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The title page should include the authors' names, degrees, and institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to their institution, which is listed separately. Please provide contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

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Abstract and Keywords: The second page should include an abstract that does not exceed 300 words. Moreover, as various electronic databases integrate only abstracts into their index, important findings should be presented in the abstract.

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Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

Other types of manuscripts, such as case reports, reviews and others will be published according to uniform requirements. Provide at least 3 keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies a CONSORT abstract should be provided (<http://www.consort-statement.org>).

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Original articles should have the following sections;

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains interesting, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study, its design, and its objective(s).

Materials and Methods: Clearly describe the selection of observational or experimental participants, such as patients, laboratory animals, and controls, including inclusion and exclusion criteria and a description of the source population. Identify the methods and procedures in sufficient detail to allow other researchers to reproduce your results. Provide references to established methods (including statistical methods), provide references to brief modified methods, and provide the rationale for using them and an evaluation of their limitations. Identify all drugs and chemicals used, including generic names, doses, and routes of administration. The section should include only information that was available at the time the plan or protocol for the study was devised on STROBE (<http://www.strobe-statement.org>).

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Results: Present your results in logical sequence in the text, tables, and figures. Do not present all the data provided in the tables and/or figures in the text; emphasize and/or summarize only important findings, results, and observations in the text. For clinical studies provide the number of samples, cases, and controls included in the study. Discrepancies between the planned number and obtained number of participants should be explained. Comparisons, and statistically important values (i.e. p value and confidence interval) should be provided.

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Bonanni E, Tognoni G, Maestri M, Salvati N, Fabbri M, Borghetti D, DiCoscio E, Choub A, Sposito R, Pagni C, Iudice A, Murri L. Sleep disturbances in elderly subjects: an epidemiological survey in an Italian district. *Acta Neurol Scand* 2010;122:389-397.

2. Organization as Author

American Geriatrics Society 2015 Updated Beers Criteria Expert panel. American geriatrics society 2015 updated Beer criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-2246.

3. Complete Book

Ham RJ, Sloane PD, Warshaw GA, Potter JF, Flaherty E. Ham's primary care geriatrics : a case-based approach, 6th ed. Philadelphia, Elsevier/Saunders, 2014.

4. Chapter in Book

BG Katzung. Special Aspects of Geriatric Pharmacology, In: Bertram G. Katzung, Susan B. Masters, Anthony J. Trevor (Eds). *Basic and Clinical Pharmacology*. 10th edition, Lange, Mc Graw Hill, USA 2007, pp 983-90.

5. Abstract

Reichenbach S, Dieppe P, Nuesch E, Williams S, Villiger PM, Juni P. Association of bone attrition with knee pain, stiffness and disability; a cross sectional study. *Ann Rheum Dis* 2011;70:293-8. (abstract).

6. Letter to the Editor

Rovner B. The Role of the Annals of Geriatric Medicine and Research as a Platform for Validating Smart Healthcare Devices for Older Adults. *Ann Geriatr*. 2017;21:215-216.

7. Supplement

Garfinkel D. The tsunami in 21st century healthcare: The age-related vicious circle of co-morbidity - multiple symptoms - over-diagnosis - over treatment - polypharmacy [abstract]. *J Nutr Health Aging* 2013;17(Suppl 1):224-227.

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Using Ultrasound in the Assessment of Muscle

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Of all organs, muscle is possibly the most underrated. First, it is seldom thought of as an organ. Second, for many years it was placed low on the ladder of interest around the medical community due to its apparent singular locomotor effects. Third, even if the only perceived function of movement seemed to fail, other causes were quickly to be blamed, most often neurological. Fortunately, during the past 30 years, the intrinsic worth of the muscle has been appreciated more. Slowly, it has become evident that muscle as an organ undertakes an important endocrine function, in addition to its vital role as the sole source of protein reserve in the body—truly indispensable for whole body metabolism (1). The recent insights to this "newly discovered" organ have enhanced interest in pathologic alterations, sarcopenia being one of the most important.

This chronic and, in old age, seemingly inevitable muscle affliction, is currently defined by the European Working Group on Sarcopenia in Older Persons (EWGSOP) as a progressive and generalised skeletal muscle disorder. It consists of deficits in three main components, being muscle quantity or quality, muscle strength, and physical performance (2,3). The importance of sarcopenia is reflected in its relation with many negative health outcomes, of which perhaps the most evident being mortality. With an odds ratio (OR) of 3.6, it could be regarded as even more relevant than other comorbidities in older persons, such as heart failure (OR 1.66), dementia (OR 2.01) or even cancer (OR 3.02) (4,5). Another factor is the issue of quality of life, which declines in patients with sarcopenia (3). Although sarcopenia has received its own ICD-10 code (6), there is still a lot of debate about the exact value of the different components described. Over the last years, physical performance has been viewed as either diagnostic criterion, severity grading assessment

or as an outcome (7). Muscle strength seems to be better at predicting adverse outcomes (3), but this may be due to its ease of measurement in comparison to either muscle function or quality/quantity. The most difficult issue seems to be the most basic one, which is defining muscle mass. In primary sarcopenia, there are changes in both muscle quantity and quality, the latter being described as micro- and macroscopic aspects of muscle architecture and composition (3,8). Despite these changes being clearly paramount in the genesis of sarcopenia, technological limitation so far have limited the transposition from knowledge to practice. In the current FACS-algorithm (Find cases-assess-confirm-severity) proposed by the EWGSOP2 for the diagnosis of sarcopenia, a proposition is made to measure either muscle quantity or quality. Unfortunately the algorithm does not specify what parameters of quality should be measured (3). This renders muscle mass a non-defining parameter, creating another obstacle in making an accurate diagnosis (7).

The key to overcome this problem is twofold. First, relevant anatomic and architectural changes should be defined. Second, the technique to measure these parameters should be widely available in clinical practice. Currently, both issues are still obstacles. The currently proposed techniques for muscle mass assessment are bioelectrical-impedancemetry, dual energy X-ray absorptiometry, computed tomography or magnetic resonance imaging (3). However, where the two former are incapable of looking into muscle quality parameters, the two latter are impossible to be used bedside. Therefore, we must turn to new technologies in order to advance.

To be clear, ultrasound is not a new technique. It has been present since the late 1950's and has continued to improve in ease of use and portability. Although its use in medicine is

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widespread, its application in musculoskeletal research is often limited. However, in recent years ultrasound was hypothesized as the perfect alternative for the current muscle assessment problems (9). As a portable, cheap and easy technique that can be performed bedside, ultrasound is positioned as a patient-centred diagnostic tool. In addition, ultrasound enables the physician to visualise a wide range of components of muscle architecture, hence underlining all the advantages of becoming the new standard tool in screening for the presence of sarcopenia. However, some obstacles still stand in the way of it being used as a first line tool.

Knowledge of the relevance of the different muscle components is still in its early phase. Although muscle thickness, cross-sectional area, pennation angle, fascicle length and echo-intensity have been proposed earlier (9), other measurements such as elastography (10) or vascularisation could offer important information. Another issue is the lack of standardisation of measurements, which is a must in order to be able to compare research data. Until very recently this was only provided for a limited amount of muscles (9). Nowadays, standardisation for 39 muscles/muscle groups are present (11), making it possible for researchers worldwide to investigate effects of specific muscles. Until now, the quadriceps is the muscle most investigated as it is easy to measure and can be linked directly to measures of physical performance (12,13). The final hurdle that it needs to take now, is the collection of reference data in different age cohorts and populations (13). This way, pathological values can be distilled, cut-off lines can be drawn and correlations can be made with the other aspects of sarcopenia—strength and function.

Hereby we call upon all researchers interested to look into this new and very exciting field of using ultrasound in muscle assessment. It is our firm belief that only through using ultrasound, the true diagnostic approach of muscle mass loss will be taken bedside -into clinical practice- where it so urgently is needed. This advancement needs worldwide collaboration, of which the first steps are already taken through the European initiative of SARCUS, a project of the European Geriatric Medicine Society (14). This project tries to answer the remaining gaps in knowledge that currently restrain the use of ultrasound in clinical practice. Besides standardisation, current projects are acquiring reference data and looking into the most relevant muscle parameters to be linked with clinical outcomes. This way, the future hope is to include muscle ultrasound as a part of comprehensive geriatric assessment, giving a deeper understanding of how to better treat our older patients.

Keywords: Aging, clinical geriatrics, frailty, geriatric care management, sarcopenia, ultrasound

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: G.B., S.P., Desing: S.P., Literature Search: S.P., K.B., C.W., G.B., Writing: S.P., K.B., C.W., G.B.

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Nutritional Profile and Serum Uric Acid are Associated with Metabolic Syndrome in Community-dwelling Older Adults: A Cross-sectional Study

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Abstract

Objective: This study aimed to evaluate the prevalence of metabolic syndrome in community-dwelling older adults and compare the nutritional profile in macronutrient and micronutrient intakes and serum uric acid in community-dwelling older adults with and without metabolic syndrome.

Materials and Methods: Overall, 155 community-dwelling older adults were enrolled and were stratified into two groups: with and without metabolic syndrome. The estimated daily macronutrient and micronutrient intakes and the single umbilical artery (SUA) were obtained and compared between the groups.

Results: The prevalence rate of metabolic syndrome was 38.7%, and older adults with metabolic syndrome exhibited greater carbohydrate and lower protein and lipid consumptions. It was observed that the older adults without metabolic syndrome showed higher daily mono- and poly-unsaturated fatty acids, copper and vitamins A and B6 intakes, whereas those with metabolic syndrome exhibited higher daily manganese and vitamin C intakes. Higher SUA was found in older adults with metabolic syndrome, characterising a pro-oxidant state.

Conclusion: The nutritional profile adopted by older adults with metabolic syndrome may induce the development of a worrying pro-oxidant state. High carbohydrate consumption could blind the protective effect of a high antioxidant micronutrient intake.

Keywords: Nutrients, micronutrients, oxidative stress, ageing

Introduction

Metabolic syndrome (MetS) is a worrying health problem, especially for old adults, owing to a higher risk to developing cardiovascular complications, stroke and atherosclerosis (1). Genetic and lifestyle factors, such as the nutritional profile, are the major factors predisposing to this condition (2).

The prevalence is high among the old adults, reaching 50% to 63% (3,4), which is explained by the aging-associated metabolic changes, characterized by the free radicals accumulation and subsequent deoxyribonucleic acid, proteins

and lipids damage, compromising the homeostasis and favoring the pathological states, such as the degenerative diseases, cancer, cardiovascular diseases, diseases related to the immune system decline, cerebral dysfunction and cataract (5). Considering that this worrying pro-oxidant state is involved in the genesis of several aging-associated metabolic disorders, preventive actions, such as the adequacy of the macro and micronutrient intake, especially micronutrients with antioxidant potential, is an important intervention to treat and prevent MetS (2).

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In this context, participants from 18 to 84 years old, showed that the intake of vitamin C, a relevant antioxidant micronutrient, was lower in subjects with MetS, which increases the risk to develop diabetes and cardiovascular diseases (2). The investigations regarding the micronutrients intake demonstrate relevant insights, but an in-depth analysis, including the investigations of macro and micronutrients intake could provide a larger comprehension about the relationship among nutritional profile and the MetS, especially if the investigations include a biomarker of oxidative stress.

Serum uric acid has been suggested as a biomarker associated with MetS, since it is related to oxidative state (6). This biomarker is interesting when studying the interaction among MetS, nutritional profile and oxidative stress, since it is useful and easily accessible in the evaluation of oxidative stress, and may be directly and indirectly associated with the nutritional profile (6-8). Notwithstanding, the highest serum concentration of uric acid is indicated as an independent risk factor for MetS and target organ damage in Korean old adults (9,10) and the reduction in serum levels of uric acid is presented as a potential strategy for prevention and treatment of systemic metabolic abnormalities in old adults (6,11,12).

Thus, this study aimed to verify the prevalence of MetS in community-dwelling old adults and to compare the nutritional profile in macronutrients and some micronutrients intake, and serum uric acid in community-dwelling old adults with and without MetS.

