these different procedures permitted to calibrate the questionnaire and to eliminate problematic items which presented one or more drawbacks.

The validation study was thereafter conducted on the remaining items. A further Partial Credit Model was conducted on the whole sample. Then, construct validity was determined through exploratory and confirmatory factor analyses on two different samples, obtained by the initial sample randomizing the assignation to the two sub-sample. Exploratory factor analysis (EFA) was performed using a principal axis factoring with Oblimin rotation. Appropriateness of EFA was evaluated through Kaiser-Meyer-Olkin (KMO) values (excellent if > .90) and significance of Bartlett score. Explained variance, factor loadings evaluation and eigenvalue > 1 were used to define the factorial structure of the scale. Furthermore, a model was considered acceptable if factors loadings exceeded $r = .40$. Therefore, confirmatory factor analysis (CFA) was performed to test the model.

Goodness-of-fit indexes (i.e., chi-square with degrees of freedom, comparative fit index – CFI –, root mean square error of approximation – RMSEA –) were evaluated. A CFI > .90 was considered a good model fit²⁹, whereas a RMSEA < .08 indicated an acceptable fit³⁰. Finally, Hoelter test scores were used to evaluate suitability of the sample size.

Concurrent validity with the PAM and with the Stage of Change Scale scale was also determined by using Pearson's correlation. Criterion validity of the developed scale was evaluated by comparing the results from the EHAP-S to a selected a priori measure of wellbeing of older Italian citizens (BEN-SSC). Indeed, we hypothesized that engagement in healthy ageing promotion would be positively related to an overall measure of perceived wellbeing. Criterion-related validity was assessed by examining Pearson's correlation coefficients and by conducting linear regression analyses.

Internal consistency reliability was determined through the Cronbach's alpha. A reliability coefficient exceeding 0.70 was considered acceptable, exceeding 0.80 was considered good. Moreover, Item-Total Correlation index and Cronbach's Alpha if Item Deleted were calculated.

Analyses were conducted using SPSS 23 version with a level of significance set at 0.05 and R.3.2.4 (package eRm).

RESULTS

SAMPLE'S DESCRIPTION

540 participants aged 60 years and older participated in the study. The overall response rate was 91%. 51.7% of participants were female. 253 participants (46.9%) did not report to be affected by a chronic disease condition. Respondents' age ranged from 60 to 92 years (average = 69.3; SD = 8.5), with 27.4% of participants being in the range 60-74 years, 45.2% of participants being in the range 75-84, and 27.4% of participants being in the range > 85 years-old. Looking at the civil status, 63% of participants was married/widowed. 74.4% of respondents was retired, 8.3% was unemployed, 5.4% worked full-time, and 2.2% worked part-time. 32.8% of participants completed a secondary education, 31.1% completed an upper secondary education, 18% completed an elementary education, 8% received a post-secondary education, and 0.4% received no education. In Table II further details about the socio-demographic characteristics of the sample are provided.

ITEM ANALYSIS FOR CALIBRATION

Descriptive statistics of the individual items were calculated to conduct the initial exploration of the data. Table III provides the item-level descriptive statistics for

Table II. Characteristics of participants (n = 540).

	mean (SD)/n (%)
Age	69.3 (8.5)
Sex	210 (38.9%)
Male	279 (51.7%)
Female	2 (0.4%)
Education	97 (18%)
No education	177 (32.8%)
Elementary	168 (31.1%)
Secondary	43 (8%)
Upper-secondary	238 (44.1%)
Post-secondary	253 (46.9%)
Diagnosis	
Yes	340 (63%)
No	33 (6.1%)
Civil status	26 (4.8%)
Married/widowed	90 (16.7%)
Single/unmarried	402 (74.4%)
Divorced	
Widowed	
Occupation	45 (8.3%)
• retired	
• unemployed	
Full-time work	29 (5.4%)
Part-time work	12 (2.2%)

all items (range, minimum, maximum, mean, standard deviation, asymmetry and kurtosis). The frequencies of the response categories showed little use of the category "Strongly Disagree" and "Disagree". The categories "Agree" and "Strongly Agree" were used with the highest frequency for all the items.

The mean scores ranged from 3.47 (item 12) to 4.11 (item 4). Standard deviations showed a constant variability in all items, ranging from 0.76 (item 4) to 0.96 (item 12). Calibration and validation analyses were conducted only on the 500 participants' responses without missing values.

Items 1-I, 3-I, 4-I and 5-I presented drawbacks of kurtosis (out of normal range between -1 and +1) and ceiling effect (more than 80% of responses were distributed in the two highest categories).

A Partial Credit Rasch Model (PCM) was implemented to examine the psychometric properties of the items, and to calibrate the questionnaire. PCM is useful to investigate uni-dimensionality of the construct (fundamental requisite of the summarization of the raw scores), the fit and the reliability of each item (Tab. IV). Items 1-I, 4-I and 5-I presented drawbacks of monotonicity of steps (in particular Item 1-I between categories 2 and 3, Items 4-I and 5-I between categories 1 and 2). Item 12-I had an Outfit MSNQ value over the acceptable range (Outfit value equal to 1.57, acceptable range between 0.6-1.4). Moreover, Items 12-I and 13-I resulted

Table III. Item-Level Descriptive Statistics for each item.

Item	Range	Min	Max	Mean	Std. Dev.	Asymmetry	Kurtosis
Item 1-I	1-5	1	5	3.88	.79	-.99	1.57
Item 2-I	1-5	1	5	3.84	.81	-.85	0.97
Item 3-I	1-5	1	5	3.96	.78	-.89	1.53
Item 4-I	1-5	1	5	4.11	.76	-.86	1.48
Item 5-I	1-5	1	5	3.98	.84	-.81	1.10
Item 6-I	1-5	1	5	3.78	.83	-.73	.79
Item 7-I	1-5	1	5	3.82	.87	-.75	.69
Item 8-I	1-5	1	5	3.64	.80	-.45	.03
Item 9-I	1-5	1	5	3.65	.84	-.57	.12
Item 10-I	1-5	1	5	3.80	.93	-.58	.08
Item 11-I	1-5	1	5	3.76	.81	-.57	.47
Item 12-I	1-5	1	5	3.47	.96	-.57	-.12
Item 13-I	1-5	1	5	3.72	.80	-.70	.76
Item 14-I	1-5	1	5	3.74	.87	-.70	.52

Table IV. Item fit statistics.

Item	Difficulty	Step 1	Step 2	Step 3	Step 4	Outfit MSNQ	Infit MSNQ	Chi Square (df=499)	P-value
Item 1-I	.64	-1.20	.17	.07	3.52	1.07	1.08	536.09	0.12
Item 2-I	.65	-1.21	.01	.36	3.46	0.83	0.84	415.32	1.00
Item 3-I	.52	-.74	-.49	.20	3.09	0.95	0.97	475.66	0.76
Item 4-I	.30	-.34	-1.15	.09	2.59	0.88	0.85	438.58	0.98
Item 5-I	.55	-.06	-1.03	.56	2.72	0.70	0.74	349.63	1.00
Item 6-I	.76	-1.00	-.19	.69	3.54	0.76	0.74	378.40	1.00
Item 7-I	.75	-.67	-.20	.71	3.18	0.84	0.84	420.64	1.00
Item 8-I	.66	-2.39	-.06	1.09	4.01	0.87	0.90	436.95	0.98
Item 9-I	.79	-1.81	.21	.92	3.85	0.85	0.84	426.79	0.99
Item 10-I	.72	-.77	-.21	1.06	2.82	1.02	1.02	510.75	0.36
Item 11-I	.67	-1.38	-.35	.86	3.56	0.78	0.79	392.58	1.00
Item 12-I	1.28	-.64	.61	1.20	3.95	1.57	1.31	787.68	0.00
Item 13-I	.82	-1.24	-.20	.79	3.91	1.09	1.07	556.40	0.04
Item 14-I	.82	-1.02	.02	.77	3.49	1.04	1.00	521.29	0.24

significant in Chi square test, which compared the observed answer distribution with the estimated one.

For all these reasons (drawbacks of distribution, asymmetry, kurtosis, ceiling effect, monotonicity of steps in PCM, outfit MSNQ value and Chi square test), Items 1-I, 3-I, 4-I, 5-I, 12-I and 13-I were eliminated.

Only 8 items (2-I, 6-I, 7-I, 8-I, 9-I, 10-I, 11-I and 14-I) were selected for the validation study.

ITEM ANALYSIS FOR VALIDATION

The validation study was conducted on 8 items, reported, with new labels, in Table V.

A new estimate of PCM was performed on the 8 selected items. Results are reported in Table VI. Problems of monotonicity of steps, of Chi square test and of Outfit MSNQ and Infit MSNQ values (ranging, respectively, from 0.75 to 1.04 and from 0.70 to 1.04) were not observed among the selected items. Rasch Model confirmed the uni-dimensionality of the EHAP scale and the fit of each item to the data. To explore and verify the factorial structure of the scale, the overall sample was randomly divided into two main groups: Group 1 (n = 308) was used to conduct the exploratory analysis, Group 2 (n = 232) was used to conduct the confirmatory analysis.

Table V. Set of items for validation study (english translation).

EHAP-1	I listen to my body to consequently adapt my lifestyle
EHAP-2	I am satisfied with how I am managing my health
EHAP-3	Over years I improved my way of managing my health
EHAP-4	I have life plans that make me feel good
EHAP-5	The way I am managing my health reflects what I think it should be done
EHAP-6	My health is in my hands
EHAP-7	Thinking on what I can do to feel better is a daily habit
EHAP-8	I encourage the people I care to lead a healthy lifestyle

EXPLORATORY ANALYSES

The KMO value was good (.856) and the Bartlett's Test of Sphericity reached statistical significance ($p < 0.01$), supporting the use of EFA. EFA revealed a one-factor structure explaining 44% of variance and with an eigenvalue equal to 3.5. Factor loadings are reported in Tables VII-VIII, and they ranged from .51 to .72.

CONFIRMATORY ANALYSES

CFA were conducted to verify the latent structure of the hypothesized eight-items one-factor model. Hoelter test score for .05 was 242, indicating an adequate sample size. The chi-square (df), CFI, and RMSEA values of the final model were 81.38(20), .937, and .079, respectively. Those values indicated a good model fit. The factor loadings from the CFA of all 8 items ranged from .43 to .72 and they were absolutely comparable with the correspondent obtained by EFA.

INTERNAL CONSISTENCY AND RELIABILITY

EHAP scale had a very good internal consistency, since the value of the Cronbach's Alpha was equal to 0.81. In Table IX, the Cronbach's Alpha was evaluated after deleting individual items. Moreover, Item-Total Correlation

Table VII. Factor loadings.

EHAP-1	I listen to my body to consequently adapt my lifestyle	.71
EHAP-2	I am satisfied with how I am managing my health	.72
EHAP-3	Over years I improved my way of managing my health	.68
EHAP-4	I have life plans that make me feel good	.70
EHAP-5	The way I am managing my health reflects what I think it should be done	.70
EHAP-6	My health is in my hands	.55
EHAP-7	Thinking on what I can do to feel better is a daily habit	.71
EHAP-8	I encourage the people I care to lead a healthy lifestyle	.51

Table VIII. Item loadings in confirmatory factor analysis of the 8-items engagement in Healthy Ageing Promotion Scale.

	Estimate
EHAP-1	.580
EHAP-2	.720
EHAP-3	.653
EHAP-4	.577
EHAP-5	.663
EHAP-6	.467
EHAP-7	.630
EHAP-8	.435

index was calculated for each item. Each item contributed significantly to the EHAP scale score. The internal consistency of the 8-item EHAP scale was satisfactory.

CONCURRENT VALIDITY

Pearson's correlation revealed good correlation levels with the PAM scale ($r = .401$; $p = .000$) and with the

Table VI. Item fit statistics.

Item	Difficulty	Step 1	Step 2	Step 3	Step 4	Outfit MSNQ	Infit MSNQ	Chi Square (df = 499)	P-value
EHAP-1	0.69	-1.21	-0.18	0.13	3.68	1.01	1.02	500.02	0.42
EHAP-2	0.82	-1.01	-0.18	0.76	3.70	0.71	0.70	354.99	1.00
EHAP-3	0.81	-0.69	-0.19	0.78	3.32	0.80	0.79	396.539	1.00
EHAP-4	0.73	-2.40	-0.03	1.17	4.21	0.84	0.86	414.912	1.00
EHAP-5	0.86	-1.82	0.24	1.01	4.03	0.81	0.79	400.488	1.00
EHAP-6	0.78	-0.79	-0.20	1.14	2.96	1.03	1.03	509.552	0.33
EHAP-7	0.74	-1.39	-0.33	0.94	3.73	0.75	0.76	370.351	1.00
EHAP-8	0.88	-1.03	0.04	0.85	3.65	1.09	1.04	539.069	0.08

Table IX. Internal consistency and reliability analysis.

Item	Cronbach's Alpha if item deleted	Corrected item-total correlation
EHAP-1	.79	.52
EHAP-2	.77	.62
EHAP-3	.78	.56
EHAP-4	.79	.50
EHAP-5	.78	.58
EHAP-6	.80	.43
EHAP-7	.78	.58
EHAP-8	.80	.41

Stage of Change Scale ($r = .211$; $p = .000$), revealing that the developed scale is significantly related but sufficiently divergent from these reference measures.

CRITERION VALIDITY

Significant and positive correlation levels were revealed by Pearson's correlation analyses with the BEN-SSC scale of Italian older adults' wellbeing ($r = .205$; $p = .000$). To further examine criterion validity, linear regression with overall perceived wellbeing as dependent variable and the factors of engagement in healthy ageing promotion as independent variables was employed. The regression analysis was significant ($F 1,499 = 21.971$, $p < .001$) and explained 42% of the variance of the model. Therefore, results suggest that the proposed one factor of older people engagement in health promotion is related to the construct of wellbeing (has criterion validity).