Materials and Methods

Studied population

This was a cross-sectional, home-based, descriptive and analytical study that included all community-dwelling older people (≥ 60 years old) from Aiquara, Bahia, Brazil. Two hundred eighty-nine old adults were screened, but only 155 old adults presented the complete data from the interest variables to meet the proposed aim in this study. Bedridden individuals and/or those with severe cognitive impairment ($n=20$) were excluded. All procedures were conducted in conformity with the Helsinki Declaration and the study was submitted and approved by the local Human Research Ethics Committee (protocol#:729.303). Written informed consent was obtained from the volunteers.

Data collection was carried out from January to July 2015, and involved three groups of variables: questionnaires, clinical assessment, and collection of biological samples. Data recordings from the questionnaires, socio-demographic characteristics and self-reported health status were used in this study. After recording questionnaires during home visit, participants were scheduled to attend in Aiquara Municipal Hospital, where they underwent a blood pressure measurement, anthropometric

assessment and venous blood withdrawal (10 mL from the antecubital vein). Blood samples were used to biochemical analysis and, in this study, the blood triglycerides, high-density lipoprotein (HDL) cholesterol, fasting glycemia and serum acid uric were measured. From clinical assessment, systolic and diastolic blood pressure, height and abdominal circumference measures were used in this study.

Systolic and diastolic blood pressures were assessed using oscillometric method with a validated automatic device (model HEM 742 Intellisense, Omron Healthcare, Inc.). With old adults sitting comfortably, two blood pressure measures were taken 5 minutes apart. All blood pressure measures were taken at morning (08:00-11:30 hours).

The smoking habit, self-reported race, income and age were obtained from socio-demographic questionnaires. The physical activity level was obtained from the International Physical Activity Questionnaire, and data were dichotomized according to the proposed cut-point of 150 min/week of moderate and vigorous activity (i.e., 150 min/wk, sufficiently active and <150 min/wk, insufficiently active) (13).

Definition of MetS and serum uric acid dosage

We used the criteria proposed by National Cholesterol Education Program- Adult Treatment Panel III (NCEP-ATP III) to classify the old adults as with or without MetS, which was diagnosed when at least three of the five listed characteristics are present: abdominal circumference (men >102 cm, women >88 cm); hypertriglyceridemia (≥ 150 mg/dL), HDL cholesterol (men <40 mg/dL, women <50 mg/dL), hypertension (prior diagnosis or blood pressure $\geq 130/85$ mmHg), and fasting glycemia ≥ 110 mg/dL or previous diagnosis of diabetes mellitus.

Dosage of triglycerides, HDL cholesterol, fasting glycemia, and serum uric acid was performed using standard laboratory methods in a venous blood sample collected after 8 to 12 hours of fasting and results given in mg/dL.

Estimated daily calorie intake and nutritional profile

Daily food and beverages were recorded through a 24-hour recall as recommended by Rutishauser (14) and done by da Silva et al. (15). Researchers were trained to apply the 24-hour recall and data extraction was standardized. Estimated daily calorie and protein intake were calculated using the software DietPro® version 5.8.1. The estimated daily caloric intake was expressed in absolute values (Kcal) and normalized by the resting energy expenditure for each volunteer, then, values below 1.0 indicated that the estimated daily caloric intake was not adequate to the Resting Energy Expenditure, indicating a deficit in the caloric intake. The estimated daily protein intake was expressed in absolute values (grams of protein) and normalized (grams of protein/total body mass).

The estimated daily intake of mono and polyunsaturated fatty acids and micronutrients (copper, manganese, niacin, riboflavin, vitamins A, B6, C and zinc) were expressed in absolute values (grams or milligrams).

The estimated daily intake of macro and micronutrients were also calculated with DietPro® software version 5.8.1 and adjusted for the estimated total daily intake, as suggested by Willett et al. (16) and done by da Silva et al. (15).

Statistics

Normality of the data distribution was tested using the Shapiro-Wilk test. Considering that, for old adults with MetS, all studied variables did not present normal distribution, the results were presented as median and interquartile range (ie: cut to the first and third quartiles). The chi-square test was used to verify the distribution of the sex between the groups with and without MetS. The Mann-Whitney U test was used to compare the nutritional profile, the serum uric acid concentration and the income between groups. The effect size for each comparison was calculated according to the following equation $r=Z/\sqrt{N}$, where N is the total number of repetitions and Z is the z-value obtained from the Mann-Whitney U test (17). An effect size was considered as small when $r\leq 0.1$, medium when $r\geq 0.24$, large when $r\geq 0.37$ (18).

Since the serum uric acid could be influenced by antihypertensive drugs (19), especially beta-blockers, alfa-1 blockers, angiotensin-converting enzyme inhibitors, Calcium channel blockers and angiotensin-II receptor blockers, the association between each antihypertensive drug and MetS diagnoses was analyzed using chi-square test.

The level of significance for all tests was set as $p\leq 0.05$. All statistical procedures were performed with SPSS Statistics software for Windows (SPSS 21.0, 2012, Armonk, NY: IBM Corp.).

Results

The prevalence of MetS in the studied population was 38.7%, with a similar distribution of men and women in each group (with MetS =26 men and 34 women; without MetS =41 men and 54 women; $p>0.05$). The mean age was 71.0 ± 8.2 and 71.6 ± 8.0 years old ($p>0.05$, mean \pm standard deviation) for old adults with and without MetS, respectively. The income, a socio-demographic variable able to influence the access to nutrients, was similar between groups [without MetS: R\$ 774.00 (700.00-788.00), with MetS: R\$ 788.00 (705.00-788.00), $p>0.05$]. Table 1 presents other socio-demographic and clinical characteristics of the studied population. There were no differences between groups for self-reported race, smoking habit, and physical activity habit ($p>0.05$). Among clinical characteristics, the prevalence of hypertension was high in the studied population (62.5%), but the distribution of hypertensive old adults was not different

between old adults with and without MetS ($p>0.05$). However, the prevalence of diabetes mellitus, hypertriglyceridemia, dyslipidemia (low HDL) and obesity (abdominal circumference) was 23.3%, 46.9%, 34.4%, 71.9% among the studied population, respectively, and were significantly higher among old adults with MetS ($p<0.05$, see Table 1).

The distribution of daily intake of macronutrients was significantly different between the groups with and without MetS ($p\leq 0.05$). The old adults with MetS showed a nutritional profile composed by a higher percentage of carbohydrates, while those without MetS had a nutritional profile composed by a greater percentage of lipids and protein (Table 2).

The resting energy expenditure did not present a significant difference between the groups without MetS [1636.27 (1466.29-1809.17) Kcal] and with MetS [1680.36 (1513.83-1918.41) Kcal] ($p=0.192$). Similarly, the total energy intake was not significantly different between the groups without MetS [1301.24 (953.75-1691.35) Kcal] and with MetS [1166.73 (843.79-1567.96) Kcal] ($p=0.400$).

In addition, the values of normalized estimated daily caloric intake indicated that both groups were below the energy requirements [without MetS: 0.76 (0.56-1.01); with MetS: 0.68 (0.55-0.89)], without difference between the groups for this variable ($p=0.180$). The daily intake of potentially antioxidant nutrients (i.e., monounsaturated and polyunsaturated fatty acids and micronutrients) revealed a significantly higher daily intake of mono and polyunsaturated fatty acids, copper and vitamins A and B6 among old adults without MetS, while those with MetS exhibited a higher daily intake of manganese and vitamin C (Table 2).

Serum uric acid was significantly higher in the MetS group compared to the without MetS group [without MetS: 6.69 (6.60-6.80) mg/dL, with MetS: 7.43 (7.35-7.54) mg/dL, $p<0.001$, effect size (r)=0.76] (Figure 1).

There was not observed significant association between antihypertensive drugs use and studied old adults with and without MetS ($p>0.05$, see Table 3). Then the proportion of old adults with and without MetS using each relevant class of antihypertensive drugs was similar, which is relevant, since the serum uric acid levels could be influenced by antihypertensive drugs.

Discussion

The present study aimed to verify the prevalence of MetS in community-dwelling old adults and to compare the nutritional profile in macronutrients and some micronutrients intake, and serum uric acid in community-dwelling old adults with and without MetS. The main results of this study showed a high prevalence of MetS in the studied population, and a higher

Variables		Without MetS	With MetS	p
Race/color	White	10 (11.1%)	8 (13.3%)	0.682
	Nonwhite	80 (88.9%)	52 (86.7%)	
Smoking habit	No	78 (88.6%)	52 (92.9%)	0.405
	Yes	10 (11.4%)	4 (7.1%)	
Physical activity habit	Sufficiently active	53 (57.6%)	29 (52.7%)	0.564
	Insufficiently active	39 (42.4%)	26 (47.3%)	
Hypertension	No	36 (37.9%)	22 (36.7%)	0.878
	Yes	59 (62.1%)	38 (63.3%)	
Diabetes	No	82 (86.3%)	37 (61.7%)	<0.001
	Yes	13 (13.7%)	23 (38.3%)	
Dyslipidemia*	No	58 (65.2%)	20 (34.5%)	<0.001
	Yes	31 (34.8%)	38 (65.5%)	
Hypertriglyceridemia**	No	82 (87.2%)	19 (31.7%)	<0.001
	Yes	12 (12.8%)	41 (68.3%)	
Obesity***	No	33 (38.4%)	8 (13.3%)	0.001
	Yes	53 (61.6%)	52 (86.7%)	

*Dyslipidemia = HDL cholesterol: men < 40 mg/dL, women < 50 mg/dL, ** Hypertriglyceridemia = Triglycerides: ≥ 150 mg/dL; *** Abdominal circumference: men > 102 cm, women > 88 cm, MetS: Metabolic syndrome, HDL: High-density lipoprotein

Variables	Without MetS	With MetS	p	Effect size (r)
Macronutrients				
Estimated daily carbohydrate intake (g)	112.95 (157.01-206.47)	166.43 (125.48-217.30)	0.149	0.12 [¥]
Estimated daily lipid intake (g)	39.32 (29.33-50.54)	28.93 (19.65-40.47)	0.002*	0.25 [§]
Estimated daily protein intake (g)	79.68 (59.34-102.51)	60.13 (41.23-83.62)	0.005*	0.22
% of total caloric intake from carbohydrates	0.49 (0.47-0.51)	0.58 (0.56-0.60)	<0.001*	0.76 [§]
% of total caloric intake from lipids	0.26 (0.25-0.27)	0.22 (0.21-0.23)	<0.001*	0.71 [§]
% of total caloric intake from protein	0.24 (0.23-0.25)	0.20 (0.19-0.20)	<0.001*	0.78 [§]
Estimated daily protein intake normalized by body weight (g/BW)	1.39 (1.05-1.76)	0.91 (0.59-1.29)	<0.001*	0.33 [§]
Fatty acids & micronutrients				
Estimated daily monounsaturated fatty acids intake (g)	10.51 (8.49-12.79)	8.76 (6.87-11.09)	0.016*	0.19 [¥]
Estimated daily polyunsaturated fatty acids intake (g)	5.93 (4.69-7.32)	4.48 (3.33-5.92)	0.001*	0.27 [§]
Estimated daily copper intake (mg)	0.85 (0.71-1.01)	0.71 (0.58-0.87)	0.005*	0.22 [¥]
Estimated daily manganese intake (mg)	1.22 (1.02-1.45)	1.34 (1.16-1.58)	0.004*	0.22 [¥]
Estimated daily niacin intake (mg)	23.64 (18.32-29.61)	20.22 (15.28-26.36)	0.103	0.13 [¥]
Estimated daily riboflavin intake (mg)	1.21 (1.01-1.44)	1.09 (0.90-1.32)	0.151	0.11 [¥]
Estimated daily vitamin A intake (mg)	527.55 (496.99-561.85)	396.58 (368.18-431.87)	<0.001*	0.68 [§]
Estimated daily vitamin B6 intake (mg)	1.70 (1.33-2.10)	1.30 (0.97-1.72)	0.001*	0.25 [§]
Estimated daily vitamin C intake (mg)	54.35 (50.85-58.27)	108.12 (104.87-112.16)	<0.001*	0.76 [§]
Estimated daily zinc intake (mg)	12.14 (8.43-16.30)	9.75 (6.30-14.03)	0.102	0.13 [¥]

(*) Significant difference between groups (p < 0.05), the effect size (r) was considered as small when r ≤ 0.1, (¥), medium when r ≥ 0.24 (°), large when r ≥ 0.37 (§), MetS: Metabolic syndrome

serum uric acid among the old adults with MetS, indicating a worrying pro-oxidant state. These results were associated to a dietary profile characterized by a higher percentage of carbohydrates and lower percentage of proteins and lipids among old adults with MetS, when compared to old adults without MetS. Additionally, the daily intake of potentially antioxidant micronutrients, mono and polyunsaturated fatty acids, copper and vitamins A and B6 were higher among old adults without MetS, while manganese and vitamin C was higher among those with MetS.

The high prevalence of MetS in this population is like previous study developed in Brazil. Salaroli et al. (20) found a prevalence of 48.3% in adults between 55 and 64 years, demonstrating a trend to higher prevalence of MetS among old adults. The fact that most studies report the prevalence of MetS in the general population, regardless of age, limits the comparison of

our results with other studies, although the high prevalence of MetS in the studied population is expected, owing to the aging-associated metabolic changes. Considering a global scenario, previous studies report very different prevalences, which can be justified by the different diagnostic criteria used, as well as the different populations involved. Ford et al. (21), found a prevalence of 43.5% of MetS among American old adults, while Miccoli et al. (22) found a prevalence of 25% in Italian individuals over 70 years old. Cankurtaran et al. (23) identified a MetS prevalence of 23.8% in Turkish old adults, whereas in a study conducted among Ecuadorians older adults, it was found a prevalence of 66% of MetS among women and 47% among men (24).

In our study, the sex was not an associated factor with MetS. However, MetS is admittedly a clinical condition associated with several intervening factors, and in addition to sex, other factors, such as the nutritional profile (25), may contribute to the development of this clinical condition. Indeed, the nutritional profile presented by the studied old adults with and without MetS was significantly different, old adults with MetS presented a nutritional profile with a distribution of caloric intake composed by a higher percentage of carbohydrates and lower of proteins and lipids, when compared to those without MetS. It is proposed that a daily intake greater than 1.2 g/kg to 1.5 g/kg of protein and less than 130 to 150 grams of carbohydrates per day is associated with weight loss, but with maintenance of muscle mass, improved glycemic control, and reduction of plasma triglyceride levels, as well as an effective treatment of MetS (26,27).

Although this population presented a daily protein intake higher than that recommended by the World Health Organization (WHO) (28), which is 0.8 g/kg, individuals without MetS had an even higher estimated daily intake of protein when compared to the MetS group. This fact indicates that the WHO recommendation may possibly be underestimated for the daily required intake for old adults, making old adults with low protein consumption prone to develop MetS. Then, it is suggested that the future recommendations should consider an increased value of daily protein intake to prevent MetS, following the recommendation proposed to the maintenance of lean mass and prevention of sarcopenia, which suggests a daily protein intake of 1.2 g/kg (29). The loss of lean mass, a natural consequence of the aging process, accelerated by a low daily protein intake may help to explain the greater susceptibility to metabolic disorders typical of MetS, since the muscle is a metabolically more active tissue than adipose tissue (26).

The highest lipid intake observed among the old adults without MetS seems to be in contradistinction to the concepts related to the nutritional recommendations to the clinical condition studied here, since it is a risk factor for the development of

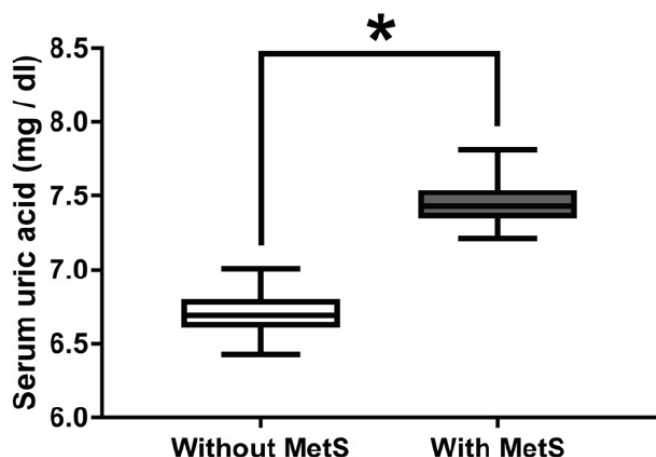


Figure 1. Serum uric acid from the community-dwelling old adults with and without Metabolic syndrome (*) Significant difference between groups (p<0.05)

MetS: Metabolic syndrome

Variables		Without MetS	With MetS	p
ACE inhibitors*	No	74 (83.1%)	46 (85.2%)	0.748
	Yes	15 (16.9%)	8 (14.8%)	
β blockers	No	80 (89.9%)	42 (79.2%)	0.078
	Yes	9 (10.1%)	11 (20.8%)	
α-1 blockers	No	89 (100.0%)	53 (100.0%)	-
	Yes	0 (0.0%)	0 (0.0%)	
Ca blockers**	No	74 (85.1%)	43 (81.1%)	0.543
	Yes	13 (14.9%)	10 (18.9%)	
ARB***	No	67 (75.3%)	40 (75.5%)	0.980
	Yes	22 (24.7%)	13 (24.5%)	

*Angiotensin-converting enzyme (ACE) inhibitors, **Calcium channel blockers, ***Angiotensin-II receptor blockers (ARB), MetS: Metabolic syndrome

dyslipidemias and cardiovascular diseases (27). However, two factors need to be noted: 1) despite being significantly greater among old adults without MetS, lipid intake was within the recommended range (20%-35% of caloric intake) (27) and, 2) proportionally, a high consumption of unsaturated fatty acids in relation to the saturated fatty acids is indicated as a metabolic protective strategy (30,31). In our study, the old adults without MetS, despite presenting higher consumption of lipids, also presented higher intakes of unsaturated fatty acids. In this context, a diet with a higher amount of unsaturated fatty acids (32), as well as with a higher amount of micronutrients with antioxidant potential, is efficient for weight loss and blood pressure reduction, important strategies for coping with MetS (27,33).

Many micronutrients have been widely pointed as potential antioxidant agents and therefore, metabolic and cardiovascular risk protectors (2). Several studies suggest that the increase of micronutrients consumption, such those studied here (ie, copper, manganese, niacin, riboflavin, vitamins A, B6, C and zinc) and the consequent increase in their plasma levels may be strategies potentially beneficial for the reduction of MetS risk factors (34,35).

Serum low levels of vitamin B6 were associated with a pro-inflammatory status and high oxidative stress rates in Puerto Rican adults (36). In fact, vitamin B6 is reported in the literature as an important antioxidant agent, being able to minimize the inflammatory status, as observed in obese individuals (37). Additionally, Gregory et al. (38) showed metabolic changes after inducing B6 hypovitaminosis in healthy subjects. Our results, together with above cited studies, may help to support the association between low vitamin B6 intake, MetS and high serum concentration of uric acid, a biomarker of pro-oxidant state, present among old adults with MetS. In the same perspective, a low vitamin A intake is also reported as associated to MetS and non-alcoholic fatty liver disease (39), also due to its antioxidant potential, which corroborate with our results, since we observed that old adults with MetS presented a lower daily intake of this vitamin.

The relationship between the daily intake of copper and the health status is really complex, once its intake above the recommended upper limit may induced a pro-inflammatory and pro-oxidant status, on the other hand, copper deficiency, owing to a low daily consumption of this micronutrient, is associated with an unfavorable metabolic pattern (38). Our results showed a higher consumption of copper among the old adults without MetS, but within recommended ranges in the literature (up to 3 mg/day) (39), which does not put these old adults in a health risk condition.

The vitamin C, widely recognized for its antioxidant properties and whose intake was associated with a reduction in the

risk of MetS in Korean adults (40), presented a controversial result in our study, since the old adults with MetS exhibited a higher intakes of this vitamin, when compared to old adults without MetS. Likewise, the old adults with MetS presented greater daily consumption of manganese, a micronutrient also recognized for its antioxidant properties and association with a lower risk to develop MetS (41). These results of daily consumption of vitamin C and manganese indicate that the greater consumption of these important micronutrients with protective role against MetS had no positive impact on the disease and, in addition, did not contribute to the control of the pro-oxidant status in these individuals, since they had a higher serum uric acid concentration. It is plausible to hypothesize that the inadequate nutritional profile of macronutrients observed here could minimize the protective effect of a higher vitamin C and manganese intake among old adults with MetS.

The use of a 24-hour recall for estimate the daily nutritional profile could be pointed as a limitation of this study, but it was considered an adequate tool for the use with elderly population (14).

Study Limitations

Additionally, the lack of standard diagnostic criteria for MetS, specifically for elderly population, could also be listed as limitations. Although the limitations, our results indicate that a nutritional profile with a high proportion of carbohydrates and low proportion of lipids and proteins, together with a lower daily intake of the micronutrients copper, vitamin A and B6 is associated to MetS in the community-dwelling old adults. Such nutritional profile may affect the possible benefits of a higher daily intake of important antioxidant micronutrients, such as vitamin C and manganese, and this fact may be related to the inability to correct the pro-oxidant status observed among old adults with MetS, evidenced by the higher serum levels of uric acid. It is important to note that there was not observed significant association between antihypertensive drugs use and MetS diagnosis. Antihypertensive drugs, especially diuretics, beta-blockers and alpha-1 blockers (19), could influence the serum uric acid.

Conclusion

This find reinforce the hypothesis that the association between serum uric acid and MetS occur owing to metabolic imbalance present in the patients with MetS.

Further studies should expand our analysis with greater sample, the main limitation from our study, aiming to confirm or refute our findings. Additionally, further studies should focus on refining/standardize the diagnostic criteria for MetS specifically for the elderly population, as well as expanding the analysis proposed here, evaluating the consumption of

more micronutrients and the serum concentration of other biomarkers of pro-oxidant and pro-inflammatory status.

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Ethics

Ethics Committee Approval: All procedures were conducted in conformity with the Helsinki Declaration and the study was submitted and approved by the local Human Research Ethics Committee (protocol#:729.303).

Informed Consent: Written informed consent was obtained from the volunteers.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.D.S.C., R.P., Design: C.A.C., R.P., Data Collection or Processing: I.V.F., D.P.D.S., Í.J.S.R., Analysis or Interpretation: C.S.D.S., R.D.S.C., C.A.C., R.P., Literature Search: I.V.F., D.P.D.S., Í.J.S.R., C.S.D.S., Writing: I.V.F., D.P.D.S., Í.J.S.R., C.S.D.S., R.D.S.C., C.A.C., R.P.

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Frequency of Poor Sleep Quality and Related Factors in Geriatric Patients

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Abstract

Objective: Sleep is a necessary and indispensable activity of human life, and it is a physiological need as crucial as eating, drinking, breathing and excretion. This study aims to investigate the frequency of poor sleep quality and related factors in patients admitted to a geriatric outpatient clinic.

Materials and Methods: The study was performed by a retrospective file scanning method. It included 100 random geriatric patients who applied to the geriatric outpatient clinic. The data were collected using the "comprehensive geriatric assessment form" and the "Pittsburgh Sleep Quality scale" and evaluated using SPSS version 22.0.

Results: Poor sleep quality was detected in 60% of patients. Geriatric patients with poor sleep quality had increased frequency in obesity and polypharmacy, increased Geriatric Depression scale scores, lower handgrip strength and decreased walking speed that were statistically significant ($p < 0.005$).

Conclusion: We have shown that at least half of geriatric patients might have poor sleep quality associated with multiple clinical conditions. Sleep disorders are important health problems affecting the geriatric individuals' quality of life and well-being. Asking pertinent questions to treat poor sleep quality effectively is recommended to increase this population's quality of life and well-being.

Keywords: Sleep quality, obesity, polypharmacy, depression, elderly

Introduction

The phenomenon of aging, which is more prominent in developed countries, is also gaining importance for developing countries; and hereby geriatric population is ever-increasing in our country. As the world population progresses to an older population pattern day by day, the frequency of chronic diseases increases concordantly, and measures on quality of life criteria, such as healthy living, healthy aging also start to come to the agenda (1).