DISCUSSION

With this study, we aimed to develop and validate a new brief scale to measure older people engagement in health promoting behaviors. Although there are some scales assessing health promoting behaviors or activation of people towards their health management and promotion, there are no instruments specifically developed for older citizens. However, engagement in health promoting behaviors during ageing is a particularly relevant issue to date, as measuring this aspect can help collecting the needs for engagement of a similar population and assessing active healthy ageing initiatives. The development and validation of a scale measuring a similar dimension might help covering an essential prerequisite of promoting healthy ageing that is the emotional, cognitive, and behavioral disposition and attitude of older citizens to engage in healthy aging. The EHAP-Scale appears to have both good reliability and good content validity. Furthermore, it is easy to complete,

as demonstrated by the fact that most of participants completed the questions (91%). In terms of content validity, the principal components analysis supports the view that the scale is tapping into one unique meaningful constructs of engagement in healthy ageing, as proposed by other scales measuring similar constructs of engagement and activation^{23 24}. The high correlation between EHAP-S score and activation towards care management suggests that the disposition to engage in health promoting behaviors and being behaviorally active in managing physical health problems are connected aspects of one's life. Furthermore, also the correlation of the scale with readiness to change lifestyle suggests that there is a relationship between the EHAP scale and behavioral health outcomes. Finally, results suggest that the factor of older people engagement in health promotion is significantly related to the construct of wellbeing. This highlights the importance of a similar variable to develop targeted intervention that can be able to improve the wellbeing of older citizens. Indeed, this scale can be considered a useful tool to implement monitoring strategies of attitudes of older citizens towards health promotion activities as well as to develop intervention focused on improving preventive behaviors and wellbeing outcomes in older citizens and evaluate their effectiveness.

Some limitations can be observed in our study. First, the purposive sample adopted for this study does not allow generalization to the entire Italian population to be driven. A stratified random population sample would have allowed to provide normative data. However, the balanced representation of socio-demographical categories in the sample suggests that results of this study can probably be applied to a wider population. It will also be necessary to demonstrate the predictive validity of the scale and its sensitivity to change following interventions. Furthermore, the next step in the validation of the EHAP scale will be to demonstrate that it has comparable reliability and validity across a range of languages and cultural settings.

To conclude, the developed scale to measure the engagement in healthy ageing promotion among older Italian adults has close continuity with the best existing measure of activation and readiness to change, its psychometric properties are excellent, and it is able to assess aspects relating to the attitude and disposition of individuals towards engaging in health promoting activities in the specific population of older citizens.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Effect of homotaurine in patients with cognitive impairment: results from an Italian observational retrospective study

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Background & Aims: This observational retrospective study aimed at evaluating the effects of one-year administration of homotaurine (tramiprosate) in a sample patients presenting with symptoms of mild cognitive impairment.

Methods: Patient's demographic data and medical history are reported. Each patient performed brain imaging and neuropsychological assessment to reach the diagnosis. Each patient assumed 100 mg total dose of homotaurine/day. The evolution of the cognitive decline over time was evaluated by means of the Mini Mental State Examination (MMSE).

Results: 245 patients from 28 different centres in Italy were recruited. Significant improvements from baseline expressed as mean MMSE total score were observed in patients with aMCI at months 8 and 12 ($p < 0.0001$), and in those with mMCI at month 4 ($p < 0.05$).

Conclusions: Administration of homotaurine revealed beneficial effects in our sample population of MCI patients. Our results indicate clearly that homotaurine may well be considered as a potential symptomatic treatment for cognitive symptoms. Further research is however needed to clarify whether this compound could influence the progression of cognitive decline.

Key words: Homotaurine, Mild cognitive impairment, Alzheimer's disease

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INTRODUCTION

Cognitive decline consists in an acquired progressive decrease of efficiency of cognitive function (e.g. attention, executive function, learning and memory, language, perceptual-motor, and social cognition) that is more marked than the physiological age-related decline^{1,2}. The spectrum of severity of neurocognitive disorders varies from mild cognitive impairment (MCI) to the most severe cases of dementia. In this view, MCI should be considered as a transitional state evolving from normal cognition to cognitive impairment with essentially preserved functional abilities^{1,3,4}. MCI as a clinical category is difficult to put in the correct frame. MCIs are subdivided in amnesic (aMCI), non-amnesic single and multi-domain (mMCI) based on empirically based classification. Such classification yielded two main categories: those presenting with aMCI that in late stages progressed to Alzheimer's disease (AD) and those presenting with dis-executive or visuo-spatial impairment that evolved either in AD or in non-AD syndrome. Such empirically derived classification however provided several false positive diagnosis^{5,6}. Recently, due to the introduction of biomarkers, namely the cerebrospinal fluid ones and positron emission tomography ligand tracers, in the refinement of clinic-pathological diagnosis, MCI category showed a great heterogeneity leading to the need for refinement of clinical criteria to improve MCI diagnosis^{7,8}. Despite that, MCI is a clinical entity often diagnosed in our hospital practice, and the need for a pharmacological treatment to alleviate cognitive symptoms is of course welcome. In this view, recent clinical and population-based data suggest that MCI have a prevalence of 10-20% for adults aged ≥ 65 years, a condition that resulted strictly associated with population aging⁹. Despite the extensive research in the past few years, the current treatment options for MCI have a limited impact on the pathophysiology of the disease and treatments acting on disease progression remain an unmet medical need. Recent research on AD pathogenesis has highlighted the role of amyloid beta ($A\beta$) cascade events¹⁰. Despite multifaceted, $A\beta$ -based theory claims that $A\beta$ aggregates and forms oligomers, peptides with highly toxic effects on synapses. Oligomers produced in condition of sustained synaptic transmission, induce stable change in synaptic plasticity mechanisms leading to impairment of neural transmission, oxidative stress and chronic inflammatory response, responsible for neuronal degeneration¹¹. These findings led to the development of potential anti-amyloid therapies and, overall, of new pharmacological interventions since the very early stages of AD-related pathology¹². Among them, homotaurine (tramiprosate), a natural aminosulfonate compound that is present

in different species of marine red algae, has shown anti-amyloid effects with neuroprotective properties in a number of in-vitro and in-vivo models¹³. The therapeutic efficacy of homotaurine has been investigated in clinical trials as well. In the ALPHASE study, conducted in more than 1000 patients with mild to moderate AD, treatment with homotaurine for 18 months was associated with a trend towards benefit on memory, language and praxis skills¹⁴, and reduced hippocampus volume loss¹⁵. The positive effects of homotaurine supplementation on hippocampus atrophy and memory were recently confirmed in patients with aMCI¹⁶. Furthermore, the potential beneficial effects of homotaurine in other diseases than cognitive impairment were investigated. Dose-dependent neuroprotection against ischemic stroke was demonstrated in *in vitro* and *in vivo* models¹⁷. In patients with Parkinson's disease (PD) and cognitive impairment, homotaurine was shown to have beneficial effects on sleepiness and possibly on memory¹⁸.

Based on this background, we have considered of interest to collect retrospective data of patients treated with homotaurine according to common clinical practice in Italy, in order to add further information on the effects on cognitive function in patients with cognitive impairment seeking for specialist consultation.

PATIENTS AND METHODS

This observational, retrospective, non-interventional study was conducted in 28 sites in Italy. The main objective of the study was to collect clinical information on patients diagnosed as mildly cognitive impaired according to Petersen criteria³. All patients underwent a complete clinical investigation, including medical history, neurological examination, mini mental state examination (MMSE), a complete blood screening (including routine exams, thyroid hormones, level of B12), neuropsychological examination, neuropsychiatric evaluation, and neuroimaging consisting of magnetic resonance imaging (1.5 T MRI).

The objective of this study was to evaluate the effect of homotaurine administration (100 mg/day) in the sample patients with a diagnosis of MCI as a whole. Then, we evaluated the effect of homotaurine in different subcategories of MCI: aMCI, mMCI, vascular dementia (VAD) and MCI due to other causes (in this case brain traumas, Parkinson's disease, post-hemorrhagic hematoma).

Treatment with homotaurine was at the discretion of the physician, according to the local standard of medical care, and the decision of starting treatment with homotaurine was independent from the inclusion in the study. Patients with aMCI and mMCI did not assume

any cognitive enhancer drug (i.e. antidepressants, mood stabilizers etc.) at the beginning of the study. Patients with AD and VAD assumed stable therapy with donepezil 10 mg or rivastigmine patch 9.5 mg since 6 months before study start. Patients with PD assumed pharmacological treatment with L-Dopa or dopamine agonists, and their doses remained unchanged since at least 3 months before the study start. Post-haemorrhagic hematoma patients assumed pharmacological treatment for hypertension.

The evolution and outcome of the cognitive symptoms over time were evaluated by means of the Mini Mental State Examination (MMSE), which was performed at the baseline, 4, 8 and 12 months.

Data are reported as mean value and standard deviation (SD). The evolution over time of MMSE total score was analysed by means of an analysis of variance (ANOVA) and the categorical results from baseline to month 12 (improved, unchanged, worsened) were analysed by means of a pseudo-marginal Markov chain method. The Markov Chain Monte Carlo (MCMC) method was used for imputation of missing data of MMSE. The analysis of the results of MMSE was performed in each subgroup of diagnosis. The study was performed according to the Declaration of Helsinki.

RESULTS

245 patients were enrolled in this study. Of them 106 presented with aMCI, while 47 with mMCI. 32 presented with incipient AD, 12 had a diagnosis of VAD, based on the presence of strategic infarcts (mainly anterior thalamic, frontal or fronto-parietal) or diffused vascular burden of the brain microvasculature. 48 patients had a diagnosis of MCI with a history of other neurological pathology such as PD, brain subdural hematomas or traumas. Homotaurine was well tolerated and side effect were never reported by patients and their care givers.

The mean (\pm SD) age in the total population was 72.9 ± 9.7 years (median 75 years, range 30-94 years), and was similar in males (73.3 ± 9.3 years) and in females (72.6 ± 9.8 years). The mean age was higher in patients with AD (77.1 ± 6.8 years) and in those with VAD (77.9 ± 8.0 years) than in the other subgroups. The distribution of age range showed that the highest prevalence was in the range of 76-80 years (86 patients, 27.5%), followed by the ranges 71-75 years (53 patients, 16.9%) and 81-85 years (55 patients, 15.6%). Consistently with data of mean age, AD and VAD were prevalent in older age ranges, whereas mMCI and aMCI were more frequent in younger patients. Data of mean age at onset of the disease reflected those of age at

the time of study entry (Tab. I). At baseline, patients with aMCI or mMCI had a higher mean MMSE total score (i.e. a lower cognitive impairment) than those with AD or vascular dementia. In particular, MMSE score of the aMCI group of patients was 25.1 ± 3.0 , MMSE score of mMCI was 25.0 ± 2.7 , AD patients scored 20.3 ± 4.2 , VAD patients scores 21.7 ± 4.7 , while patients with MCI due to other diagnosis scored 24.9 ± 3.7 . Improvement vs. baseline in mean MMSE total score was observed in patients with diagnosis of aMCI and mMCI. Conversely, a general cognitive decline was observed in patients with AD and VAD. The increase vs baseline in mean MMSE score was statistically significant in patients with aMCI at months 8 and 12 (month 8: 27.2 ± 2.6 , month 12: 26.9 ± 3.2 ; $p < 0.0001$ for both comparison), in those with mMCI at month 4 (27.3 ± 2.6 ; $p < 0.05$), and in those with MCI due to other diagnoses at month 12 (26.1 ± 3.8 ; $p < 0.01$). The decrease in mean MMSE score was statistically significant at month 12 vs baseline in patients with AD (18.0 ± 3.6 ; $p < 0.0001$). Figure 1 shows the results of the MMSE at baseline and at the post-baseline time points.

DISCUSSION

The aim of this retrospective observational study was to evaluate the cognitive effects of homotaurine administration (100 mg/day) in a population of individuals with diagnosis of MCI, treated for 12 months. Cognitive effects were evaluated in terms of mean MMSE total score. Main findings of our study showed that patients with diagnosis of aMCI, and to a lesser extent those with mMCI, showed marked improvement from the

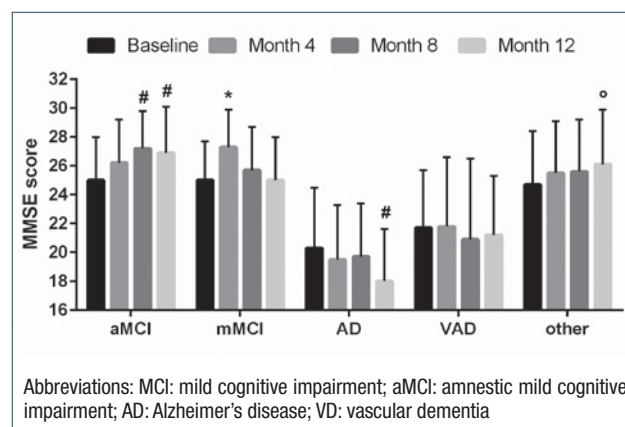


Figure 1. Results of MMSE at baseline and at the post-baseline time points by subgroup of diagnosis (values are means). Bars are standard deviations. * $p < 0.05$, ° $p < 0.01$, # $p < 0.0001$ vs baseline.