Covering 1/3 of the human life cycle and ensuring the continuity of health, sleep is considered as one of the basic physiological needs of mankind (2). Geriatric individuals experience excessive daytime sleepiness in relation to the decrease in sleep quality. In addition to productivity and efficiency, sleep also affects

cognitive functions (e.g. memory, concentration) positively and contributes to the physical and psychological restoration (3). Because of these positive effects, sleep is considered as an important health variable affecting the individual's quality of life and well-being.

Regular sleep routine has such positive effects on human life; therefore its disruptions affect individuals negatively and causes problems such as lack of attention, anxiety, depression, increased sensitivity to pain, irritability, hallucinations, loss of appetite, difficulty in excretion, memory disorders, increased risk of falls and decreased physical activity. Problems that arise due to sleep disorders lead to impaired quality of life and increased morbidity and mortality rates (4).

Sleep disorders such as difficulty in falling asleep and maintaining sleep, frequent awakening, and restless legs

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syndrome are frequent in geriatric patients. In addition to chronic diseases, these problems negatively affect functionality and quality of life. This study was planned in order to investigate the frequency of poor sleep quality and related factors in this population.

Materials and Methods

This study was planned with a retrospective file scanning method to investigate the frequency of poor sleep quality and related factors in 100 patients who applied to the Geriatric Outpatient Clinic of Gaziantep University Research and Application Hospital for any reason. The data were collected using the "comprehensive geriatric assessment form" and "Pittsburgh Sleep Quality scale (PSQI)". PSQI was developed in 1989 by Buysse et al. (5). PSQI has 7 components, and each component is rated between 0 and 3 points. The total score ranges from 0 to 21 (6). A total score higher than 5 indicates poor sleep quality (7).

As parts of the Comprehensive Geriatric Assessment, the Geriatric Depression scale (GDS) with 15 questions, the mini-mental state examination (MMSE), Barthel index of activities of daily living (ADL), Lawton&Brody index of the instrumental activities of daily living (IADL), and short form of the mini nutritional assessment tool-short form (MNA-SF) were used.

GDS scores of 5 and over indicate depression (8). MMSE assess five different areas in cognitive functions such as orientation, registration, attention and calculation, recall and language. MMSE scores of 24 and below were considered as impaired, suggesting dementia (9).

Barthel index of ADL was used for evaluating subjects' physical disability. This scale includes dressing, bathing, grooming, using the toilet, eating, transferring and incontinence (10). Scores can range from 0 to 100 and higher scores indicate higher independence.

Lawton&Brody index was used to evaluate the disability in IADL and this scale aims to find out subject performance in the following activities; doing laundry, shopping, taking medicine, housekeeping, food preparation, using the telephone, using transportation, and managing money. Higher scores indicates higher independence (11). The nutritional status of participants was determined by using MNA-SF. It is a simple and validated screening tool for nutritional risk and if the score was ≤ 7 , it is accepted as malnutrition (12).

Although there is no consensus on the definition of "polypharmacy", which refers to the use of multiple drugs in the elderly, it usually means the use of many drugs for more than one indication at the same time. In our study, we used the National Service Framework definition of polypharmacy as four or more drugs usage.

Individuals with established adverse drug effects on sleep were excluded from the study. Evaluation scales were applied by face to face interview techniques. Ethical approval was obtained. The study was carried out in accordance with the Helsinki Declaration.

Statistics

The data were analyzed with IBM SPSS Statistics version 22.0. Descriptive (number, percentage, mean and standard deviation) and parametric tests were used for the analysis. T-test or Mann-Whitney U tests were used to compare continuous parameters between groups with and without sleep quality and groups by gender. Chi-square test was used to compare categorical parameters. A p-value of less than 0.05 was considered significant.

Results

A total of 100 random patients admitted to the geriatric outpatient clinic were included in the study. The mean age was 71.17 ± 5.49 (65-89 years). 56% were women (56) and 44% were men (44). The mean PSQI score was 6.17 ± 3.79 , and the lowest and highest scores were 0 and 16, respectively. The PSQI score of 60% of the group was between 5-16, and these individuals had poor sleep quality. 75.9% of women and 38.1% of men had poor sleep quality ($p < 0.005$). The comprehensive geriatric evaluation results are summarized in Table 1.

Age, marital status, educational status, lifestyle, smoking, drinking alcohol, regular exercise, scores of the ADL, Mininutritional assessment and MMSE, and presence of chronic disease showed no significant difference between groups with and without poor sleep quality ($p > 0.05$).

It was found that geriatric patients who had significant poor sleep quality showed more frequent high body mass index (BMI) and obesity, increased drug use and polypharmacy, increased score of the Geriatric Depression scale, low handgrip strength, and relative incompetence in instrumental ADL ($p < 0.005$) (Table 2).

Discussion

Sleep is a daily life activity that is one of the basic needs of humans. Therefore, sleep is seen as an important variable of health, affecting the quality of life and well-being of the individual.

Sleep, which constitutes an important part of human life has attracted the attention of many researchers. It is noteworthy that 60% of patients who applied to the geriatric outpatient clinic have poor sleep quality in our study.

Sleep problems are an inevitable part of the aging process and are manifested by a decrease in the sleep quality of

individuals (13). In the literature, there are studies showing that 50% to 77% of elderly individuals have sleep problems (14,15). 60% of the individuals who participated in our study had sleep problems. This supports the results of the studies that previously examined the prevalence of sleep problems of elderly individuals.

Adequate sleep is important for the renewal of the body, regular brain functions, energy storage, good appearance, and protection from diseases. It was determined that sleep time and quality affect memory, learning, performance, metabolic and endocrine system, and decrease in sleep time disrupts neurohormonal balance, causes weight gain and obesity (16).

Table 1. General characteristics of patients, PSQI scores and poor sleep quality frequency

n=100	
Age (years)	71.17±5.49
Gender (F/M) (n)	56/44
Marritage status (n)	
• Married	72
• Widow	25
• Single	3
House partner (n)	
• Spouse	72
• Alone	15
• Relatives	11
• Caregiver	2
Education level	
• Uneducated	40
• Primary school	47
• High school	5
• College	8
Comorbidities	
• Diabetes mellitus	33
• Coronary artery disease	27
• Cerebrovascular disease	20
• Gastrointestinal diseases	12
• Musculoskeletal system diseases	8
Smoking (n)	19
Drinking alcohol (n)	3
Regular exercising (n)	26
Global PSQI score	6.17±3.79 (0-16)
• Sleep duration	0.40±0.86
• Sleep disturbance	1.35±0.58
• Sleep latency	1.17±0.78
• Daytime dysfunction	1.02±0.76
• Sleep efficiency	0.58±0.83
• Subjective sleep quality	1.01±0.72
• Use of sleep medication	0.74±1.15
Poor sleep quality (n)	60
BMI (kg/m ²)	29.73±4.49 (20-40)
Obesity (n)	54
Number of drugs routine used	4.04±2.93
Polipharmacy (n)	46
BMI: Body Mass index, PSQI: Pittsburgh Sleep Quality scale	

In the literature, obesity is the most important disease seen as a result of sleep disorders (17). The decrease in sleep time causes an increase in the circulating ghrelin level and a decrease of the leptin level. As a result, energy expenditure decreases, appetite, and therefore the risk of obesity increase (16). Studies have shown that there is a relationship between sleep disorder, sleep deprivation, and BMI (18). In the community-based Wisconsin Cohort Sleep study conducted by Taheri and Thomas (19), which included 1.024 people, it was found that the participants slept less than 8 hours and the duration of sleep decreased as the BMI increased. In the Valencia-Spain Health and nutrition survey, a cross-sectional study involving 1.772 people over the age of 15, less than half of the individuals stated that they slept 9 hours and more, and the rest 6 hours and less. Those who slept less were found to be at risk for obesity (18). The results of our study also support the relationship between obesity and impaired sleep quality in geriatric patients.

In the aging process, organ functions decrease and the number of chronic diseases increases.

In a recent study from our country, the frequency of polypharmacy in patients who applied to the geriatric outpatient clinic was 59.8% (20). In a recent study in our country, a statistically significant (p=0.021) correlation was shown between sleep disorders and polypharmacy (21). The results of our study also show that there is a high frequency of polypharmacy in geriatric patients and proves that there is a relationship between polypharmacy and impaired sleep quality.

Depression is one of the common mental disorders in the elderly. It is an important factor affecting the quality of life with various diseases or alone. Generally, in addition to slowing down in mental processes, it causes important but reversible impairment in high cognitive functions such as short-term memory, learning, voluntary attention, and purposeful functions. If depression is not treated, it causes consequences such as death at an early age and deterioration in general health status and the quality of life of the elderly increases with appropriate treatment (22). The reason why depressive patients seek support is generally insomnia, and improvement of sleep disturbance is an important determinant of compliance with treatment. Apart from the discomfort they cause, sleep problems can lead to burnout, poor functionality throughout the day, accidents, and are associated with an increased risk of suicide (23). Sleep changes can also affect mood disorders. It was observed that people who reported insomnia both at the initial interview and during the one-year follow-up were more likely to develop a new major depression than those who recovered at the second interview (24). For these reasons, depression and sleep disturbance are conditions that should be evaluated together. The results of our study also support the relationship between the high GDS and impaired sleep quality in geriatric patients.

Table 2. Factors associated with poor sleep quality			
n=100	Poor sleep quality (n=60)	Normal sleep quality (n=40)	p
Age (years)	70.70±5.31	71.87±5.76	>0.05
Gender (F/M) (%)	73.3/26.7	35/65	0.000
Marritage status (%)			
• Married	66.7	80	>0.05
• Widow	28.3	20	
• Single	5	-	
House partner (%)			
• Spouse	66.7	80	>0.05
• Alone	15	15	
• Relatives	15	5	
• Caregiver	3.4	-	
Education level			
• Uneducated	51.7	35	>0.05
• Primary school	35	52.5	
• High school	6.7	2.5	
• College	6.7	10	
Comorbidities			
• Diabetes mellitus	36.7	27.5	>0.05
• Coronary artery disease	23.3	32.5	
• Cerebrovascular disease	21.7	17.5	
• Gastrointestinal diseases	8.3	17.5	
• Musculoskeletal system diseases	10	5	
Global PSQI score	7.83±3.97	4.76±3.09	0.000
Smoking (%)	20	17.5	>0.05
Drinking alcohol (%)	1.7	5	>0.05
Regular exercising (%)	23.3	30	>0.05
BMI (kg/m ²)	31.10±4.50	27.69±3.66	0.000
Obesity (%)	80.4	42.6	0.000
Number of drugs routine used	4.84±3.05	2.88±2.32	0.002
Polipharmacy (%)	58.3	27.5	0.004
ADL (/100 points)	61.41±17.96	78.33±15.63	>0.05
IADL (/17 points)	8.471±3.52	5.12±2.42	0.025
MMSE	25.12±2.11	25.87±2.19	>0.05
GDS	4.88±4.11	2.57±3.14	0.003
Walking speed (m/s)	0.66±0.35	0.88±0.46	0.011
MNA-SF	10.80±2.76	11.67±2.15	>0.05
Handgrip strength	20.24±8.82	27.98±11.41	0.000

BMI: Body mass index, PSQI: Pittsburgh Sleep Quality scale, ADL: Activities of daily living, IADL: Instrumental activities of daily living, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, MNA-SF: Mini nutritional assessment tool-short form

Sarcopenia is one of the important health problems frequently seen in the elderly. While the prevalence of sarcopenia is 5-25% in individuals aged 60-70 years, it is 11-50% in individuals over 80 years of age (25). This age-specific condition increases the risk for the poor quality of life, risk of falling, and negative outcomes that can result in death. Physical inactivity, prolonged bed rest, sedentary life, limitation of movement, or loss of mobility increase sarcopenia (26). Due to physical inactivity, sarcopenia occurs and creates a vicious circle, causing adverse effects on the body. In order to diagnose sarcopenia, the

variables that need to be measured are; muscle mass, muscle strength, and physical performance (27). In our study, when we measured muscle strength and walking speed, two important elements of the diagnosis of sarcopenia, we found that muscle strength and walking speed were significantly lower in elderly patients with poor sleep quality ($p<0.005$). When we scan the literature as sleep disorders and sarcopenia, we see the recent studies of Ida et al. (28) friends in 318 elderly diabetic patients. As a result of this study, they showed that there was a positive correlation between sarcopenia and sleep

disorders (28). Furthermore, few studies have examined the relationship between various sleep parameters and muscle power, such as sleep quality, sleep fragmentation, diurnal variation, use of sedative agents, and primary sleep disorders (26-29). The results of our study also support the relationship between decreased muscle strength and walking speed and impaired sleep quality in geriatric patients.