treatment with homotaurine. MMSE improvement was sustained up to 12 months of observation, whereas the maximum improvement in mMCI patients was observed after 4 months from the start of treatment. Patients with diagnosis of AD or vascular dementia did not apparently benefit from the treatment. Furthermore, patients with MCI due to non-AD related pathology showed improvement as well. The latter subcategory, although heterogeneous, indicates that in MCI due to brain traumas and/or hemorrhagic hematomas, and to Parkinson's disease, homotaurine induces a measurable and long-lasting efficacy in terms of cognitive functions. Hence, we can conclude that homotaurine administration is effective on cognitive symptoms of MCI individuals, both in AD and non-AD pathologies. Reasons of such results however need to be interpreted with caution, and recent experimental and clinical data yielded on homotaurine effects on cognitive function could be helpful. Homotaurine is known to act through a double mechanism: the modulatory activity on cortical GABA A receptors, and the anti-amyloid activity, both effects well documented in vitro studies¹³. Recently two main studies has been published on the effects of homotaurine administration in MCI subjects due to AD pathology. First, an electrophysiological study¹⁹ showed the ability of homotaurine to modulate short latency afferent inhibition (SLAI) after 4 weeks of treatment. SLAI is considered an in vivo measure of central cholinergic transmission thus suggesting for homotaurine a modulatory effect on cortical GABA interneurons activity and in the regulation of the cholinergic control of cortical excitatory transmission. In this view, it is known that cortical GABA transmission is

involved in several functions ranging from the control of the excitatory activity^{20 21} to the regulation of parietal-frontal connections. These structures are strictly involved in the control of executive functions²², memory and attention, co-operating with cholinergic transmission^{19 23 24}. Thus, it is conceivable to suppose that some of the effects of homotaurine observed in our MCI subcategories might be related to its effect on cortical GABA A receptors. The second recent study performed in patients with aMCI¹⁶ showed that patients treated with homotaurine for one year had decreased volume loss in the bilateral hippocampus tail and in other brain areas, such as the bilateral fusiform gyrus and the right inferior temporal cortex. These morphological changes in patients treated with homotaurine were paralleled by beneficial effects in the short component of episodic memory, compared to untreated subjects. Both studies clearly confirmed a valuable effect of homotaurine on MCI individuals. However, whether the effects observed on cognition are attributable to GABA modulatory activity, anti-amyloid effects or both remains to be established. Moreover, the finding that homotaurine concur to reduce brain atrophy, although indirectly, led to suppose that an effect on amyloid metabolism is likely. As claimed by amyloid hypothesis cascade, A β pathology occur years before the appearance of cognitive decline, and initiate a pathological process that tau pathology make manifest^{10 25}. This hypothesis would also highlight the importance of an early correct diagnosis of MCI and AD. Within this context, the identification of pathogenic A β by means of molecular neuroimaging or biological markers will help identify cases at the earliest stages

Table I. Demographic data and disease characteristics overall and by type of diagnosis.

	aMCI (N = 106)	mMCI (N = 47)	AD (N = 32)	VD (N = 12)	Other (N = 48)	Total (N = 245)
Age (years), mean \pm SD	71.2 \pm 10.6	73.5 \pm 7.1	77.1 \pm 6.8	77.9 \pm 8.0	72.6 \pm 9.9	72.9 \pm 9.7
Age range, N (%)						
66-70 years	21 (13.9%)					
71-75 years	22 (14.6%)	11 (21.2%)	2 (5.3%)	1 (6.7%)	9 (15.8%)	44 (14.1%)
76-80 years	37 (24.5%)	13 (25.0%)	4 (10.5%)	1 (6.7%)	13 (22.8%)	53 (16.9%)
81-85 years	19 (12.6%)	15 (28.8%)	12 (31.6%)	3 (20.0%)	19 (33.3%)	86 (27.5%)
\geq 86 years	7 (4.6%)	8 (15.4%)	14 (36.8%)	7 (46.7%)	7 (12.3%)	55 (15.6%)
Sex, N (%)						
Males	61 (40.4%)	22 (42.3%)	13 (34.2%)	2 (13.3%)	25 (43.9%)	123 (39.3%)
Females	86 (57.0%)	30 (57.7%)	23 (60.5%)	13 (86.7%)	30 (52.6%)	182 (58.1%)
Missing	4 (2.6%)	-	2 (5.3%)	-	2 (3.5%)	8 (2.6%)
Age at onset of symptoms (years), mean \pm SD	69.4 \pm 10.6	70.9 \pm 7.8	73.5 \pm 8.0	76.4 \pm 7.4	70.7 \pm 9.8	70.7 \pm 9.7
Yes	64 (42.4%)	5 (9.6%)	7 (18.4%)	7 (46.7%)	18 (31.6%)	101 (32.3%)
No	85 (56.3%)	46 (88.5%)	31 (81.6%)	8 (53.3%)	37 (64.9%)	207 (66.1%)
Missing	2 (1.3%)	1 (1.9%)	-	-	2 (3.5%)	5 (1.6%)

Abbreviations: N: number of patients; MCI: mild cognitive impairment; aMCI: amnesic mild cognitive impairment; AD: Alzheimer's disease; VD: vascular dementia; SD: standard deviation

of the disease process^{26,27}. The early diagnosis of MCI relies on the hypothesis that pharmacological interventions with disease-modifying compounds are more likely to produce clinically relevant benefits if started early before the progression towards dementia²⁸. With this respect, the apparent lack of effects in patients with AD enrolled in this study may be due to the small sample with this diagnosis, which could also have included patients with advanced age that were less likely to benefit from treatment with homotaurine than younger subjects. Post-hoc analyses of results of the ALPHASE study and of other studies have shown that beneficial effects of homotaurine were mainly observed using adjusted predictive models or in selected groups of patients. An exploratory analysis performed in the subgroup of 312 participants in the ALPHASE study who underwent longitudinal volumetric resonance imaging (vMRI) and were evaluable for assessing hippocampus volume changes²⁹, showed that homotaurine slowed hippocampal atrophy and revealed some evidence of a beneficial effect on cognition. A post-hoc analysis of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) observed in the ALPHASE study revealed statistically significant differences, in favour of homotaurine vs placebo, thus suggesting that homotaurine may have beneficial and protective effects on memory, language and praxis in mild to moderate AD patients¹³.

Further analyses in 599 patients of the ALPHASE study with at least one $\epsilon 4$ allele of apolipoprotein E gene (APOE4+), i.e. the major genetic risk factor for AD³⁰, showed that homotaurine given for 18 months in addition to acetylcholinesterase inhibitors and/or memantine produced a clinically meaningful improvement in cognition and function¹³.

The same findings were observed in an analysis that included 909 APOE4+ patients from the two phase III trials on homotaurine, i.e. the ALPHASE study conducted in North America and another study conducted in Europe. Furthermore, a higher efficacy of homotaurine was observed in the APOE4/4 homozygous subgroup compared to the heterozygotes patients, thus suggesting a gene dose effect of APOE4, potentially due to larger amyloid burden in APOE4/4 homozygotes. These novel findings indicate that further research is needed to identify biomarkers that help in selecting the subgroups of patients which may have the highest benefit from treatment with homotaurine³¹.

Of course our study is unable to indicate a clear mechanism of action, although confirm the positive effects on cognition. Despite these limitations, available data have shown that patients with a diagnosis of MCI, whatever the cause, had improvements or stabilization of cognitive decline, whereas the results in patients diagnosed

with AD or vascular dementia, although evaluated in small samples, did not show evidence of benefit following treatment with homotaurine. Currently, no drug has been proven effective in the treatment of MCI³² and appropriate strategies to treat MCI and prevent the progressive decline of cognitive functions include the control of vascular risk factors, treatment of lifestyle-related diseases and training on cognitive function³³. In conclusion, this study provides further information on the effectiveness of homotaurine in the management of patients with cognitive impairment. The results have shown that patients with MCI were more likely to benefit from treatment with homotaurine. Prospective controlled studies conducted in adequate samples are needed to assess the long-term effectiveness of homotaurine, given as monotherapy or in addition with other drugs, in the management of patients with different stages of cognitive decline.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Cardio-protective effects of statin therapy in elder patients undergoing coronary artery bypass grafting

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Background and aims: Statins exhibit cardiovascular pleiotropic effects for primary and secondary prevention in patients with coronary artery disease. A debate exists to statin treatment-risk paradox in elderly. The aim of the study is to investigate the cardio-protective effects of preoperative statin therapy against adverse cardiovascular events after coronary artery bypass grafting (CABG).

Methods: This retrospective study included consecutive patients underwent CABG between January 2010 and December 2015. The study included all patients underwent isolated primary CABG. The age of 65 years old was used to define elderly. The evaluated endpoints of postoperative adverse outcome included postoperative in-hospital all-cause and cardiac mortality, major adverse cardiovascular events (MACE), myocardial infarction (MI) and stroke. Hazard ratios (HRs) of statin therapy relative to no statin therapy were adjusted for preoperative risk scores, the extent of coronary artery disease (CAD) and administration of other cardiovascular protective medications.

Results: Preoperative statins were prescribed only in 903 patients (16.6%) out of 5437 patients underwent CABG. Regardless of age, statins reduced the HRs for in-hospital mortality, MACE, MI and stroke after CABG, with non-significant differences in the interaction of HRs between elder and non-elder patients. The adjusted HRs did not support the use of high dose intensity in elder patients, especially for the occurrence of MACE.

Conclusions: Elder patients undergoing CABG should not be deprived of any suspected benefit of preoperative statins to avoid repeated unfavorable events. Further studies are recommended to evaluate the benefits of high-intensity statins.

Key words: Statins, Coronary artery disease, Elderly, Coronary revascularization

INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which have been used for many years to prevent coronary artery disease (CAD) and stroke. Their primary mechanism of action is the lowering of serum cholesterol through inhibiting of hepatic cholesterol biosynthesis^{1,2}.

Statins also exhibit cardiovascular pleiotropic effects, as it is directly involved in restoring or improving endothelial function, attenuating vascular remodeling, inhibiting

the vascular inflammatory response, and stabilizing atherosclerotic plaques. Inhibition of Rho intracellular signaling molecules and its downstream target, Rho-associated coiled-coil containing protein kinase (ROCK), has emerged as the main mechanisms underlying the pleiotropic effects of statins³. Therefore, statins have become a pivotal component in the primary and secondary prevention of coronary artery and vascular disease⁴. Although coronary artery bypass grafting (CABG) remains the gold standard therapy for the majority of patients with CAD, the short-term and long-term mortality

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of patients undergoing CABG is higher than the general population^{5,6}. Both co-morbidity and age have a great impact on mortality and morbidity after CABG⁷. Age is associated with vascular changes that result in reducing physiological reserves. In elder patients undergoing cardiothoracic surgery, stresses of anesthesia may often uncover the limited cardiac reserve despite the absence of impaired hemodynamic performance before surgery⁸.

Many studies suggest that preoperative statin therapy has a beneficial effect on adverse events after coronary artery bypass grafting (CABG) with reduction of in-hospital major adverse cardiac events (MACE)^{9,10}. The American College of Cardiology Foundation/American Heart Association Practice Guideline for CABG surgery provides a class I recommendation that all patients undergoing CABG surgery should receive statin therapy unless contraindicated¹¹, however the results of a current meta-analysis of randomized controlled trials suggest that perioperative statin therapy is not protective against postoperative adverse events after cardiac surgery¹², which give open questions about the effect of patient population, preexisting chronic diseases and statin dose on postoperative outcome.

Therefore the aim of our study is to investigate the cardio-protective effects of preoperative statin therapy against adverse cardiovascular events after CABG in elder patients with a coronary artery disease requiring coronary artery revascularization.

PATIENTS AND METHODS

This retrospective study included consecutive patients underwent CABG between January 2010 and December 2015 at Nasser Institute Hospital, Minia Cardiothoracic University Hospital, and Suez Canal University Hospital. The data were extracted from hospital databases and patients' medical records. The study included all patients underwent isolated primary CABG through median sternotomy during the study period. Patients with concomitant acquired or congenital cardiac surgery, patients with reoperative CABG and records with invalid data of preoperative cardiovascular medications were excluded. The evaluated endpoints of postoperative adverse outcome included postoperative in-hospital all-cause, cardiac mortality, major adverse cardiovascular events (MACE), MI and stroke.

DEFINITIONS

The definitions of certain preoperative variables included: 1) elder patient is identified when the age at surgery was

equal or greater than 65 years old; 2) obesity at body mass index (BMI) ≥ 30 kg/m²; 3) Unstable angina when there was an evidence of acute coronary syndrome without ST elevation and without detectable release of the enzymes and biomarkers of myocardial necrosis and/or class IV angina; 4) impaired left ventricular (LV) systolic function was defined when preoperative left ventricular ejection fraction (LVEF) was $< 50\%$; 5) multi-vessel CAD when the patient had 2 or more coronary vessels disease; and 6) emergent surgery when CABG needs to be performed without any impediment before the beginning of the next working day after the decision to operate.

Preoperative risk scores were defined using additive European system for cardiac operative risk evaluation (EuroSCORE)¹³, which is calculated as a sum of scores for the patient, procedure, and cardiac-related risk factors. High-intensity statin therapy referred to statins predicted to reduce plasma low-density lipoprotein cholesterol (LDL-C) levels from baseline by approximately $\geq 50\%$ (rosuvastatin 20-40 mg and atorvastatin 40-80 mg), while low- and moderate- intensity statins are predicted to reduce plasma LDL-C $< 50\%$ ¹⁴.

Regarding postoperative outcome, in-hospital mortality was defined as death due to any cause during hospital stay after CABG or within 30 days of the procedure. All-cause mortality referred to a total number of deaths, regardless of the cause. Cardiac mortality was defined as death due to postoperative MI, atrial fibrillation (AF), heart failure or cerebrovascular accident. Perioperative stroke was defined as any new focal or global fixed neurologic deficits lasting for more than 24 hours after surgery. Major adverse cardiovascular events (MACE) were defined as a composite of cardiovascular death, non-fatal MI, and stroke.

DATA COLLECTION

The collected preoperative data included: age, gender, body mass index (BMI), obesity, New York Heart Association (NYHA) functional class, unstable angina, congestive heart failure (CHF), Q wave MI, previous percutaneous coronary intervention (PCI), history of diabetes mellitus (DM) and insulin treated-diabetes mellitus (ITDM), hypercholesterolemia, hypertension, history of smoking, liver dysfunction, renal insufficiency, chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), peripheral vascular disease (PVD), atrial fibrillation (AF), left ventricular dysfunction (LVD), serum creatinine, total bilirubin, total cholesterol, the extent of CAD, priority of surgery, cardio-vascular protective drugs (Aspirin, β -blockers, ACE inhibitors, calcium channel blockers and oral nitrates). The EuroSCORE was calculated prospectively.

STATISTICAL ANALYSIS

The statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 16.0 (SPSS, Inc, Chicago, IL, USA) and R Statistical Software version 2.14.0 (Foundation for Statistical Computing, Vienna, Austria). Qualitative data were expressed as number and percent, and continuous data were expressed as the mean and standard deviation (SD). Comparison of qualitative data between independent groups was performed using Chi-square or Fisher's exact test, while quantitative data were compared using t-student test. To determine the effect of preoperative statin therapy relative to no statin therapy, multivariate analysis was performed with Cox proportional hazards regression. Hazard ratios (HRs) were

estimated with its 95% confidence interval (95% CI). Adjusted HRs of preoperative statin therapy for end-points of the outcome, were calculated after adjustment for preoperative risk scores, the extent of CAD and administration of other cardiovascular protective medications. P-value was considered significant at a level of 0.05.

RESULTS

Out of 5437 patients underwent CABG during the study period, there were 745 patients (13.7%) aged ≥ 65 years (Elder group) and 4692 patients (86.3%) aged < 65 years assigned (Non-elder group). Statins were given preoperatively for 122 elder patients (16.4%) and 781 not elder patients (16.6%). As shown in Table I, the significant

Table I. Preoperative characteristics according to statin therapy, relative to age of patients

Variables	Elder (n = 745)			Non-elder (n = 4692)		
	Statins (n = 122)	No statins (n = 623)	P-value	Statins (n = 781)	No statins (n = 3911)	P-value
Age	68.39 \pm 2.96	68.27 \pm 3.20	0.71	53.43 \pm 6.96	53.54 \pm 6.81	0.67
Female gender	22 (18%)	94 (15.2%)	0.41	116 (14.9%)	586 (15%)	0.92
BMI	28.56 \pm 5.10	28.32 \pm 4.82	0.62	28.37 \pm 4.89	28.62 \pm 5.1	0.20
Obesity	40 (32.8%)	20 (33.2%)	0.92	236 (30.2%)	1260 (32.2%)	0.27
NYHA III-IV	66 (54.1%)	349 (56%)	0.69	404 (51.7%)	1895 (48.5%)	0.09
Unstable angina	2 (1.6%)	26 (4.2%)	0.17	17 (2.2%)	125 (3.2%)	0.12
CHF	6 (4.9%)	27 (4.3%)	0.77	19 (2.4%)	84 (2.1%)	0.62
Q wave MI	21 (17.2%)	122 (19.6%)	0.54	178 (22.8%)	938 (24%)	0.47
Previous PCI	14 (11.5%)	50 (8%)	0.21	84 (10.8%)	404 (10.3%)	0.72
DM	67 (54.9%)	305 (49%)	0.22	394 (50.4%)	1855 (47.4%)	0.12
ITDM	25 (20.5%)	106 (17%)	0.35	182 (23.3%)	820 (21%)	0.14
Hypercholesterolemia	43 (35.2%)	201 (32.3%)	0.52	289 (37%)	1383 (35.4%)	0.38
Hypertension	74 (60.7%)	358 (57.5%)	0.51	419 (53.9%)	2213 (56.6%)	0.13
Current smoking	10 (8.2%)	32 (5.1%)	0.18	115 (14.7%)	583 (14.9%)	0.89
Liver dysfunction	1 (0.8%)	2 (0.3%)	0.42	7 (0.9%)	26 (0.7%)	0.48
Renal insufficiency	3 (2.5%)	15 (2.4%)	0.97	8 (1%)	50 (1.3%)	0.55
COPD	2 (1.6%)	2 (0.3%)	0.06	6 (0.8%)	25 (0.6%)	0.68
Cerebrovascular accident	4 (3.3%)	22 (3.5%)	0.88	20 (2.6%)	87 (2.2%)	0.56
Peripheral vascular disease	5 (4.1%)	8 (1.3%)	0.03*	8 (1%)	54 (1.4%)	0.42
Atrial fibrillation	1 (0.8%)	4 (0.6%)	0.82	3 (0.4%)	13 (0.3%)	0.82
LVD	29 (23.8%)	135 (21.7%)	0.60	200 (25.6%)	949 (42.3%)	0.42
Serum creatinine (mg/dl)	0.88 \pm 0.27	0.87 \pm 0.96	0.96	0.95 \pm 0.49	0.87 \pm 0.80	0.007*
Total bilirubin (mg/dl)	0.62 \pm 0.25	0.64 \pm 0.47	0.71	0.64 \pm 0.48	0.63 \pm 0.37	0.52
Multi-vessel disease	43 (35.2%)	138 (22.2%)	0.002*	306 (39.2%)	980 (25.1%)	< 0.001*
Emergent surgery	1 (0.8%)	10 (1.6%)	0.51	12 (1.5%)	79 (2%)	0.37
EuroSCORE (additive)	3.08 \pm 1.02	2.82 \pm 0.88	0.003*	0.69 \pm 0.78	0.69 \pm 0.81	0.98
Cardio-protective drugs:						
Aspirin	21 (17.2%)	122 (19.6%)	0.54	203 (26%)	835 (21.4%)	0.004*
β -blockers	92 (75.4%)	200 (32.1%)	< 0.001*	584 (74.8%)	1289 (33%)	< 0.001*
ACE inhibitors	29 (23.8%)	55 (8.8%)	< 0.001*	262 (33.5%)	360 (9.2%)	< 0.001*

BMI: Body mass index, CHF: Congestive heart failure; NYHA: New York Heart Association; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; ITDM: Insulin treated diabetes mellitus; COPD: Chronic obstructive pulmonary obstruction; LVD: Left ventricular dysfunction; EuroSCORE: European system for cardiac operative risk evaluation; ACE: angiotensin converting enzyme. *significant difference

preoperative characteristics of not elder patients on statin therapy included the presence of higher levels of serum creatinine (0.95 ± 0.49 versus 0.87 ± 0.80 mg/dl, $p = 0.007$), multi-vessel CAD disease (39.2% versus 25.1%, $p < 0.001$), administration of aspirin (26% versus 21.4%, $p = 0.004$), administration of β -blockers (74.8% versus 33%, $p < 0.001$) and administration of ACE inhibitors (33.5% versus 9.2%, $p < 0.001$). The preoperative profile of elder patients on statin therapy included also significant presence of multi-vessel CAD disease (35.2% versus 22.2%, $p = 0.002$), administration of β -blockers (75.4% versus 32.1%, $p < 0.001$) and administration of ACE inhibitors (23.8% versus 8.8%, $p < 0.001$), in addition to peripheral vascular disease (4.1% versus 1.3%, $p = 0.03$) and higher additive risk scores (3.08 ± 1.02 versus 2.82 ± 0.88 , $p = 0.003$).

In all patients the hazard ratio of statin therapy relative to no statin therapy was less than 1 for all-cause mortality, cardiac mortality, MACE, MI, and stroke, which favors statin therapy whether the patient is elder or not, however, these ratios did not reach the level of significance (Tab. II). In elder patients, there was no significant association between preoperative statin therapy and post-operative in-hospital occurrence of all-cause mortality,

cardiac mortality, MACE, MI and stroke before or after adjustment to preoperative risk scores, cardiovascular protective medications and extent of coronary artery disease (Tab. II). In the non-elder group, patients on pre-operative statin therapy had marginally significant lower hazard risks for cardiac mortality ($p = 0.03$), before and after adjusting confounders by multivariable analysis, however, the risks of the statin relative to no statin therapy for other evaluated end-points of outcome were not statistically significant (Tab. II). Comparing the adjusted HRs of preoperative statin therapy between elder and non-elder patients revealed non-significant interaction p -values for any of the studied end-points (Tab. III).

The adjusted HRs for all-cause mortality, cardiac mortality and MACE favor statin therapy in all patients and non-elder patients, however, it favors no statin therapy in elder patients (Fig. 1). The adjusted HRs for MI and stroke were nearly similar between the study age groups and favor statin therapy in all patients, elder patients and non-elder patients (Fig. 1). The adjusted HRs for all-cause mortality, cardiac mortality, MACE, MI, and stroke did not favor preoperative administration of high dose intensity statins in elder patients, however, its use was favorable for all end-points of outcome in all patients and non-elder

Table II. Influence of statins on end-points of outcome within 30 days after surgery, relative to age of patients, before and after adjustment to preoperative risk scores, cardiovascular protective medications and extent of coronary artery disease. Cox regression was used to calculate hazard ratio (HR) and its 95% confidence interval (CI).

Outcome	Statins	No statins	Unadjusted		Adjusted	
			HR (95%CI)	P-value	HR (95%CI)	P-value
Elder patients						
Number	122	623				
All-cause mortality	5 (4.1%)	21 (3.4%)	1.22 (0.46-3.23)	0.68	1.26 (0.47-3.36)	0.63
Cardiac mortality	2 (1.6%)	7 (1.1%)	1.46 (0.30-7)	0.63	1.52 (0.31-7.32)	0.60
MACE	5 (4.1%)	22 (3.5%)	1.16 (0.44-30)	0.75	1.21 (0.46-3.2)	0.69
MI	2 (1.6%)	12 (1.9%)	0.85 (0.19-3.83)	0.83	0.89 (0.19-3.98)	0.88
Stroke	1 (0.8%)	6 (1%)	0.85 (0.10-7.12)	0.88	0.89 (0.10-7.4)	0.91
Non-elder patients						
Number	781	3911				
All-cause mortality	26 (3.3%)	161 (4.1%)	0.80 (0.53-1.21)	0.30	0.81 (0.53-1.23)	0.33
Cardiac mortality	4 (0.5%)	58 (1.5%)	0.34 (0.12-0.94)	0.03*	0.34 (0.12-0.93)	0.03*
MACE	16 (2%)	124 (3.2%)	0.66 (0.39-1.11)	0.12	0.66 (0.39-1.12)	0.13
MI	9 (1.2%)	43 (1.1%)	1.04 (0.50-2.13)	0.91	1.01 (0.49-2.07)	0.97
Stroke	3 (0.4%)	27 (0.7%)	0.55 (0.16-1.81)	0.32	0.52 (0.15-1.73)	0.28
All patients						
Number	903	4534				
All-cause mortality	31 (3.4%)	182 (4%)	0.85 (0.58-1.24)	0.41	0.86 (0.59-1.27)	0.46
Cardiac mortality	6 (0.7%)	65 (1.4%)	0.46 (0.20-1.06)	0.07	0.46 (0.19-1.06)	0.07
MACE	21 (2.3%)	146 (3.2%)	0.71 (0.45-1.13)	0.15	0.71 (0.45-1.13)	0.15
MI	11 (1.2%)	55 (1.2%)	0.99 (0.52-1.90)	0.99	0.98 (0.51-1.88)	0.95
Stroke	4 (0.4%)	33 (0.7%)	0.60 (0.21-1.70)	0.34	0.57 (0.20-1.64)	0.30

MACE: Major adverse cardiovascular events; MI: Myocardial infarction; HR: Hazard ratio; CI: Confidence interval. *significant difference

Table III. Comparing adjusted hazard ratios of pre-operative administration of statins and use of high dose intensity statins for end-points of outcome, between elder and non-elder patients.

Outcome	Administration of statins		High dose intensity statins	
	Ratio of HRs (95%CI)	Interaction p-value	Ratio of HRs (95% CI)	Interaction p-value
All-cause mortality	1.55 (0.53-4.53)	0.20	2.40 (0.81-7.07)	0.055
Cardiac mortality	4.47 (0.67-29.4)	0.059	4.57 (0.46-44.7)	0.09
MACE	1.83 (0.60-5.52)	0.44	3.60 (0.97-13.28)	0.02*
MI	0.88 (0.16-4.74)	0.44	3.85 (0.40-36.57)	0.11
Stroke	1.71 (0.14-20)	0.33	2.29 (0.22-23.81)	0.24

HR: Hazard ratio; CI: Confidence interval. *significant difference

group (Fig. 2). Comparing the adjusted HRs of preoperative high-intensity statin therapy between elder and non-elder patients revealed non-significant interaction p-values except for the occurrence of MACE (Tab. III).

DISCUSSION

The number of elderly patients with CAD has substantially increased in recent decades. Treatment of CAD in

these patients may be challenging due to the greater severity of coronary damage and the higher risk profile¹⁵. Coronary artery disease accounts for more than half of cardiovascular disease-related deaths and nearly 82% of all deaths attributable to CAD occur in patients older than 65 years¹⁶.