Study Limitations

There are some important limitations in our study. The most important of these is that the decrease in sleep quality is evaluated only subjectively. The inadequate size of the sample group prevented the generalization of the results. Finally; the existing chronic diseases of individuals participating in the study may have caused a decrease in their sleep quality. However, the proportion of the elderly who do not have a chronic disease is quite low in the population. The quality of sleep is impaired in the majority of geriatric patients. Obesity, depressive mood, polypharmacy, and female gender appear to be the most important factors affecting sleep quality.

Conclusion

It is thought that the quality of life of the elderly will increase with the evaluation of the sleep quality and intervention planning to increase it by the healthcare professionals taking care of older individuals if necessary.

Ethics

Ethics Committee Approval: Ethical approval was obtained. The study was carried out in accordance with the Helsinki Declaration (Gaziantep University Faculty of Health Sciences, protocol no: 218).

Informed Consent: Patient consent form was not received as it is a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.H.T., Concept: Z.A.Ö., Design: Z.A.Ö., Data Collection or Processing: A.Ç., Analysis or Interpretation: İ.H.T., Literature Search: E.M.E., Writing: A.Ç.

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Characteristics and Outcomes of Frail Patients Hospitalised with Cardiovascular Diseases

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Abstract

Objective: Frailty, a pre-disability state, is highly prevalent in older patients and negatively affects prognosis during or after hospitalisation. We examined the factors associated with a frailty index and this index's prognostic significance in a patient cohort with cardiovascular disease.

Materials and Methods: In this prospective study, patients aged ≥ 65 years were admitted to a cardiology department for acutely decompensated cardiovascular diseases. The identification of seniors at risk-hospitalised patients (ISAR-HP) score was measured at admission, and two threshold values (≥ 2 and ≥ 4) were considered to define high-risk patients. Other variables included physical examination, laboratory testing, electrocardiogram, echocardiography, final diagnosis, course of hospitalisation and one-year mortality.

Results: We enrolled 166 patients with a mean age of 79.2 ± 7.6 years, and 51.2% of them were males. The main final primary diagnoses were as follows: 38.1% had acute heart failure, 15.1% supra-ventricular arrhythmias, 6.1% cardiac syncope, 5.4% deep vein thrombosis/pulmonary embolism, 4.8% acute coronary syndromes and 4.8% acute hypertension. The ISAR-HP was measurable in 97% of the cohort and identified 70.5% and 32.5% of patients at high risk of further decline depending on the threshold value retained. Among the baseline characteristics and blood tests, advanced age, female gender, past or present heart failure, lower haemoglobin concentration, increased N-terminal pro-B-type natriuretic peptide concentration, increased troponin concentration and the need for oxygen support were associated with ISAR-HP ≥ 2 ($p < 0.05$ for all). ISAR-HP scores of ≥ 2 and ≥ 4 were associated with a statistically significant seven-to-nine-fold increase in one-year mortality, respectively.

Conclusion: A high ISAR-HP ≥ 2 score is prevalent in patients with cardiovascular disease and strongly affects one-year mortality. Age, past or present heart failure and increased cardiac biomarkers are the primary factors associated with a high ISAR-HP score.

Keywords: Ageing, frailty, cardiovascular diseases, heart failure

Introduction

With rises in life expectancy, increasing numbers of old patients are hospitalized in departments of cardiology. Mortality or functional decline are, unfortunately, very widespread outcomes after these patients are discharged, with an incidence ranging from 25% to 59% (1). Frailty is defined as an increased vulnerability to developing dependency when exposed to a stressor, such as hospitalization (2,3). Frailty contributes to disease prognosis and negatively affects mortality in various conditions, including heart failure (HF) and acute coronary

syndromes (ACS) (4-6). Frailty screening of aged patients is strongly recommended, and a comprehensive care plan should be implemented; this may include screening and treatment for sarcopenia and exhaustion, referral to a geriatrician, physical activity programs, nutritional supplementation, or social support programs (3).

Since the first description of physical frailty by Fried et al. (2), many frailty screening instruments have been developed, but consensus on which is optimal has not yet been reached (6,7). In addition, these scales are rarely used in routine practice

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because they are time-consuming, and many non-geriatricians are unaware of the robustness of the scores obtained. However, the identification of seniors at risk-hospitalized patients (ISAR-HP) is a very simple scale that is based on four yes/no questions (8,9). The sensitivity and specificity of the ISAR-HP score for predicting further decline were 87% and 39% in a study of patients hospitalized in the department of internal medicine, and 85% and 48% in a study of patients undergoing cardiac surgery, respectively (8,9). To date, the ISAR-HP has mostly been studied in older patients admitted to departments of medicine, and little is known about its use in cardiology (1,8). Our objectives were to measure the ISAR-HP scores of patients with various acute cardiovascular diseases, to determine the characteristics of patients with high ISAR-HP scores, and to examine its prognostic significance.

Materials and Methods

Study design and population

The SENIOR study is a prospective study that enrolled patients aged ≥ 65 years who presented with any acute cardiovascular disease and were admitted to the department of cardiology of the university hospital of Avicenne from September 2017 to March 2018. Data on baseline characteristics, the results of laboratory testing, cardiac investigations, and mortality after discharge were collected. The exclusion criteria were as follows: death during the index period of hospitalization; transfer from or discharge to another department (except for rehabilitation); and inability to measure the ISAR-HP score (e.g., patients with mild/severe cognitive impairment who had no relatives present at admission, foreign patients who did not speak French or English, etc.). The study was approved by the local Ethics Committee, Comité de Protection des Personnes Ile de France III, and all patients granted their informed consent to participate in the study.

Routine clinical assessment

At admission, all patients underwent a physical examination and standard laboratory testing, including measurements of plasma high-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and albumin concentration. They also underwent an electrocardiogram and echocardiography within 24 hours of admission. The necessity of other exams and aspects of patient management were at the discretion of the cardiologist and not specified by the study protocol.

ISAR-HP determination

The ISAR-HP score was determined by the admitting nurse present for each patient. In brief, the ISAR-HP is a scorecard with four yes/no questions on 1) needing assistance with instrumental activities of daily life (IADL), 2) the use of a

walking device, 3) the need of assistance for travelling and 4) a low level of education. Each item is scored 0 or 1 except for the need for a walking device, which is scored as 0 or 2 (8,9). Two threshold values have been proposed in the literature and were used in our study to define high-risk patients as scoring ≥ 2 and ≥ 4 (low risk if patients score 0 or 1, intermediate risk for 2 or 3 points, and high-risk for those who score 4-5 points) on the ISAR-HP (1,8,9).

Follow-up

All these data, as well as information about the course of hospitalization and final and associated diagnoses, were entered in a dedicated database. One-year mortality was determined by follow-up phone calls with the patients, their relatives and their physician if necessary. Follow-up information was entered in the database by the research nurse.

Statistics

The distribution of quantitative data was evaluated by histograms, coefficients of variation and a skewness and Kurtosis Normality test. Quantitative data are presented as means \pm standard deviation or medians (interquartile range) accordingly, qualitative data are presented as numbers (percentages) as appropriate.

The possible association between baseline characteristics and ISAR-HP ≥ 2 scores was investigated using the Student's t-test, the Mann-Whitney U test, a chi-squared test, or Fisher's Exact test, as appropriate. A multivariate logistic regression was then applied, accepting all variables (from demographics, past medical history and treatments, baseline characteristics, screening blood tests, echocardiography and the final diagnosis) at $p < 0.05$. The R-squared value was 0.43. A similar analysis was performed with the 3-category classification of the ISAR-HP (low, intermediate or high risk) using the Kruskal-Wallis Rank-sum test, the chi-squared or Fisher's Exact test.

Time-to-death at 1 year is presented as Kaplan-Meier curves stratified according to the ISAR-HP score, comparisons between groups were performed with the Logrank test. Results are reported as relative risk (hazard ratios) with a respective confidence interval of 95%. A p-value of < 0.05 was considered significant. STATA statistical software (StataCorp, 2014) was used for all analyses.

Results

In total, 166 patients acutely hospitalized and discharged alive were included in the study. Five patients were not included in the study due to an incomplete ISAR-HP score because the level of education could not be ascertained. The mean age was 79.2 ± 7.6 years: 51.2% were male, 18.1% were living alone, and 7.1% were rest-home residents. The final diagnosis was acute

HF in 38.0% of patients, supra-ventricular arrhythmias in 15.1%, conduction-disease related syncope in 6.1%, deep vein thrombosis or pulmonary embolism in 5.4%, non-ST segment elevation ACS in 4.8%, the same as for acute hypertension and valvular disease, reflex and other causes of syncope in 4.2%, specific cardiomyopathy in 3.6%, acute pericarditis in 3.0%, the same as for myocarditis, endocarditis in 2.4%, ventricular arrhythmias in 1.8%, pulmonary hypertension in 1.8%, and chronic coronary syndrome in 1.2%. It is noteworthy that 23.6% of patients had concomitant infectious disease (mostly upper respiratory tract infection).

The median duration of hospitalization was 5 (3-7) days, 80.7% of patients were discharged home and 8.4% needed additional home support at discharge. After discharge, 46.4% visited their general practitioner within 1 month and only 16.9% visited a cardiologist within 1 month. Table 1 summarizes the main demographic and clinical characteristics of our cohort according to their ISAR-HP scores (<2 or ≥2), and Table 2 presents the data collected during the hospitalization and the follow-up period. Seven patients (4.2%) were lost to follow-up, including four patients who scored <2 and three patients who scored ≥2; all of these patients were foreigners or homeless people. Mortality within 1 year occurred in 31/159 patients (19.5%).

ISAR-HP score and associated factors

The ISAR-HP scores ranged from 0 to 5 (Figure 1); 105 (63.3%) patients needed some help in IADL, 69 (41.6%) used a walking device, 92 (55.4%) needed help for travelling and 93 (56.0%) had a low level of education. In all, 117 (70.5%) patients scored ≥2; 29.5%, 38.0%, and 32.5% of patients respectively were considered at low, intermediate and high risk of further decline according to the 3-class risk stratification.

Patients who scored ≥2 were older (p<0.001), were more likely to have histories of chronic HF and were more often admitted for acute HF, had increased systolic blood pressure, more frequently required oxygen support, had lower haemoglobin concentrations, increased NT-proBNP and hsTnT concentrations (p<0.05 each) and a trend toward reduced albumin concentrations (p=0.064). The length of hospitalization was on average one day longer in patients with ISAR-HP ≥2 when compared to patients who scored <2 (p=0.027). We observed no significant differences in atherosclerosis risk factors, treatment at admission, mode of discharge, need for additional home support, or outpatient visits (Table 1, 2). In the multivariate analysis, age was the only factor independently associated with an ISAR-HP score of ≥2. Analyses using the 3-class risk stratification of the ISAR-HP score and a threshold value of ≥4 to define high-risk patients yielded similar results.

The ISAR-HP score and one-year mortality

Figure 2 shows that when compared to survivors, patients who died within one year of enrolment had higher ISAR-HP scores [2.0 (1-4) vs. 3.5 (2-4) respectively, p=0.007] and more often scored ≥2 (64.3% vs. 92.9% respectively, p=0.003). Table 3 demonstrates that when compared to patients at low risk of future decline, those at high risk had a 7.2-fold risk of death at one year (if expressed as two categories, ISAR-HP ≥2 vs. <2) or a 9.0-fold risk of death at one year (if expressed in three categories, low, intermediate and high risk). Similar results were found after excluding patients with acute HF (respective hazard ratios of 6.3 and 15.2).