Multiple clinical trials have consistently demonstrated the beneficial role of statins to reduce the risk of recurrent cardiovascular events and improve survival in patients with

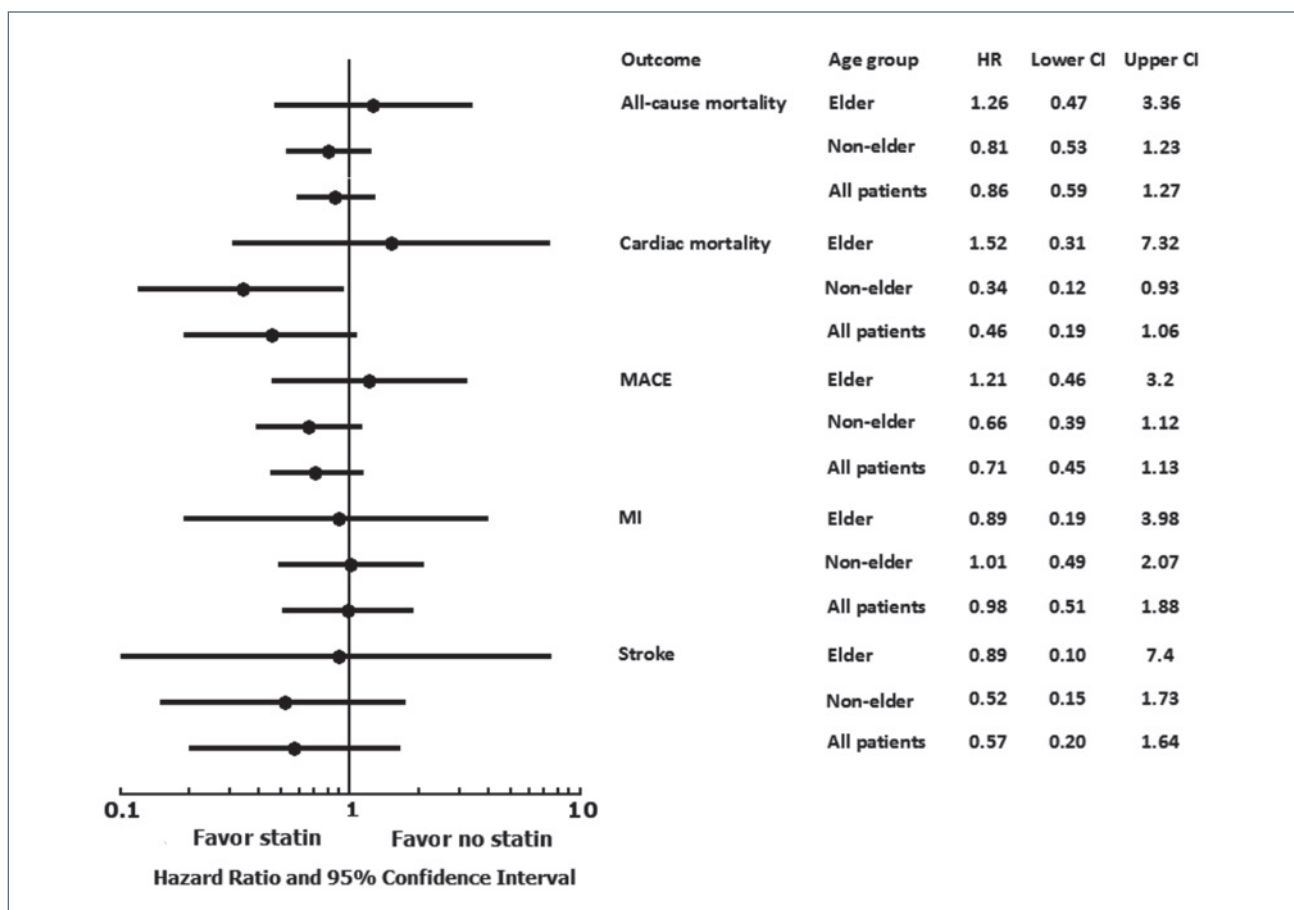


Figure 1. Forest-plot of adjusted hazard ratio (HR) of pre-operative statin administration, relative to age of patients, for post-operative all-cause mortality, cardiac mortality, myocardial infarction (MI) and stroke.

CAD, even after CABG surgery^{9 10 17}, which is considered as an effect not shared by the other cardiovascular drugs¹⁸. In elderly, statin therapy has been demonstrated to be effective for primary and secondary prevention of CAD in regard to coronary heart disease mortality, myocardial infarction, need for revascularization, and stroke¹⁹⁻²¹. Despite the considerable benefits of statins, a debate exists to the contemporary statin treatment-risk paradox and the need to balance the benefits of statins with the potential risks to the elderly especially altered metabolism, comorbidities, polypharmacy and drug-drug interactions, side effects, cognitive limitations, and cost^{22 23}. In the present study, there was an underuse of statins pre-operatively as it was prescribed only in 903 patients (16.6%) out of 5437 patients underwent CABG. In fact, despite the established benefits of statin use in patients with a proven CAD, a significant underuse of statins among these patients has been reported. Arnold et al.²⁴ concluded that despite the robust clinical trial evidence, a substantial number of patients with obstructive CAD remained untreated with statins. The study by

Gamboa et al.²⁵ showed that statins were used only by 58.4% of patients with CAD, as they do not receive guideline-concordant lipid-lowering therapy. The underuse of statins in patients with proven CAD may be explained by the concerns about increased risk of adverse side effects associated with statin therapy, however, studies on patients undergoing major vascular or cardiac operations reported no increase in the risk of post-operative statin-related adverse effects^{26 27}. The significant pre-operative characteristics of our elder patients on statin therapy included peripheral vascular disease (PVD), multi-vessel CAD and higher risk scores. On the other hand, significant preoperative characteristics of elder patients on statin therapy included raised serum creatinine and multi-vessel CAD. These findings confirm the extension of statin use beyond its anti-hyperlipidemia effect, as it is widely recommended for secondary prevention of cardiovascular adverse events in a wide range of risky individuals²⁸. Consistent with other studies, we favored preoperative statin therapy in patients with CAD regardless of

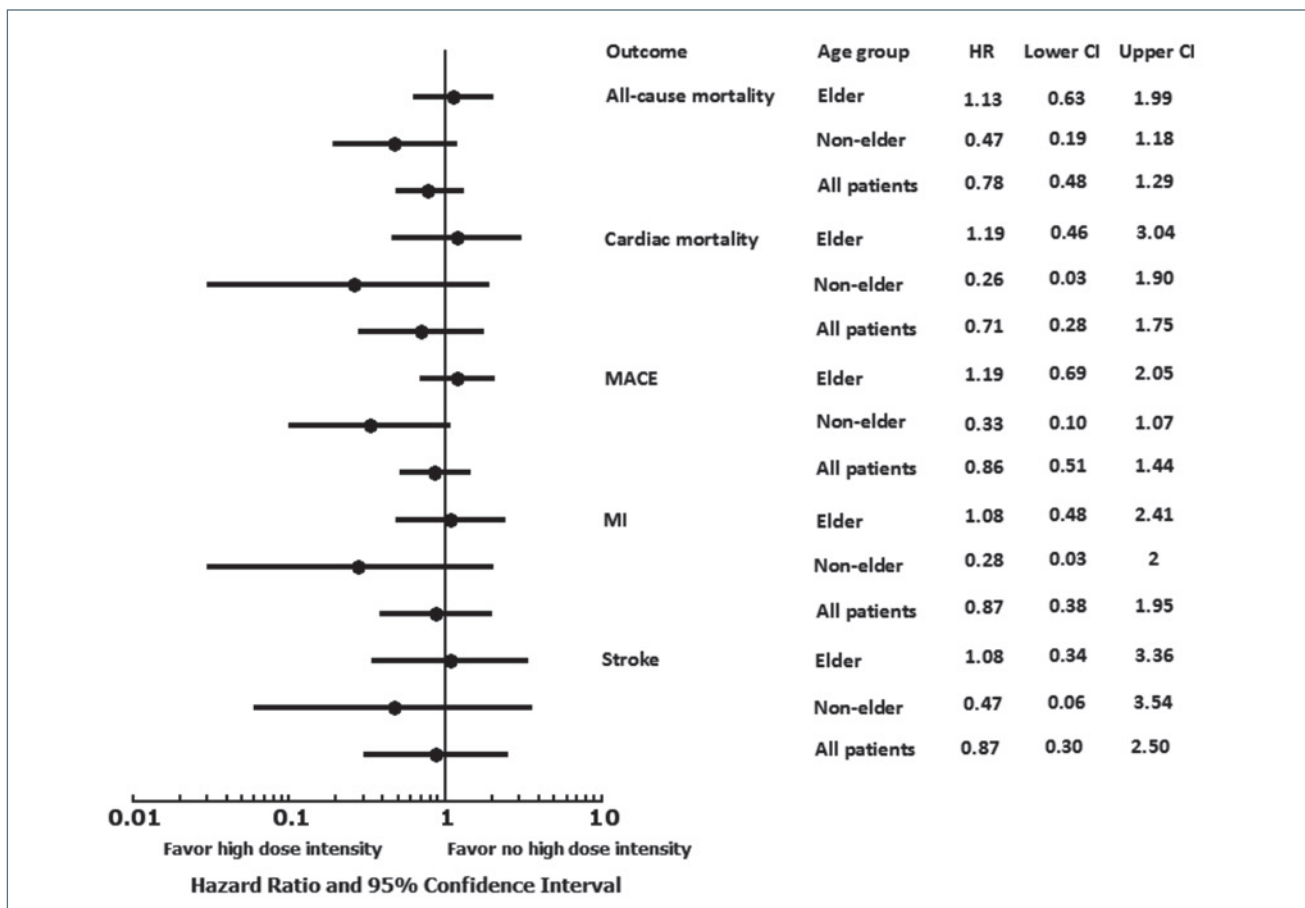


Figure 2. Forest-plot of adjusted hazard ratio (HR) of preoperative dose intensity of statins, relative to age of patients, for post-operative all-cause mortality, cardiac mortality, myocardial infarction (MI) and stroke.

patient age to reduce the hazard for repeated adverse cardiovascular events. The effects of pre-operative statin therapy were not significantly different between elder and non-elder patients, thus we should not deprive elder patients with CAD from any suspected benefit of statin therapy.

However, there is a lack of statistical significance of our obtained data regarding the comparison of the effects of statin and no-statin groups on post-operative adverse outcomes (all-cause mortality, MACE, MI and stroke) after CABG, which is consistent with certain retrospective CABG studies which have not demonstrated a positive effect of pre-operative statin therapy. The inclusion of younger patients, as well as better pre-operative medical treatment has been advocated by these studies to explain the beneficial effects of statins on early outcomes after CABG^{29,30}.

Therefore, adjusting for pre-operative patient characteristics and constricting of prospective randomized trials were recommended to confirm the role of statin therapy for secondary prevention in patients with CAD³¹. However, after adjusting for pre-operative risk factors and medications, the study by Liakopoulos and Wahlers³², showed that statin therapy was not independently associated with improved survival after surgery. This finding also contradicted evidence suggesting that preoperative statin therapy favorably impacts early mortality after CABG and raised questions regarding recommendations for routine statin pre-treatment before surgery. In a recent study by Kunt et al.³³, after matching of statin and no-statin groups by propensity score analysis, peri-operative atorvastatin treatment was not found to be associated with reduced post-operative AF and cardiac mortality in patients undergoing isolated CABG above the age of seventy years. Also, recent randomized controlled trials show potential detrimental effects. In a recent meta-analysis of 23 randomized controlled trials involving 5102 patients³⁴, there is no evidence that statin therapy in the days prior to cardiac surgery is beneficial for patients' outcomes. Particularly, statins are not protective against postoperative AF, MI, stroke, or infections. Statins are associated with a possible increased risk of acute kidney injury and a detrimental effect on hospital survival could not be excluded. This meta-analysis raised open questions on patient population, preexisting chronic disease, and length and dose of the treatment.

An interesting finding in our study is the significant difference between elder and non-elder patients in adjusted hazard ratios of high dose intensity statins (rosuvastatin 20-40 mg and atorvastatin 40-80 mg) for the occurrence of MACE, which favors statins of low and moderate dose intensity in elder patients and high dose intensity in non-elder patients.

The role of high dose intensity statins for secondary prevention in patients with CAD is currently evaluated in an observational study of 509 766 veterans with established atherosclerotic CVD which suggest that high-intensity statins reduce all-cause mortality, even in older adults currently not recommended for such intense therapy³⁵. A debate exists when the efficacy of statin doses are evaluated in elder patients. In aged 65 years and over, the efficacy of statins for secondary prevention of acute MI and death appears to be a class effect, with no difference observed between high or low potency statins²⁰. This may be explained by that lowering LDL-C has a smaller impact on the relative risk of CAD as age increases³⁶.

Little data exists in the literature regarding the evaluation of the effect of preoperative statin dose intensity on adverse outcome after CABG. In a study by Elmarasawi et al.³⁷, the higher-dose regimen of atorvastatin (80 mg/day) resulted in a significant reduction in the C-reactive protein (CRP) level, which may explain the benefits of high-intensity doses. In a recent study by Curtis et al.³⁸, pre-operative statin therapy with a dose of more than 20 mg atorvastatin or equivalent were independently associated with decreased 30-day all-cause mortality after CABG.

In our study, the questionable beneficial effect of pre-operative high dose intensity statins in elderly could not urge us to avoid these doses in such age group, as the status of CAD may indicate high doses when a risk for recurrent serious events exists. However, limitation of the routine use of high dose intensity statins irrelevant to the patient condition may be adequate to obtain optimal benefit/risk balance of preoperative statin therapy. The limitations of this study included: First, the retrospective nature, however adjustment to risk scores, cardio-vascular medications and extent of CAD may reduce the suspected bias of this type of studies; Second, small number of elder patients on pre-operative statin therapy, explained by underuse of statins; and Third, our definition of elderly is based on age cut-off of 65 years, while other cutoff points exist, but we chose this cutoff due to small number of septuagenarians and octogenarians in our patient cohort during the study period.

In conclusion, due to the lack of statistical significance, questions are raised about the benefits of the pre-operative use of statins before CABG. However, we could not neglect the proved benefits in other studies, thus patients with CAD should not be deprived of any suspected benefit of statins if they had an increased risk for recurrence of serious events. Although the hazard ratios for postoperative adverse events favor no pre-operative statin therapy in elder patients aged 65 years old or more, these ratios were not significantly different

between elder and non-elder patients. The cardio-protective effects of preoperative high-intensity statins are questionable in elder patients. High dose intensity statins associated with increased hazard ratios for adverse events after CABG in elder patients particularly for MACE. The use of statins preoperatively regardless to dose intensity or age of patients is favored which support the need to increase its prescription, however, cautions are recommended to reduce unnecessary routine use particularly with high-intensity doses in elder patients. Further large-scale and prospective studies are recommended to obtain more conclusive findings.

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DECLARATION OF SOURCES OF FUNDING

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Older adult perspectives on their role in a Community-Based Health Profession Education Project

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Background and Aims: Although 18.7 million adults ages 55 and older volunteer in their communities each year, it is unclear which factors motivate them to participate in community-based education programs, such as the Partners in Care program. Partners in Care pairs medical, physical therapy, and nursing students together to conduct home care visits with older adults. This project seeks to understand how older adults define their role as educators and learn which factors motivate them to volunteer.

Methods: This mixed-methods study employed a survey measuring attitudes about volunteering and an optional focus group. The research team developed the survey tool, which included 25 Likert scale items and two open-ended questions. The focus group consisted of 13 randomly selected program volunteers.

Results: A total of 101 surveys were sent with a response rate of 62%. Respondents' ages ranged from 65 to > 80. Alpha factor analysis of the survey and thematic analysis of focus group data revealed seven themes for why older adults volunteer: altruism, personal development, feeling part of a community, education of students, uniqueness of program, engagement with students, and sharing unique health experiences as older adults. Feedback and suggestions were also collected.

Conclusions: Partners in Care provides students with an opportunity to engage older adults, meet established geriatric competencies, and gain insight into interprofessional teamwork. By understanding older adults' perspectives on their role as educators, we hope to improve volunteer satisfaction, expand the program, and encourage further interactions between older adults and health professional students.

Key words: Geriatrics, Volunteers, Medical education, House calls, Interdisciplinary communication

INTRODUCTION

Longer life spans and aging members of the baby boomer generation will have an immense impact on the landscape of healthcare in America. By 2030, the population of Americans aged 65 and above is projected to double, to account for approximately 20% of the U.S. population¹. Regardless of which specialty graduating healthcare professional students choose to pursue, nearly all will be faced with the challenge of providing care to older adults. In recent years, the American Geriatrics Society has called for increased exposure to geriatric medicine during medical school, and in 2009

the Association of American Medical Colleges (AAMC) released a consensus on 26 minimum geriatrics competencies for graduating medical students^{2,3}. Unfortunately, medical schools have limited time in the curriculum to dedicate to the aforementioned competencies. We believe community-based education experiences led by older adult educators can facilitate the acquisition of these skills.

One such program, Partners in Care (PIC), exists at the Oakland University William Beaumont School of Medicine (OUWB). PIC seeks to provide students with an experience of what it means to live with a chronic condition as an older adult. This required program

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takes place during the second semester of the first year of medical school. First-year medical and nursing students and third-year physical therapy students are paired together so that each has a partner from a different professional program. Before conducting visits, students attend lectures by geriatric care providers on the intricacies of conducting histories, physicals, and assessments in older adults. Students complete two visits, during which they conduct various assessments on fall risk, nutritional and functional status, activities of daily living, environmental hazards, and perform an abbreviated physical exam. After each visit students write a reflection, and after all teams have completed both visits, larger groups of approximately 30 students participate in a debriefing session led by faculty.

Research on similar undergraduate medical schools' home-visit programs suggests that participation in a home-visit improves students' comfort and attitudes toward older adults^{4,5}. O'Donnel et al. found that home visits facilitated the teaching of multiple AAMC Minimum Geriatric Competencies, and provided information about community resources and teamwork among healthcare professionals⁶. Although 18.7 million adults ages 55 and older volunteer in their communities each year⁷, it is unclear which factors impel them to participate in community-based education programs. While much data exists on the benefits of such programs on medical students, there are few studies that seek to understand the motivation for older adults who volunteer, and the effects that these programs have on them.

A qualitative study on patients' role as teachers in a U.K. undergraduate medical school found that patients saw themselves in active roles as teachers, as experts in their medical conditions and as facilitators in the development of students' professional skills and attitudes⁸. Furthermore, Stacy and Spencer concluded that patients themselves felt as though they had benefitted from participating, felt less isolated, learned more about their health conditions, and were overall very satisfied with their experiences. Another qualitative study that looked closely at patients' views and feelings on their participation in an undergraduate medical student program identified altruism and personal gain as underlying components to continued participation⁹. Additionally, this study by Coleman and Murray discovered that patients had concerns about embarrassment, reinforcement of the sick role, and students obtaining personal health information⁹. These findings demonstrate that home visit programs have the potential to benefit adult volunteers, but that care must be taken to ensure confidentiality and comfort just as in the clinical setting.

Older adult PIC volunteers welcome health professional students into their homes and provide them with a unique experience. We believe that this team home visit provides

opportunities and challenges that cannot be replicated in a classroom environment with standardized patients. For many students in our program, this home visit is the first opportunity to practice communication and exam skills with autonomy without direct supervision of a supervising physician. It also exposes students to older adults who wish to 'age in place,' and the various resources needed to do so safely. Without willing volunteers, community-based education programs cannot exist. Therefore, it is essential that we better understand what motivates volunteers to participate. We hypothesize that adults are motivated to volunteer due to perceived benefits to themselves, students, the education programs, and the community, as well as their connections and past experiences within the healthcare system.

METHODS

This mixed-methods study involved 1) a survey measuring attitudes and perceptions towards volunteering and 2) the option to participate in a focus group. The survey included 25 Likert-scale items, 2 open-ended questions, and 3 demographic questions. The research team created the survey tool based on five themes that were adapted from a previous study on measuring motivation to volunteer¹⁰. The five themes were as follows: benefit to volunteer, benefit to students, benefit to health profession education programs, benefit to community, and connection to health profession, health system or university. Each of the 5 themes had 5 corresponding statements for a total of 25 items. Participants were asked to indicate how strongly each statement influenced their decision to volunteer for PIC. The Likert scale ranged from "Not at all" to "very strongly." The two open-ended questions asked for additional factors other than those included in the Likert scale items that influenced volunteers' motivation to participate in the program, and whether or not they would recommend a friend or family member to become a volunteer for PIC. Additionally, a focus group was held with 13 randomly selected PIC volunteers. The discussion was led using a pre-determined set of semi-structured interview questions. Participants were asked to describe their role and how they felt it impacted students, reasons for volunteering, and who in their opinion benefited from older adults volunteering. The discussion was transcribed and analyzed by the authors.

RESULTS

A total of 101 surveys were sent with a response rate of 62%. Sixty-three percent of responders were female,

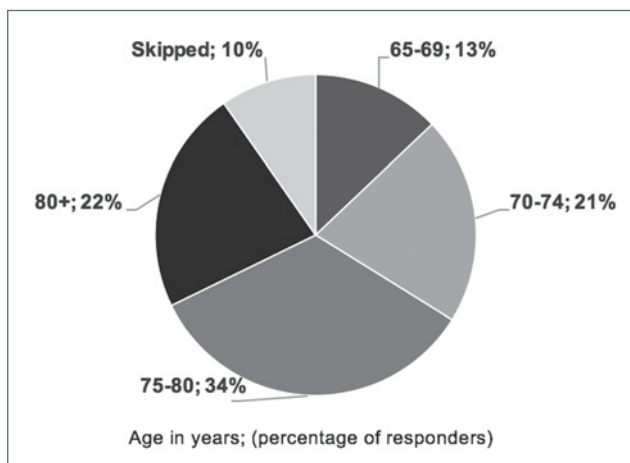


Figure 1. Survey demographic data: age.

27% were male, and 10% did not specify their sex. Ages of responders ranged from 65 to over 80 years old (Fig. 1), and numbers of years of participating in the PIC program ranged from 1 to 4 (Fig. 2).

Survey data for the 25 Likert scale items were analyzed to determine which factors were rated as having most strongly influenced survey respondents' motivation to volunteer. A value was assigned to each of the 5 Likert scale options (0 = not at all, 1 = very little, 2 = moderately, 3 = strongly, and 4 = very strongly). The number of responses, mean, and standard deviation are listed in Table I.

The top 3 rated variables in order of significance were:

5. "Home visits provide students with a better understanding of patients' true lifestyle compared to a clinic/hospital encounter";
6. "By volunteering for Partners in Care, I am helping educate future health professionals," and;

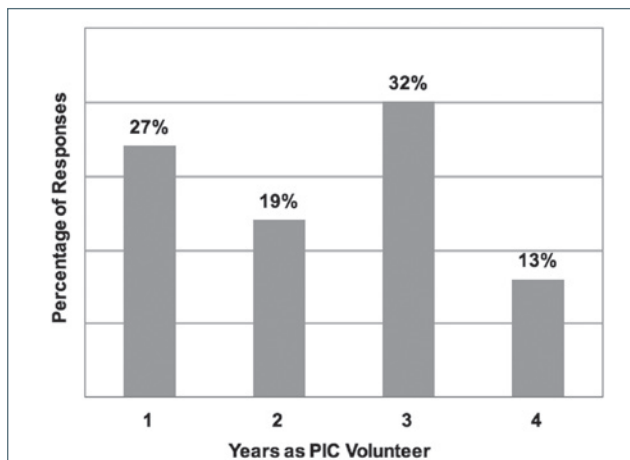


Figure 2. Survey demographic data: years participating in PIC.

8. Students who participate in Partners in Care will have a better understanding of health conditions of their future patients".

Additionally, the 25-question survey was examined to investigate the internal relationships between the questions using alpha factor analysis. A promax rotation was used instead of a varimax rotation because it is believed that the factors would be correlated. Typically, with a factor analysis it is best to have at least 100 survey respondents or 10 times the number of questions. Two items from the original 25-item survey (Tab. I, items 18 and 23) were removed from the final alpha factor analysis due to ambiguity in wording that was recognized after the survey was sent. There were 46 surveys that had complete data for the 23 items that were included in the final alpha factor analysis. Given this, all results should be interpreted with extreme caution due to the small sample size. Alpha-factor analysis revealed four groups of items that loaded high on a factor, defined as a loading value of > 0.40 . Based on the survey items that made up each of the four factors, a unifying theme was developed by the authors: 1) personal development; 2) education of students; 3) altruism; and 4) feeling part of a community. The results from the alpha factor analysis are shown in Table II. Questions that loaded high (≥ 0.40) on a factor are displayed with different shades corresponding to different themes. Questions that loaded on more than one factor and those that did not load on any factor are indicated with asterisks. Personal development and education of students had the highest Cronbach values (0.93, 0.81 respectively) and altruism and feeling part of a community had the lowest Cronbach values (0.69, 0.74 respectively) (Tab. I).

Because many of the returned surveys had incomplete data, analysis was conducted to see if there was bias for who completed each of the 25 survey questions. This was done with a Fisher's Exact test looking at missing data (yes/no) for each of the 25 survey questions with respect to the respondent's gender, age and number of volunteer years. There was no systematic bias with respect to missing values (all p-values were > 0.05) (Tab. II). The transcript of the discussion from the focus group was analyzed using grounded theory by the three authors¹¹. This revealed seven themes: altruism, personal development, feeling part of a community, uniqueness of program, engagement with students, education of students, and sharing unique experiences as older adults (Tab. III).

DISCUSSION

While existing literature focuses on students' perspectives of community-based education programs, we

Table 1. Survey Analysis. A value was assigned to each of the survey's 5-likert scale options (0: not at all; 1: very little; 2: moderately; 3: strongly; and 4: very strongly). The number of responses, mean, and standard deviation are listed.

Survey Item	N mean (SD)
1. Volunteering for partners in care is a good way to interact with healthcare students	60 3.30 (0.79)
2. Volunteering for partners in care makes me feel better about myself	56 2.50 (0.91)
3. I wanted to improve my own knowledge of medicine	57 2.21 (1.08)
4. Home visits are convenient for me	59 2.98 (0.96)
5. Volunteering improves my own attitude towards my health	58 2.69 (0.90)
6. Home visits provide students with a better understanding of patients' true lifestyle compared to a clinic/hospital encounter	60 3.50 (0.60)
7. By volunteering for partners in care, I am helping educate future health professionals	60 3.48 (0.65)
8. Students who participate in Partners in Care will have a better understanding of health conditions of their future patients	60 3.38 (0.69)
9. Because I volunteer, students have a unique experience	59 3.12 (0.70)
10. Students will benefit because of volunteers like myself	59 3.08 (0.62)
11. I feel I can make a positive impact on the education program through volunteering	60 3.17 (0.74)
12. Because I volunteer, students receive a well-rounded educational experience	59 2.95 (0.65)
13. My volunteering and feedback help strengthen the education program	58 3.17 (0.70)
14. Because I volunteer, this program can provide more educational experiences to students	59 3.27 (0.72)
15. My volunteering is a valuable addition to the education program	59 2.92 (0.75)
16. I volunteer to show members of the medical community that I care	58 2.74 (0.91)
17. Volunteering creates a better society	59 3.14 (0.80)
18. If I did not volunteer, the students would not have access to a home visit experience	54 2.76 (0.93)
19. I am giving back to my community through volunteering	59 3.03 (0.85)
20. My volunteering will benefit the medical community	59 2.76 (0.86)
21. I have a personal connection to Oakland University	59 1.27 (1.45)
22. I have a personal connection to Beaumont Hospitals	58 1.97 (1.62)
23. I or a member of my family has attended a health profession program	56 2.07 (1.67)
24. Volunteering is a way to continue a family tradition of helping others	59 2.59 (1.27)
25. A friend/ family member recommended that I volunteer for Partners in Care	56 2.11 (1.66)

chose to focus on the older adult volunteer perspective. Our data demonstrates that there are many factors that influence older adults' decisions to volunteer for community-based education programs such as PIC. Themes that we uncovered include: personal development, education of students, altruism, feeling part of a community, uniqueness of program, engagement with students, and sharing unique health experiences as older adults. This supports the previous studies that found positive perceptions in volunteers to such programs^{8,9}. Factors that were scored as most strongly influencing an older adult's decision to volunteer include 1) their feelings that the program provides students with a unique experience; 2) their service is helping to educate future health professionals; and 3) that in participating, students will have a better understanding of their future patients' health experiences. Overall, older adults expressed satisfaction in volunteering and in working with health professional students.