Discussion

This prospective study measured the ISAR-HP scores for patients hospitalized in a department of cardiology for acute

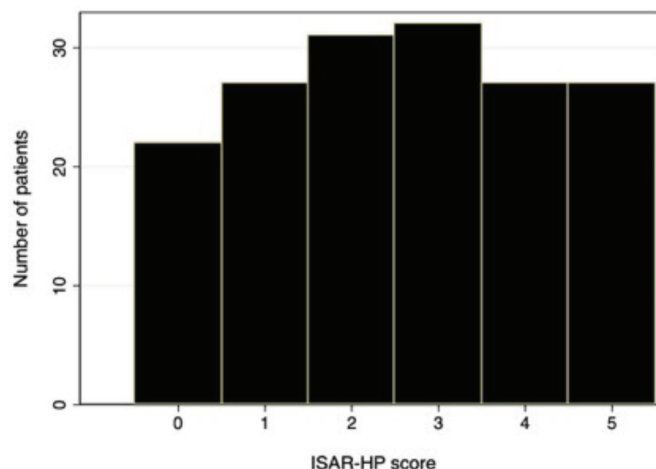


Figure 1. Distribution of the ISAR-HP score
 ISAR-HP: Identification of seniors at risk-hospitalized patients

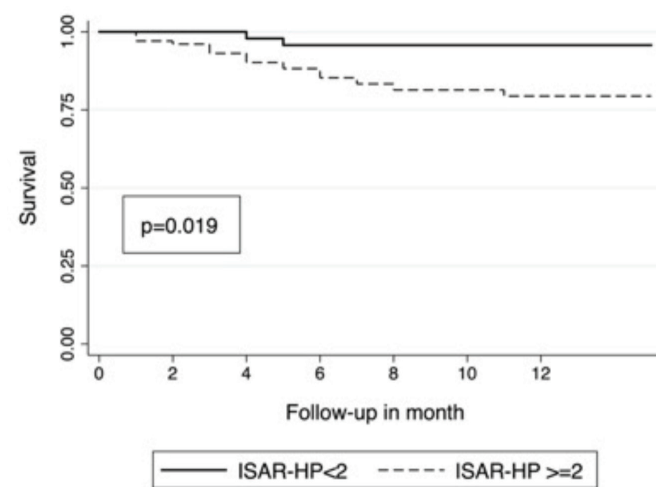


Figure 2. Kaplan Meier representation of one-year all-cause mortality in patients with and without increased ISAR-HP scores
 ISAR-HP: Identification of seniors at risk-hospitalized patients

cardiovascular disease. First, our results show that frailty is very widespread in patients with HF but also in those with other cardiovascular diseases. Second, it was feasible for the ISAR-HP scorecard to be assessed by a nurse in 5 minutes for almost all patients at presentation. Third, we found patients with ISAR-HP score ≥ 2 to be older, with past and/or present HF, have a lower haemoglobin concentration and have more severe cardiac disease at presentation. Fourth, our results show that a high ISAR-HP score is associated with a seven-to-ninefold increase in one-year mortality.

Functional decline after hospitalization, known as frailty, is highly prevalent in aged patients possibly affecting between 30% and 60% of patients (10). Several frailty indexes have

been developed and have demonstrated their capacity to predict decline as well as mortality (1,2,4,10,11). Sokoreli et al. (12) reported that a clinical model including blood tests was less effective than a clinical model enriched by frailty indexes to predict death or re-admission in patients with HF; this suggests that frailty indexes should be part of the routine evaluation of these patients (3,12). Very recently, Testa et al. (11) investigated a large cohort of old patients and reported that multidimensional frailty scores were more predictive of mortality than were physical scores, both in the absence of and even more in the presence of HF. However, the existence of multiple such risk scales and the absence of any consensus on the optimal one to perform, as well as the complexity of

Table 1. Patients' characteristics on admission

Variable	Total cohort (n=166)	ISAR-HP <2 (n=49)	ISAR-HP ≥ 2 (n=117)	p
Age, years	79.2 \pm 7.6	74.5 \pm 6.6	81.1 \pm 7.2	p<0.001
Male gender	85 (51.2%)	32 (65.3%)	53 (45.3%)	0.019
Past CAD	35 (21.1%)	9 (18.4%)	26 (22.2%)	0.579
Past CHF	35 (21.2%)	5 (10.2%)	30 (25.9%)	0.025
Past arrhythmia	51 (30.7%)	10 (20.4%)	41 (35.0%)	0.062
Diabetes	67 (40.4%)	20 (40.8%)	47 (40.2%)	0.938
Hypertension	122 (73.5%)	34 (69.4%)	88 (75.2%)	0.438
Current smoker	4 (2.4%)	2 (4.1%)	2 (1.7%)	0.582
Hypercholesterolemia	26 (15.7%)	8 (16.3%)	18 (15.4%)	0.879
Renal failure	27 (16.3%)	5 (10.2%)	22 (18.8%)	0.171
Dementia	16 (9.6%)	2 (4.1%)	14 (12.0%)	0.154
Married	136 (81.9%)	42 (85.7%)	94 (80.3%)	0.412
Drug regimen*				
Aspirin	65 (40.4%)	18 (40.0%)	47 (40.2%)	0.952
Anticoagulant	41 (25.5%)	9 (20.0%)	32 (27.6%)	0.321
Beta-adrenergic blocker	72 (44.7%)	17 (37.8%)	55 (47.4%)	0.270
Diuretics	85 (52.8%)	20 (44.4%)	65 (56.0%)	0.186
ACE inhibitor/ARB	87 (54.4%)	21 (47.7%)	66 (56.9%)	0.298
Statins	71 (44.1%)	20 (44.4%)	51 (44.0%)	0.956
Total number of treatments	6.2 \pm 3.2	5.9 \pm 3.6	6.4 \pm 3.1	0.455
Clinical presentation				
Heart rate, bpm	77 (65-94)	82 (68-100)	73 (65-90)	0.068
Systolic BP, mmHg	137 (121-156)	132 (116-150)	140 (121-160)	0.046
Diastolic BP, mmHg	70 (62-83)	70 (64-82)	70 (62-90)	0.934
Body temperature, °C	37.0 (36.5-37.2)	36.8 (36.5-37.0)	37.0 (36.6-37.2)	0.283
Need of oxygen support, n	32 (19.3%)	3 (6.1%)	29 (24.8%)	0.005
Screening blood test				
Hemoglobin, g/dL	12.3 (11.1-13.9)	12.8 (11.8-14.6)	12.1 (11.0-13.7)	0.011
Creatinine, μ mol/L	97 (75-126)	88 (74-115)	97 (78-128)	0.283
NT-proBNP, pg/mL	2.192 (506-4.863)	1.605 (137-3.800)	2.409 (921-7.896)	0.019
Hs-TnT, ng/L	26 (16-47)	21 (11-45)	30 (19-55)	0.037
C-reactive protein, mg/L	10 (4-32)	7 (2-17)	12 (5-45)	0.083
Albumin, g/L	33 (31-36)	34 (31-39)	33 (31-35)	0.064

Data are presented as mean \pm SD, median (interquartile range) or numbers (%), SD: Standard deviation, CAD: Coronary artery disease, CHF: Chronic heart failure, ACE inhibitor/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, *: Treatment at admission could not be collected in 5 patients, CAD: Coronary artery disease, CHF: Congestive heart failure, BP: Blood pressure, BNP: Brain natriuretic peptide

Table 2. Data collected during hospitalization and the follow-up period

	Total cohort (n=166)	ISAR-HP <2 (n=49)	ISAR-HP ≥2 (n=117)	p
LVEF, %	55 (45-60)	55 (42-60)	55 (47-60)	0.694
Length of hospitalization	5 (3-7)	4 (3-5)	5 (3-8)	0.027
Final diagnosis				
Acute HF	63 (38.0%)	13 (26.5%)	50 (42.7%)	0.045
Supra-ventricular arrhythmias	25 (15.1%)	9 (18.4%)	16 (13.7%)	0.454
Conduction disease related syncope	10 (6.1%)	3 (6.1%)	7 (6.0%)	0.983
DVT/PE	9 (5.4%)	3 (6.1%)	6 (5.1%)	0.726
ACS	8 (4.8%)	3 (6.1%)	5 (4.3%)	0.696
Infectious disease	39 (23.6%)	9 (18.4%)	30 (25.9%)	0.300
Total number of treatments at discharge	7.1±3.3	6.5±3.5	7.4±3.2	0.133
Discharge at home	134 (80.7%)	44 (89.8%)	90 (76.9%)	0.083
Additional home support*	14 (8.4%)	2 (4.1%)	12 (10.3%)	0.192
Outpatient visit by GP <1 mo	77 (46.4%)	24 (49.0%)	53 (45.3%)	0.664
Outpatient visit by cardiologist <1 mo	28 (16.9%)	8 (16.3%)	20 (17.1%)	0.904

*: Patients who had additional home support at discharge versus prior to hospitalization, LVEF: Left ventricular ejection fraction, HF: Heart failure, DVT/PE: Deep vein thrombosis and/or pulmonary embolism, ACS: Acute coronary syndrome, GP: General practitioner, ISAR-HP: Identification of seniors at risk-hospitalized patients

Table 3. Hazard ratios and 95% confidence interval of the ISAR-HP risk categories for 12-months mortality

Risk category	12-months mortality	p
ISAR-HP <2	Ref	
ISAR-HP ≥2	7.2 (1.6-33.5)	0.003
ISAR-HP low risk	Ref	
ISAR-HP intermediate risk	5.9 (1.1-29.3)	0.014
ISAR-HP high risk	9.0 (1.7-46.6)	0.002

ISAR-HP: Identification of seniors at risk-hospitalized patients

administering many of these, have contributed to limiting their integration in clinical practice (5,7,11).

The ISAR-HP score is one of the simpler frailty instruments. Although it has been less extensively studied than more complex tools, its prognostic significance has been demonstrated by findings from several cohorts of patients in emergency departments (EDs) (6,13-15). Additionally, the ISAR-HP score has the theoretical advantage of being easily and rapidly assessed; this is confirmed by our study, as we report 97% of the scorecards were completed by a nurse within five minutes.

In our study, we measured the ISAR-HP score and fixed two distinct threshold values, ≥2 or ≥4 (1). We reported that 70.5% and 32.5% of patients respectively were at high risk, according to these criteria. This is consistent with the study of Buurman et al. (1), who used the same scale with identical threshold values and reported that 40% of patients were at high risk; however, only 4.3% of their patients were admitted for symptoms of cardiovascular disease. Our study also shows that more patients with ISAR-HP ≥2 versus <2 had a final diagnosis of Acute HF (42.7% vs. 26.5% respectively, p<0.05) as well as ≥4 versus <4 (42.9% vs. 25.5% respectively, p<0.05). This is consistent with other studies that report a

high proportion of frailty among patients with acute/chronic HF, ranging from 30% to 56% depending on the assessment tool used (5,11,16,17). Several hypotheses can be generated to explain such a high prevalence of frailty in HF patients. Both conditions share common aspects, including more advanced age (especially in HF with preserved ejection fraction), the presence of comorbidities, inflammation, and undernutrition and deficiencies (4,11). This may also explain the increased risk of the incident of HF observed in frail patients (18).

The relationship between frailty and hospitalization is complex. On the one hand, frailty accentuates the risk of future decline after hospitalization, but on the other, it has been suggested that functional decline may even precede hospitalization and continues during hospitalization (19,20). As we collected data at admission, our results cannot have been influenced by the course of hospitalization, but likewise cannot address any possible deterioration before the event.

Only a few studies have examined the clinical and biological factors associated with frailty. In our study, we collected demographic characteristics, past medical history and treatment, cardiac echo and biomarkers, general prognostic markers (e.g., renal function, risk factors, or comorbidities) and specific geriatric indexes (including the ISAR-HP score, albumin, and number of treatments at admission). We report that advanced age, female gender, past and/or present HF, lower haemoglobin concentration, increased NT-proBNP and troponin concentrations, and the need for oxygen support are all associated with a high ISAR-HP score.

Natriuretic peptides and troponins are well-known markers of acute HF and ACSs respectively, but have also been demonstrated to be related to the severity of

various cardiovascular diseases and have high prognostic significance (21-23). Our results should be therefore interpreted as indicating increased frailty in older patients, female, HF patients and patients with more advanced cardiovascular disease. This is confirmed by the prolonged length of hospitalization we observed in patients with high ISAR-HP scores and is consistent with the few studies conducted previously (5,10). In multivariate analysis, age was the only independent factor associated with an increased ISAR-HP score. This may be a consequence of the intrinsic characteristics of the ISAR-HP score, which focuses mainly on dependency rather than on physical activity. In addition, several variables included in the multivariable models are markers of the severity of the disease and correlate with each other.

We report that patients identified as high-risk by their ISAR-HP score have a 7- to 9-fold increase in one-year mortality, whether patients were admitted for acute HF or another cardiovascular disease. This extends the previous findings of worse outcomes observed in the ED and suggests that frailty should be considered a high-priority matter in cardiology (1,15).

Study Limitations

Potential limitations of the current study merit consideration. First, more than 30% of our patients had a final diagnosis of HF, which may have increased their ISAR-HP score and accounted for the increased mortality we observed. However, high one-year mortality rates were observed in all patients with elevated ISAR-HP scores as well as in the subgroup of patients without acute HF as a final diagnosis.

Second, our study was performed in a single centre with a relatively limited number of patients. Third, only a few patients had known cognitive impairment. This may be explained by the fact that patients with dementia are more often hospitalized in geriatric units rather than in cardiology units.

Our study shows that frailty is very common in older patients with acute cardiac diseases and has a major impact on mortality. This suggests that frailty scales should be routinely measured in cardiology departments. The question of how to specifically manage these patients remains unsolved and cannot be derived from our study. Patient management may rely on programs incorporating systematic comprehensive geriatric assessment, rehabilitation, and/or nutritional support. Measurements provided by frailty indices may also enable clinicians to select the most cost-effective treatment strategies (24). This remains to be confirmed in dedicated studies.

Conclusion

The measurement of ISAR-HP scores is easily feasible in older patients hospitalized for cardiovascular disease. High ISAR-HP

scores are associated with advanced age, severity of cardiac disease, and past or present HF. The scores aid the identification of patients at a high one-year risk of mortality.

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Ethics

Ethics Committee Approval: The study was approved by the local Ethics Committee, Comité de Protection des Personnes Ile de France III.

Informed Consent: Informed consent to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.B., S.M.S., F-X.G., Concept: S.T., C.M., Design: G.S., S.T., C.M., Data Collection or Processing: N.G., Analysis or Interpretation: S.M.S., F-X.G., C.C., Literature Search: C.C., Writing: T.B., S.M.S., M.M.E., C.M.

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Retrospective Evaluation of Geriatric Inpatients with Nephrotic Syndrome: A Single Centre Experience

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Abstract

Objective: Nephrotic syndrome frequently develops because of primary kidney disease in older adults. The most common secondary cause is diabetic nephropathy. This study aims to investigate the frequency of nephrotic syndrome and the primary and secondary causes of nephrotic syndrome in hospitalised patients aged 65 years and over in our centre.

Materials and Methods: Patients aged 65 years and over who were hospitalised in the internal medicine clinic between October 2000 and 2014 using the "nephrotic syndrome" diagnostic code were selected from hospital records. Demographic, clinical, biochemical parameters and pathology results were examined retrospectively.

Results: A total of 92 patients were diagnosed with nephrotic syndrome. Thirty-one patients were included in the study after reviewing patient files (32.3% female, 67.7% male). In nine patients, biopsies were not performed because of general risk factors, atrophic kidney, bleeding diathesis and other reasons. The mean age was 72.6±5.2 (65-87) years. The records indicated that 58% of patients were hypertensive, 26% were diabetic, 23% suffered from coronary artery disease, 58% had hyperlipidaemia and 13% had connective tissue disease. In the biopsy results, 40.8% were diagnosed with membranous glomerulonephritis. Amyloidosis, diabetic nephropathy and focal segmental glomerulosclerosis diagnoses were present in 18.2%, 18.2% and 13.6% of patients, respectively.

Conclusion: Membranous glomerulonephritis was the most common type of nephrotic syndrome in our centre in accordance with the literature in older patients. We found that amyloidosis and diabetic nephropathy ranked second. The present study demonstrated the importance of renal biopsy in the presence of nephrotic syndrome in older adults.

Keywords: Elderly, nephrotic syndrome, renal biopsy

Introduction

Progressing nephron loss in the kidneys, glomerular and tubulo-interstitial damage and a decline in kidney functions occur with increasing age (1). Those changes may make it difficult to interpret the kidney lesions. The increase in the permeability of glomerulus especially for macromolecules such as albumin, lead to proteinuria at nephrotic levels (>3.5 gr/24 hour). As a result of this, hypoalbuminemia, hyperlipidemia, oedema and hypercoagulopathy may develop. These are the most significant factors that indicate morbidity and mortality for nephrotic syndrome. As one of the most frequently observed kidney diseases in older patients, nephrotic syndrome usually occurs due to primary glomerular diseases (2). Since

the symptoms of nephrotic syndrome can be confused with congestive heart failure or venous insufficiency, it might be difficult to diagnose in older patients (3). In older patients, the most common forms of primary glomerular diseases are membranous glomerulonephritis and focal segmental glomerulosclerosis while the most common causes of secondary glomerular diseases are diabetic nephropathy, amyloidosis and malignancy (3,4).

In the diagnostic assessment of nephrotic syndrome, the role of renal biopsy and identification of underlying causes are rather significant. For diagnosis, at first history of the patient, physical examination and serum biochemical examinations are assessed. In older patients, the underlying causes must be aimed for

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the treatment of secondary nephrotic syndrome. On the other hand, for primary nephrotic syndrome, conservative treatment, overall precautions and disease specific treatments must be applied. The impact of nephrotic syndrome can be more severe for older patients, at the same time renal biopsy should not be avoided no matter what the age is (2). The aims of this study were to investigate the frequency of nephrotic syndrome, and its primary and secondary causes in hospitalized patients aged 65 years and over in our center.

Materials and Methods

Patients aged 65 years and over who were hospitalized in the internal medicine clinic between October 2000 and 2014 were screened using the "nephrotic syndrome" diagnostic code. The data of 92 patients was found but, after deeper investigation, 31 patients received the exact diagnosis of nephrotic syndrome. Age, gender, comorbidity information, smoking history, serum creatinine concentration, creatinine, protein level of 24-hour urine sample, serum albumin level, hemoglobin level, total cholesterol level and renal biopsy pathology reports of these patients were recorded from their files. Nephrotic syndrome has been identified as the combination of 3.5 gr/day/1.73 m² proteinuria in the 24-hour urine sample with oedema, hypoalbuminemia, hyperlipidemia and lipiduria.

This study was presented as an oral presentation at the International Academic Geriatrics Congress 2017 on April 12-16, 2017, in Antalya, Turkey. This study was approved by the Institutional Ethical Review Board (number: 14-9.2/12).

Statistics

All the statistical analyses were done with the use of SPSS 20.0 statistics package (SPSS, Inc., Chicago, IL, USA). Normality was checked using the Shapiro-Wilk test. Descriptive statistical methods have been used. Parameters have been presented as average ± standard deviation and number.

Results

Out of 31 patients with the exact diagnosis of nephrotic syndrome; 21 of them were men, 10 were women. The mean age of the patients was 72.6±5.2 (65-87) years. 58% of the patients were hypertensive, 26% were diabetic, 23% suffered from coronary artery disease, 58% had hyperlipidemia, and 13% had connective tissue disease. Demographical, clinical and biochemical results are given in Table 1. Nine patients out of 31 were not implemented renal biopsies due to having general problems, respiratory problems, atrophic kidney disorder and hemorrhagic diathesis. The pathological results of 22 patients (8 female, 14 male) who underwent renal biopsies are given in Table 2. Renal biopsy results of four patients out of eight patients who had diabetes, indicated diabetic nephropathy. Three patients out of four patients who had amyloidosis had

type amyloid A (AA) amyloidosis, and one had systemic non-AA amyloidosis.

Discussion

A higher frequency of renal diseases have been reported in older individuals in parallel to the growing numbers of this age group. Many studies have shown that nephrotic syndrome is the most common form of glomerular diseases among older patients (2,5-10). While the ratio of older patients who had renal biopsy is 8.2% between the years of 1995-1999; this ratio has increased to 15.1% between the years of 2000-2004. In younger adults, this ratio has been identified as 23.3% and 26.8% for the years 1999 and 2004, respectively. As can be understood, indications of renal biopsy in older adults increase while in younger adults it has always been high (11). Usually, since physicians believe

Table 1. Demographic, clinical and biochemical findings of older patients with nephrotic syndrome

Variables	Values (n=31)
Age (years)*	72.6±5.2
Gender, n (%)	
Male	21 (67.7)
Female	10 (32.3)
Comorbidities, n (%)	
Hypertension	18 (58)
Diabetes mellitus	8 (26)
Coronary artery disease	7 (23)
Hyperlipidemia	18 (58)
Connective tissue disease	4 (13)
Smoking, n (%)	6 (19.3)
Serum creatinine*, mg/dL	2.4±1.8
Creatinine clearance*, mL/minute/1.73 m ²	42.5±29.0
Protein in 24-hour urine*, gr/24 s	5.7±2.4
Serum albumin*, g/dL	2.8±0.9
Hemoglobin*, g/dL	11.4±2.12
Total cholesterol*, mg/dL	260.7±107.1

* Values are given as mean ± standard deviation

Table 2. Renal biopsy findings of older patients with nephrotic syndrome

Biopsy findings	Number of cases, n (%)
Primary glomerular disease	
Membranous glomerulonephritis	9 (40.8)
Membranoproliferative glomerulonephritis	1 (4.6)
Focal segmental glomerulosclerosis	3 (13.6)
Secondary glomerular disease	
Amyloidosis	4 (18.2)
Diabetic nephropathy	4 (18.2)
Systemic lupus erythematosus	1 (4.6)
Total	22 (100)

that it is highly risky for older adults to have renal biopsies, it is difficult to identify the accurate prevalence of glomerular disease.

In the review by Burstein et al. (12), the nephrotic syndrome occurring in older patients was usually thought to be a symptom of another disease such as neoplasm. In our study, only three patients had hematologic malignancies but, no solid tumors were found in patients.

In the study by Galesic et al. (10), thirty-three older patients with nephrotic syndrome were examined. Membranous nephropathy was the most common histologic type, which was determined in 14 patients (42.4%). Rapidly progressive glomerulonephritis was present in five patients (15.2%). Other types of glomerular diseases were focal segmental glomerulosclerosis (18.2%), diabetic nephropathy (3.0%), mesangioproliferative glomerulonephritis (15.2%), amyloidosis (3.0%) and systemic lupus erythematosus (3.0%). In our study, membranous glomerulonephritis, diabetic nephropathy and amyloidosis were present in 40.8%, 18.2% and 18.2% of patients, respectively. In both studies, the most common histological type was determined as membranous glomerulonephritis, but the ratios of other glomerular disease types were different.

In the prospective study of Fawcett et al. (13), 25 elderly patients and 75 young patients with nephrotic syndrome were included. Unlike this study, our study was a retrospective study and since young patients were not included, no comparison was made with young patients. In the aforementioned study, the minimal change disease has been found to be an important cause of nephrotic syndrome in the older patients as well as in younger patients, but minimal change disease hasn't been diagnosed in our study, so that renal biopsy is even more necessary in older nephrotic patients.

According to Fawcett et al. (13), 60% of patients aged 60 years and over were diagnosed with nephrotic syndrome due to primary glomerular diseases, 12% due to amyloidosis and 28% due to other diseases (excluding diabetes). In our study, ratios of primary glomerular diseases and amyloidosis were found to be similar to the aforementioned study. Primary glomerular disease ratio was coherent with this study. However, no comparison could have been done for diabetic nephropathy ratio, as diabetic nephropathy was excluded. In our study, amyloidosis ratio (18.2%) was found to be higher, compared to this study (12%).