This study has limitations. It is a single institution study with a relatively small sample size. Additionally, the

survey tool was created by the research team and has no established reliability. Due to a small sample size, the factor analysis was not very stable, by removing just 2 questions, which resulted in including 4 more survey participants, the factors changed. Further research in this area should include multiple sites, as there are many medical schools with similar programs. Additionally, greater investigation into the potential negative effects that participation has on older adults could be researched. Finally, one might investigate if there are measurable differences in health outcomes or in compliance with treatment plans among older adults who volunteer for health profession education programs *versus* those who do not.

In gathering suggestions from program volunteers, we found that overall the adult volunteers were disappointed that they lost touch with their student visitors and expressed a desire to have some feedback from their student visitors about what they had learned from the visits, as well as general things, such as how they are progressing in their studies. The PIC program currently

Table II. Alpha-factor analysis of survey data. Questions that loaded high (≥ 0.40) on a factor are displayed with different shading.

- Personal Development (Cronbach = 0.93);
- Altruism (Cronbach = 0.69);
- Education of Students (Cronbach = 0.81);
- Feeling Part of a Community (Cronbach = 0.74)

Survey item
*PIC is a good way to interact with healthcare students
*Volunteering makes me feel better about myself
**Volunteering creates a better society
I wanted to improve my own knowledge of medicine
Home visits are convenient for me
Volunteering improves my own attitude towards my health
Visits provide students with a better understanding of a patient's true lifestyle
I am helping educate future health professionals
Students will have a better understanding of health conditions of their future patients
Because I volunteer, students have a unique experience
Students will benefit because of volunteers like myself
I can make a positive impact on the education program
Because I volunteer, students receive a well-rounded educational experience
My volunteering and feedback help strengthen the education program
Because I volunteer, this program can provide more educational experiences to students
My volunteering is a valuable addition to the education program
I volunteer to show members of the medical community that I care
I am giving back to my community through volunteering
My volunteering will benefit the medical community
I have a personal connection to Oakland University
I have a personal connection to Beaumont Hospitals
Volunteering is a way to continue a family tradition of helping others
A friend/ family member recommended I volunteer for Partners in Care

* Questions that did not load on any factor; ** Questions that loaded on more than one factor

requires students to complete two home visits over the course of 2 months. Due to the organization of the course and the large number of students compared to older adult volunteers, it would be challenging to request additional visits. Suggested solutions include 1) keeping in contact via e-mail or telephone periodically to provide continuity, as well as 2) creating an optional visiting service between the pool of adult volunteers and students interested in volunteering and providing companionship. These findings further confirm that interactions with students are a major motivating factor in an older adult's decision to participate in PIC.

PIC provides students with an opportunity to engage with older adults, practice geriatric care competencies, and gain insight into inter-professional teamwork. Additionally, PIC is a forum in which older adults can

Table III. Thematic analysis of Focus Group transcript thematic analysis was conducted based on grounded theory¹ and revealed seven themes. The table below contains quotes by volunteers that best exemplified each theme.

Theme	Quote from Focus Group participant
Personal development	...I can learn so much from everybody that I work or volunteer with. ...I've spent my whole life teaching young people, and when I retired I didn't wish to stop that.
Education of students	I think it's important to help students...especially for medical students to get the opinion of somebody other than people that they deal with all the time—other doctors, other medical people, to hear from a patient's point of view, how they feel. ...[Students] will have learned something that they might not have in, almost an ordinary sense, that isn't a classic problem, or a textbook problem that they can do...
Altruism	...Much has been given to me, so as a result, if there is anything that I can do to give something back, that is of value.
Feeling part of a community	I have to participate in the community and this is one way that I can do it very easily, and very pleurably in all of the experiences that I've had so far.
Uniqueness of program	...It was extremely important in terms of perhaps taking them out of a comfort zone. They work in exam rooms and classrooms, and now they have to go into someone's living room or home... ...I was very intrigued by the combination of the nursing student and the medical student... ...The importance of the medical students getting the real-world experience of what a senior citizen goes through, and for them to get into the homes and see what the homes are actually like...
Engagement with students	...I like [their] eagerness and [their] wanting to learn... It was delightful meeting the students. I thought we had so many interesting students and had great conversations with them...
Unique health experiences as older adults	...We as people who have experienced health problems and been in the hospital, and me as a nurse also, on the other, side...I can have something to offer. ...I think that is so important today, that they see where we are coming from at our age versus their age.

interact with young professionals while sharing unique experiences and knowledge. Students see first-hand how medicine and disease affects the lives of older adults and challenges them to think beyond diagnosis and treatment. This experience, which requires very little additional faculty time and coordination, has the potential to be an asset to any medical school or health professional curriculum, as well as the communities in which they are located.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Important considerations in the assessment of seniors who are aging with cognitive or intellectual disabilities

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The primary objective of the present review is to summarize key findings on the assessment approaches and interviewing techniques that best meet the functional capacity of elderly individuals who are aging with cognitive and/or intellectual disabilities. Assessment techniques are not always relevant to the population of seniors who are aging with cognitive impairment or intellectual disabilities, because these individuals are often unable to describe or communicate their needs effectively. This makes interviewing such clients problematic, not only for healthcare professionals, but also for everyone who is engaged in providing support and care to seniors who are aging with such disabilities. A structured literature search was conducted in PubMed, MedLine and CINAHL from 1990 until August 2017 using terms such as “elderly”, “cognitive impairment”, “intellectual impairment” and other synonyms. A total of 64 articles were identified and further analyzed. Based on the current body of literature, assessment of seniors who are aging with any degree of cognitive and/or intellectual impairments is complex and there is no gold standard. However, there are several strategies that can be helpful in clinical practice and research. Further research is needed on both cognitive and intellectual disabilities to establish a sound evidence for description, screening for risk factors or undetected problems, setting rehabilitation goals, and monitoring treatment progress.

Key words: Aging, Cognitive impairment, Intellectual disability, Functional assessment

As we drove home down the 405 that summer, I tried to think of all the parts of myself that I was ashamed of, that I thought didn't fit. I talked too fast, cursed, couldn't spell, couldn't sit still, mispronounced words, and interrupted people. I cried for a minute then told myself to stop.

Jonathan Mooney, *The Short Bus* (p. 32)

INTRODUCTION

Statistics provide considerable evidence that the population of seniors is going to increase in upcoming decades. As the older population grows in relation to the overall population, and the prevalence of chronic disabling diseases increases, the need for rehabilitation and long-term health care services will also increase. Recently,

more attention has been given to the aging population. Unfortunately, this attention has not adequately covered a very important segment of the population of seniors: the elderly individuals who are aging with cognitive or intellectual impairments. Cognitive functions are broadly defined as the ability to “think” which includes the ability to concentrate (i.e., pay attention), remember, and learn¹. Many texts refer to executive functions as cognitive in

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nature. Executive functions include the ability to plan, manipulate information, initiate, and terminate activities, and recognize errors ². According to the American Association on Intellectual and Developmental Disabilities, Intellectual disability is a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability develops before the age of 18 ³.

Assessment of functional performance in the population of seniors who are aging with cognitive or intellectual impairments is needed to make informative decisions regarding healthcare plans and interventions to improve their quality of life. However, there is little consensus and much confusion regarding how best to measure functional status in cognitively or intellectually impaired individuals. Considering that the population of seniors with such disabilities is expected to increase in the coming decades, there is a need of evidence-based research to inform practice and healthcare systems about the requirements and demands of this population. This study presents a summary and critiques of the instruments available in literature for the assessment of functional status in cognitively impaired seniors.

The primary objective of the present review is to summarize key findings on the assessment approaches and interviewing techniques that best meet the capacity of elderly individuals who are aging with cognitive and/or intellectual disabilities. Assessment techniques are not always relevant to the population of seniors who are aging with cognitive impairment or intellectual disabilities, because these individuals are often unable to describe or communicate their disabilities effectively. This makes interviewing such clients problematic, not only for healthcare professionals, but also for everyone who is engaged in providing support and care to seniors who are aging with such disabilities.

DISCUSSION

General overviews to the literature, including sources for assessment scales, recommend important considerations to be accounted when choosing a functional status measure ⁴⁻⁸. Important guidelines on the assessment of aging individuals with intellectual disabilities were suggested by North American and British publications recently ⁹⁻¹¹. Assessments are often complicated in people with cognitive or intellectual impairments, and it is therefore essential to use validated outcome measures when evaluating seniors with cognitive or intellectual disability ¹².

According to the ICF model, successful assessment of elderly persons with functional cognitive and intellectual

deficits should take in consideration, not only the physical condition, but also the patient's personality, the environment and their coping skills. Before conducting any assessments for elderly individuals, there is a very important question we should ask: who is our client?

When health care professionals are working with seniors, these clients are expected to communicate with the therapist effectively and to participate in the decision-making process. This situation changes with individuals with communication disorders, cognitive impairments, or mental (i.e., psychological) problems. Often, therapists discuss the patient's functional abilities, preferences, interests, and values with their caregivers, family members or friends instead to get all the data they need. However, it is more important to engage the client into a client-centred approach. But how can we engage cognitively or intellectually impaired elders into a client-centred approach? Hobson addressed this problem and introduced two strategies that can be used when assessing cognitively impaired and incompetent clients ¹³. These strategies are:

GRADED DECISION-MAKING

In this approach, there are two levels of decisions: Decisions with low-risk outcome (e.g., whether to have your meal in the kitchen or dining room), and decisions with high-risk outcome (e.g., whether to return to live alone in your own home or to stay institutionalized). Hobson suggested that because activity modification and alteration is part of a usual health care practice for such populations, decision making can be modified by applying these same skills. Decisions can be graded to be less cognitively demanding.

ADVOCACY

In this approach, the therapist (or health care provider), according to Hobson's suggestion, should listen and respect the client's opinions, needs and preference even though he or she is cognitively or intellectually impaired. The therapist should serve as an advocate for the client. He or she should express and explain the client's interests and needs to the people who have a legal authority to make decisions on behalf of the client ^{14 15}.

Additionally, there are several important factors which may influence assessment outcomes. It is essential to take all these factors into account before and during the assessment session of the seniors. First, it is very important to check the client's communication skills before the assessment. A speech-language pathologist can determine whether the client's communication is reliable, because mentally impaired individuals may have low receptive and expressive communication skills. Secondly, it is important to assess the sensory functions of the clients before the assessment. Sometimes

sensory disturbances may adversely affect the assessment. Visual screening and tactile sensory testing can help the therapist decide whether the client has enough sensory ability to proceed with the assessment. Also, cognitively and intellectually impaired persons may get tired easily, so it is necessary to take the time of the assessment into account and administer the assessment when the client is well-rested, possibly in the morning. Under some circumstances, when clients may be emotionally unsettled, it is important to avoid conducting the assessment when the client is emotionally distressed. Finally, it is crucial to consider the medications the client is taking, because some medications have side effects and may influence the performance during the assessment¹.

CONCLUSIONS

Little is known regarding successful strategies to perform functional assessments in the population of seniors who are aging with cognitive or intellectual impairments. Based on the current body of literature, assessment of seniors who are aging with any degree of cognitive and/or intellectual impairment is complex and there is no gold standard. However, there are several strategies, such as Hobson's strategy, that may be helpful in clinical practice and research. Further research is needed on both cognitive and intellectual disabilities in older populations to establish a sound evidence for description, screening for risk factors or undetected problems, setting rehabilitation goals, and monitoring treatment progress.

My disability exists not because I use a wheelchair, but because the broader environment isn't accessible.

Stella Young

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“Chemobrain”: the aging brain and oxidative stress

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Commentary to article:

Gaman AM, Uzoni A, Wagner AP, Andrei A, Pectu EB. *The role of oxidative stress in etiopathogenesis of Chemotherapy Induced Impairment (CICI)-“Chemobrain”*. *Aging Disease* 2016;3:302-12.

Key words: Chemobrain, Chemotherapy induced cognitive impairment, Oxidative stress

“Chemobrain” or chemotherapy induced cognitive impairment (CICI) represents a new clinical entity, characterized by executive dysfunction, deficit of memory and learning and motor function impairment after a chemotherapy (CT) regimen ^{1 2}. Cancer is an age-related disease and, due to the aging population, is going to result a relevant disease of the elders. With the advent of new surgical and chemotherapy options, oncogeriatric patients will turn to be long-term survivors and chemobrain will represent an issue of growing geriatric interest.

To a greater extent, CICI may be regarded as a drug side effect that may be a short-term event or lasting up to 10 years after chemotherapy cessation ^{3 4}, with gradual cognitive decline and great variability among patients.

Several studies have focused on the effect of cyclophosphamide and doxorubicin in breast cancer patients ^{5 6}. A recent metanalysis ⁷ has revealed that cancer patients treated with CT may develop verbal memory and executive function impairment that interfere with daily living and quality of life. Moreover, the cognitive deficit may last over 20 years, addressing the need for a better clinical identification of this issue ⁸.

The impaired neuropsychological findings correlate with neuro-structural changes. Indeed, neuro-structural brain radiology and functional imaging have recently demonstrated an association between chemobrain and lower activation of dorso-lateral, caudal frontex cortex, and

reduced glucose metabolism in frontal lobes after CT ^{9 10}. A series of different chemotherapy compounds have been implicated in the pathogenesis of chemobrain, including platinum compounds, proteasome inhibitors, tyrosine kinase inhibitors and interferon alpha.

The main mechanisms of chemotherapy induced cognitive changes include direct neurotoxicity, genetic predisposition, immune dysregulation, shortened telomeres, inflammation and oxidative stress.

Recently, an interesting review of Gaman et al. ¹¹, pointed out the state of the art and the new horizons of chemobrain with respect to the aging process, the brain aging and the underlying oxidative stress.

Both chemobrain and brain aging seem to be associated with reactive oxygen species (ROS) production and accelerated oxidative stress. CICI may be directly due to the ROS burst generated during chemotherapy. The most studied in vitro and in vivo murine models include doxorubicin (anthracycline) ^{12 13}. This common CT agent is considered to increase superoxide free radicals' production with oxidation of ApoA1 and the promotion of TNF alpha synthesis. This last cytokine mediator interacts with its receptor on the blood brain barrier (BBB) surface and reaches the brain parenchyma, generating neuronal apoptosis and death, mitochondria mutation (with increased p53) and increased lipid peroxidation, ultimately responsible for chemobrain occurrence (Fig 1). In particular, brain lipid peroxidation (leads to toxic

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compounds such as aldehyde (4-hydroxynonenal) with increased neuronal death. In parallel, reduced glutathione levels and increased glutathione-S – transferase were also detected in brain after CT.

Further understanding of the mechanisms of different CT compounds is accumulating as well. Carmustine is associated with a significant increase of oxidative stress (malondialdehyde) and overexpression of caspase ³, activation of c-jun N- terminal kinase (JNK) and ERK pathways ¹⁴. Interestingly, carmustine mediates the production of metallothionein in rat models that has an anti-oxidant protective effect.

Methotrexate is associated with increased levels of TNF alpha, increased lipoperoxidation, increased HP70 protein and reduced glutathione levels ¹⁵. Interestingly, methotrexate was found to decrease in vitro stem cells in hippocampus, that could count for the onset of cognitive impairment.

Cyclophosphamide is associated with increased levels of lipid peroxidation, TNF alpha and interleukin-6, increased production of COX2, I NOS, p38 -MAPK and NfκB 16. However, how CT oxidative stress mediated brain changes may be linked to brain aging has not yet been answered.

Thus, CT compounds seem to mediate ROS release by increasing plasma cytokines, capable of penetrating the BBB.

Normal brain aging is characterized by widespread but not homogeneous neuronal death, especially in frontal lobes and hippocampus, with reduction of grey and white matter. White matter is more vulnerable to oxidative stress and then, both chemobrain and brain aging could start from the same brain regions. During brain aging, neuronal remodelling and integrity result from the coping with perturbation of different metabolic and molecular signalling, causing endothelial damage and neuronal and cellular death ¹⁷.

Oxidative stress and vascular injury are also the biological background for cerebral atherosclerosis and small vessel disease that may be involved in both vascular and Alzheimer's type dementia.

To a greater extent, the aging process is itself a potent epigenetic modulator of brain, by increasing ROS generation and mitochondrial dysfunction with proteins and lipid and inflammatory damage, altered cell signalling pathways, apoptosis and altered gene expression ¹⁸. Indeed, the Harman's hypothesis of free radicals claims for the accumulation of oxidative damage to lipids,

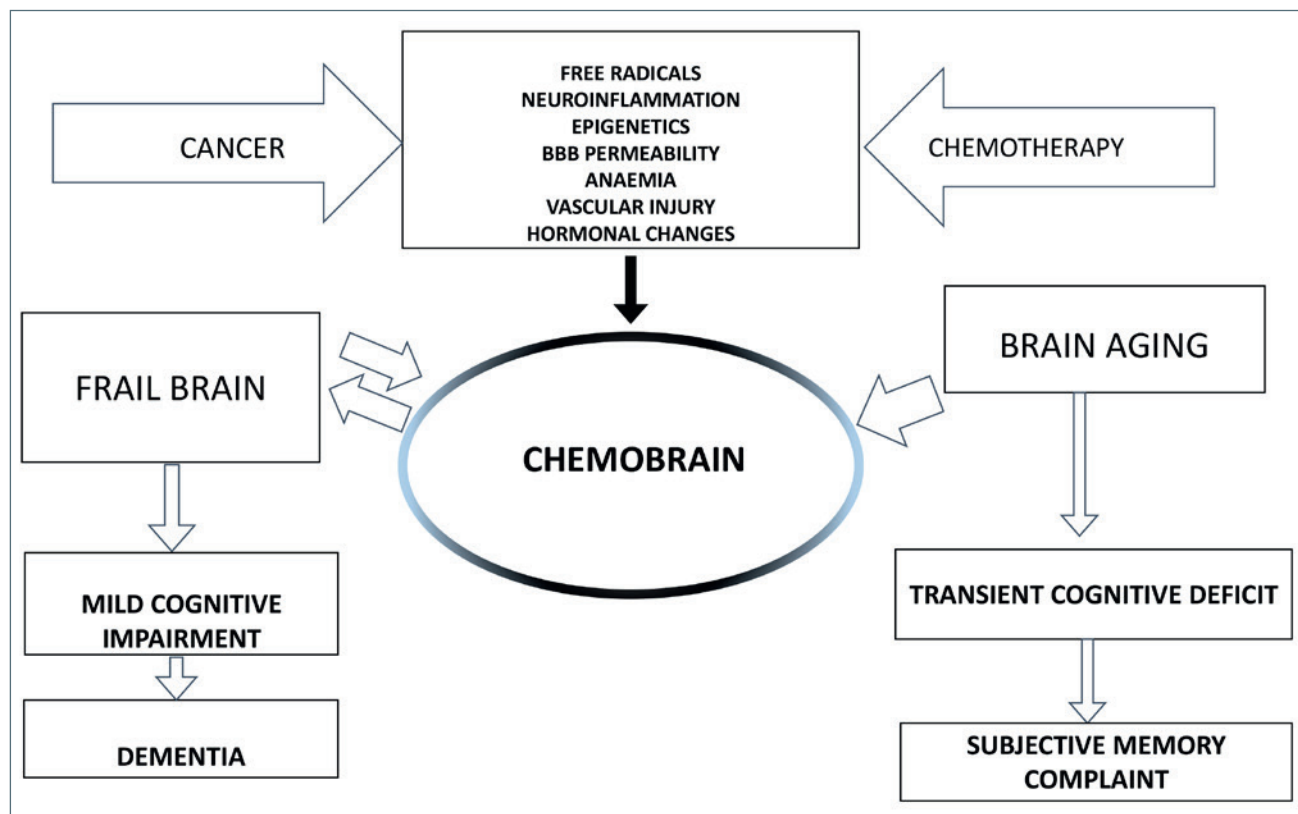


Figure 1. The multifactorial origin of chemobrain and potential neurodegenerative trajectories on the basis of the aging brain.

protein, DNA. Complementary to it, there is the mitochondrial theory of aging that mainly affect insulin/IGF-1 signalling, target for rapamycin (mTOR).

Interestingly, increasing in vivo evidence underlined that aging may promote brain alterations of TNF alpha in a similar way to chemotherapeutic compounds.

The interplay between the aging brain, chemobrain and dementia represents a challenge for geriatricians and bio gerontologists in the near future.

Research should consider cancer and chemotherapy, as potential vulnerability factors, when assessing cognitive functioning and its trajectories in elderly patients.

Chemobrain and CT should be framed in a larger conceptual framework; CT associated mechanisms mediating reversible or permanent dysregulation of an aging brain could be disentangled and integrated in the different trajectories of cognitive performance in elders. In addition, the psychological stress after the diagnosis of cancer, the psychosocial resources and the comorbidity burden may represent further moderator of the cognitive performance.

Considering it as a starting point, more explanatory models are needed to support preclinical evidence and to develop effective clinical evidence.

Chemobrain is expected to rely on different pathogenetic mechanisms; chemotherapy regimens are responsible for direct neurotoxic insult mediated by oxidative stress and neuroinflammation. All these mechanisms are responsible for increased neuronal dysfunction and death. There is great heterogeneity among different chemotropic compounds according to their blood brain barrier permeability and penetration; these different physio pathological pathways may count for different brain burden and impact on cognitive performance.

The aging brain may be temporary perturbed by a CT insult, showing cognitive decline after one- three months of therapy. However these deficits had generally resolved at one year follow up or persisting as subjective memory or cognitive impairment.

By contrast, a frail brain, that may be defined as a reduced functional reserve organ with poor homeostatic adaptation, could be heavily perturbed by a CT stressor. In turn, CT may initiate a neurodegenerative trajectory with a mild cognitive impairment that may ultimately end into a dementia conversion.

Not least, the inverse relationship between cancer and dementia of Alzheimer’s type represents a further area of inquiry that deserves clinical evidence, especially in the older populations.

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COMMENTARY

Intramuscular epinephrine as first-line treatment of anaphylaxis: still concerns about its safety in the elderly?

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Anaphylaxis is a severe condition that can affect patients of all ages. Elderly patients must be considered particularly vulnerable to severe anaphylaxis due to many risk factors such as concomitant diseases and medications. Intramuscular administration of epinephrine is recommended as first-line therapy for anaphylaxis and its use should be promoted in every setting. Intramuscular epinephrine is recognized as generally safe and there are no absolute contraindications to the prescription of self-injectable adrenaline in older patients at risk of anaphylaxis.

Key words: Anaphylaxis, Epinephrine, Adrenaline

Anaphylaxis is a severe and potentially fatal hypersensitivity reaction that can affect patients of all ages. Anaphylaxis occurring in the elderly is associated to increased mortality and occurrence of cardiovascular complications. In addition, elderly patients present many risk factors because of comorbid conditions such as cardiovascular, cerebrovascular and lung diseases, hypertension, cardiac arrhythmias and concomitant medication such as betablockers which may interfere with the pharmacologic effect of adrenaline administration¹⁻³.

Thus, elderly patients must be considered particularly vulnerable to severe anaphylaxis and concomitant medication such as betablockers may have a negative effect on the pharmacologic effect of adrenaline administration. Nonetheless, new selective betablockers are less likely to carry that risk. Moreover, the use of betablockers could improve the survival of patients suffering for heart disease and the benefit can be greater than the risk of aggravating anaphylaxis⁴. An evaluation on concomitant medication in elderly patients at risk of anaphylaxis should be made together with cardiologist on individual basis¹.

In patients with coronary artery disease mast cells are also present in the atherosclerotic plaques contributing to atherogenesis. Mast cell-released mediators potentially lead to vasospasm of large coronary arteries, to a reduction of myocardial blood flow by influencing the vasomotor tone of small intramural coronary arteries and may exert direct dysrhythmogenic effects⁵. Acute coronary syndrome may occur during anaphylaxis either through vasospasm or through acute plaque rupture and thrombus formation. This condition is known as Kounis syndrome³. Anaphylactic reaction may also induce takotsubo syndrome, a stress-induced cardiomyopathy characterized by reversible left ventricular systolic dysfunction without any significant coronary artery disease⁶.

During anaphylaxis, compensatory endogenous catecholamine is released and its increase may play a major role in pathophysiology of stress-induced cardiomyopathy. Excess doses of exogenous adrenaline would increase the plasma catecholamine levels and promote platelet activation inducing platelet aggregation and thrombosis. Exogenous adrenaline might then contribute to stent thrombosis, coronary spasm and

transient takotsubo syndrome. Since Kounis syndrome and takotsubo syndrome can also be induced by anaphylactic reactions, more research on their etiology and pathophysiology may help identify risk factors and better therapeutic approach aimed to avoid these acute conditions⁷.

Guidelines from European Academy of Allergy and Clinical Immunology and from World Allergy Organization recommend prompt intramuscular injection of epinephrine as the first-line therapy for anaphylaxis because a delayed administration has been shown to result in poor outcomes and fatality. Epinephrine can counteract some of the most severe symptoms of anaphylaxis. Adrenaline acts on the α_1 -adrenergic receptor inducing vasoconstriction, increase of blood pressure and decrease of mucosal edema. Activation of the β_1 -adrenergic receptor increases cardiac output, and activation of β_2 -adrenergic receptor increases broncodilation and reduces immune mediator release^{8,9}.

Intramuscular administration of adrenaline into the mid-antero-lateral aspect of the thigh is recommended because epinephrine has a vasodilator effect in skeletal muscle which facilitates rapid absorption into the central circulation and prompt pharmacologic effect. In contrast, the vasoconstrictor effect of epinephrine injected into subcutaneous tissue potentially delays epinephrine absorption. Therefore, subcutaneous route should be avoided³.

A recent literature review suggested that the majority of cardiovascular adverse events seem to occur when epinephrine is administered via endovenous route and epinephrine overdose seem to be responsible of many of the adverse events¹⁰.

Intramuscular administration of epinephrine is recognized as generally safe and is regarded as an effective therapy for anaphylaxis and its use should be promoted in every setting. The initial dose in the adult is 0.3-0.5 ml of a 1:1000 dilution that corresponds at concentration 1 mg/ml: if ineffective the administration can be repeated after at least a 5 minutes interval. Intravenous continuous infusion should only be given to patients not responding to intramuscular injection⁹.

There are no absolute contraindications to the prescription of self-injectable adrenaline in older patients at risk of anaphylaxis though the limited mobility of joint diseases, such as osteoarthritis of the hand could reduce the ability to use the device¹. There are no reports about significant adverse effects, such as ventricular arrhythmias, hypertensive crisis, and pulmonary edema using autoinjectors for the treatment of anaphylaxis¹¹. In conclusion allergic diseases and anaphylaxis are becoming more frequent during senescence and older population must be considered particularly vulnerable

to severe anaphylaxis also because elderly patients are less likely to be prescribed self-injectable adrenaline^{1,12}. There are no absolute contraindication to the administration of epinephrine through intramuscular route in a patient experiencing anaphylaxis since benefits outweigh the risks in the elderly and in patients with pre-existing cardiovascular disease. Epinephrine auto-injectors should be prescribed for all patients with a history of anaphylaxis. Patients and their caregivers should be taught why, when, and how to inject adrenaline and should be equipped with a personalized written anaphylaxis emergency action plan.

History of allergic reactions and anaphylaxis besides an emergency action plan should be noted in patient records in non-hospital care settings such as nursing homes and epinephrine should always be available. Further education of clinicians regarding the appropriate route of epinephrine administration in the management of anaphylaxis should be promoted to avoid adverse events.

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