In the review by Cameron (2), membranous nephropathy was particularly common as a cause of the nephrotic syndrome in older patients (35%), as well as minimal change disease (16%) and primary amyloidosis (12%). Therefore renal biopsy is even more necessary in older patients with nephrotic syndrome. In our study, membranous glomerulonephritis (40.8%) has been

found to be the most common cause, and amyloidosis ratio (18.2%) was found to be higher compared to this study. However, no minimal change disease was observed.

In a retrospective study, 76 nephrotic patients aged 50-84 years were analyzed. Primary glomerulonephritis was found to be more prevalent than secondary causes in older patients with nephrotic syndrome (5:2) (14). In our study, this rate was 13:9. In the aforementioned study, the most frequently observed primary glomerulonephritis forms were membranous glomerulonephritis and focal segmental glomerulosclerosis. The common type of secondary glomerulonephritis was lupus nephritis following by diabetic nephropathy and amyloidosis. Those findings support the results of the present study.

Ozono et al. (4) have demonstrated that membranous nephropathy was the most common type of primary nephrotic syndrome where amyloidosis and malignancy were common causes of secondary nephrotic syndrome in patients aged over 60 years. Likewise, in the present study, membranous glomerulonephritis was the most common type of primary Nephrotic syndrome, and amyloidosis was the most common secondary cause as well; however, no malignancy was observed.

In another study, like our results; Zech et al. (15) reported membranous glomerulonephritis (40%) as the most frequently observed primary cause, and amyloidosis (13%) as the most common secondary cause in patients with nephrotic syndrome aged 60 years and over.

In the present study, diabetic nephropathy was found in 18.2% of the cases (Table 2). This result is considerably different from the reports by Zech et al. (15) and by Kingswood et al. (16), in which its incidence was under 2%. High frequency of diabetic nephropathy in our internal medicine clinic might be due to the diabetology section presence besides nephrology. A study in Japan also indicated high frequency of diabetic nephropathy in older adults with nephrotic syndrome. Thus, our result does not seem to be extreme. Moreover, we do not always perform renal biopsy in patients overtly supposed to have diabetic nephropathy. Such diabetic patients without biopsies were not included in this study. For this reason, we consider that exact percentage of diabetic nephropathy was higher than the result of our study.

In several studies, primary glomerular diseases were more common than secondary glomerular diseases in elderly patients with nephrotic syndrome. It was established that membranous glomerulonephritis was the most common primary disease while diabetic nephropathy and amyloidosis were the most common secondary glomerular diseases (5,11,17). These results are also parallel to our study.

In a study by Oğuz et al. (18), the renal biopsy results from 12 older patients with nephrotic syndrome revealed that the most

common type was amyloidosis, followed by minimal change disease, membranous glomerulonephritis and focal segmental glomerulosclerosis. The number of cases was lower than that determined in our study and the results were not compatible with our data.

Study Limitations

The limitation of our study was that we have screened the patients in the electronic patient data system using a diagnostic code, we could not reach the targeted patient number as patients' files were missing the diagnostic codes or the codes were entered as wrong. This may be the reason why some of our results were not coherent with the literature.

Conclusion

In our study, the most frequent cause of nephrotic syndrome observed in older patients was membranous glomerulonephritis which is coherent with the literature. The second most frequent causes that we observed in our patients were amyloidosis and diabetic nephropathy. Nine patients were not applied renal biopsies since high risks such as high risk general problems, atrophic kidney disorder and hemorrhagic diathesis. Therefore, pathologic diagnoses were not available. Percutaneous renal biopsy provides beneficial data on older adults since clinical situation and primary diagnosis can show differences. In this study, we emphasized the importance of histopathological diagnosis by renal biopsy in older patients. In addition, the frequency of glomerulonephritis causing nephrotic syndrome in older patients followed by a single center was determined.

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Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethical Review Board (number: 14-9.2/12).

Informed Consent: Since the study is retrospective, there is no patient consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.K., S.S., F.S., F.A., Design: A.K., S.S., F.S., F.A., Data Collection or Processing: A.K., Analysis or Interpretation: A.K., S.S., F.S., F.A., Literature Search: A.K., S.S., F.S., Writing: A.K., S.S., F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Cremation Challenge Under Coronavirus Disease-2019

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Dear Editor,

World Health Organization declared Coronavirus disease-2019 (COVID-19) a pandemic on 11/3/2020. The number of COVID-19 infected cases exceeded 12 million worldwide, and 570 thousand of them were died by 4 months after the declaration. Previously a taboo subject, death is now a topic of ordinary conversation under COVID-19.

Geriatricians are now used to the fact that older persons with comorbidities were the most likely to die from COVID-19 (1), and deceased relatives are now finding no place for burial under the sudden surge in demand. Cremation becomes the trend (2), yet its safety issue on medical implants warrant attention by caring practitioners. Despite seldom implanting medical devices to patients, geriatricians are familiar with potential contraindications to cremation, such as pacemaker and radioactive implants, as we are used to accompanying patients' last journey.

Pacemaker, including implantable cardioverter-defibrillator, is an electronic device that saved millions of lives since its inventory more than half a century ago (3). Indications of a pacemaker are not uncommon among geriatric patients, including symptomatic bradycardia, long QT syndrome, advanced 2nd or 3rd-degree heart block, and certain types of cardiomyopathy (4). For the internal type of pacemaker installed through subcutaneous implantation, it could be easily inspected or palpated upon physical examination over the chest wall, or on basic chest radiography (Figure 1). Being an electronic device with a battery *in situ*, the pacemaker runs the risk of explosion upon burning in the cremator, in which the risk is even higher with advancing battery design (5).

Radioactive sources are sometimes implanted into the body as a local cancer treatment in modern medicine. Examples are gold-198 (Au^{198}), iodine-125 (I^{125}), iodine-131 (I^{131}),

radium-223 (Ra^{223}), and yttrium-90 (Y^{90}), which are used as radiopharmaceuticals for head and neck (Figure 2), lung, prostate, cervix cancer, hepatocellular carcinoma, or choroidal melanoma etc. Most of the above mentioned are of short half-lives of less than 15 days, except I^{125} which has a half-life of 60 days. Prostate implant with radioactive I^{125} was gaining popularity in the last few decades, and its radiation risks towards staff for patients or persons living close to patients are well addressed. Although cremation of radiation seeds poses minimal harm to the public after dilution by air, it carries some risks to those handling the cremated remains (6). In general, cremation

Chest radiography in anteroposterior view

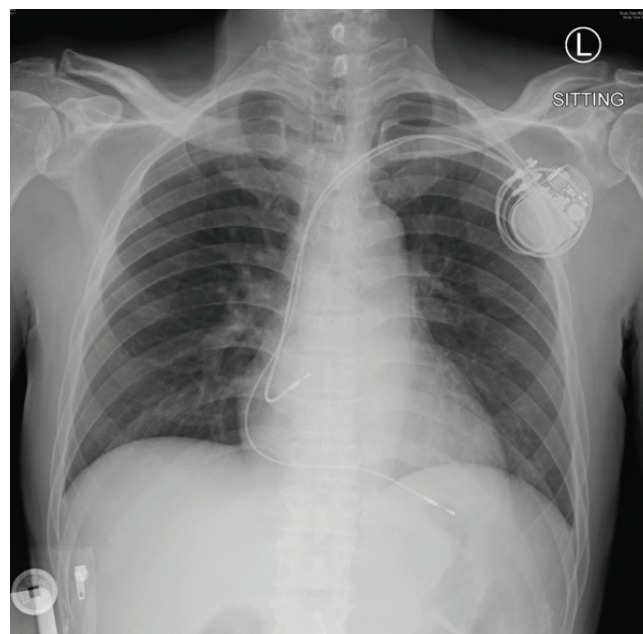


Figure 1. Pacemaker battery and main bulk was seen below the left clavicle, with electrode leads placed at AV node and ventricle

AV: Atrioventricular

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Computed tomography scan of the orbit in transverse cut

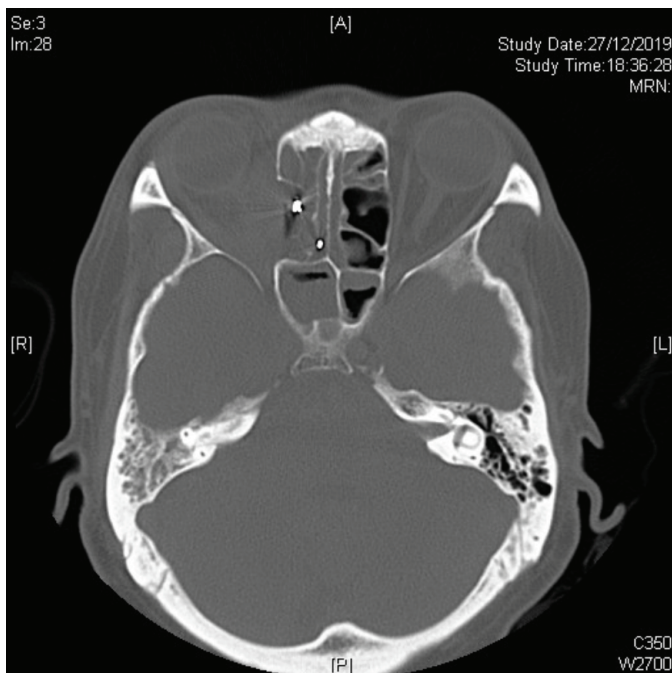


Figure 2. Two radiopaque radioactive seeds (with streak artifacts) were seen at the level of ethmoid sinus, they were implanted for metastatic sinus sarcomatoid carcinoma after repeated surgery and external beam radiotherapy

is contraindicated to bodies with the radioactive implants, and burial is suggested or even required by local legislations. Different countries have different restrictions on burial timing, and usually 10-15 half-lives are required for patients with long-lasting radioactive source implantation, e.g. ~24 months for the ^{125}I mentioned above.

Last but not least, gold weight implant is sometimes explanted from the deceased before cremation (Figure 3), not of safety but for financial concern. Patients who suffered from paralytic lagophthalmos, mainly from facial nerve palsy, would benefit from gold weight implantation over the upper eyelid to correct the lagophthalmos, thus preventing exposure keratopathy (Figure 4). Standard eyelid gold weight ranges from 1-2.5 gram, which values differently towards deceased relatives.

In conclusion, cremation demand is increasing under COVID-19. Implanted electronic devices like pacemaker, and radioactive implants warrant removal from the dead body before proceeding to safe cremation.

Keywords: Cremation, coronavirus, pacemaker, radiopharmaceuticals, computed tomography

Ethics

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

Clinical photo of an explanted gold weight from eyelid



Figure 3. The gold weight was in curved shape conforming the shape of the normal eyelid. There are few 1 mm sized holes on top for suture needle to pass intra-operatively

Computed tomography scan of the orbit in transverse cut

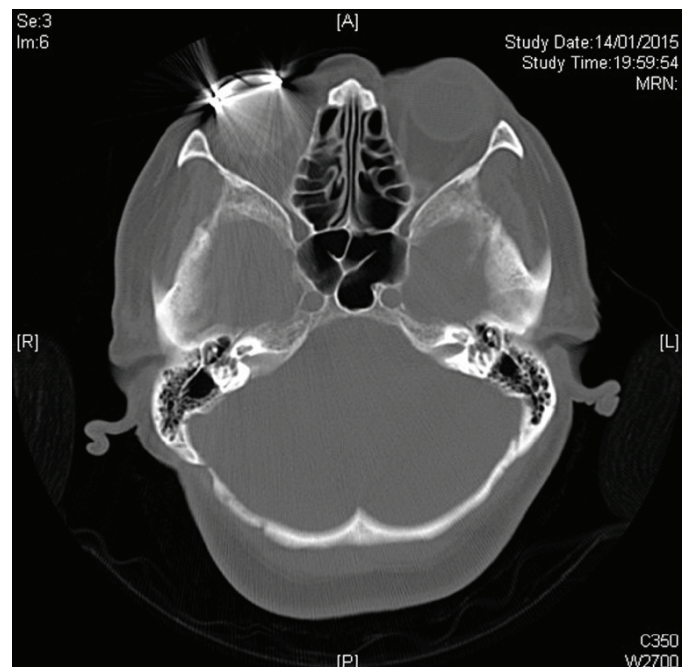


Figure 4. Right upper lid gold weight was *in situ* causing significant streak artifact

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