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Detection of Entamoeba histolytica using enzyme immunoassay (EIA) in microscopically positive faecal samples.

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Abstract

Introduction: Although several types of amoebae can be parasitic in the human digestive tract, only Entamoeba histolytica causes amoebiasis. Other intestinal amoebae (Entamoeba coli, Endolimax nana, Jodamoeba butschlii) are apatogenic and should not be related to pathological processes in the gut. Of particular importance to humans are Entamoeba histolytica as a pathogen and Entamoeba coli as a non-pathogenic species. Amebiasis is an acute or chronic disease caused by E. histolytica in the form of symptomatic or asymptomatic colon infestations, with possible localization to other organs. The route of infection is fecal-oral, whereby a person becomes infected by entering cysts through contaminated food and water, but transmission is also possible through direct contact. In its vegetative form, Entamoeba histolytica can be found in the intestine from the ileocecal region to the rectum, where it mostly inhabits the ileocecal region, colon flexure and its sigmoid part. Histolytic amoeba cysts enter the human organism mainly by oral route. After ingestion, amoeba cysts pass through the stomach and, in the small intestine, by the process of excision releases the trophozoites, which reach the colon. In the lumen of the colon, amoebae are mostly often apathogenic. If under certain conditions, such as bacterial and viral infections, a protein-poor diet or if the large amount of cysts is ingested, the natural protection of the mucosa becomes impaired, and then the histolytic properties of the amoeba will be expressed.

Material and Methods: The study was realized in Department of Clinical Microbiology Univerity Sarajevo. The study included all subjects suspected of amoebiasis of different ages, of whom faeces samples were tested by direct microscopy , as well as antigen detection on Entamoeba histolytica. The study included 100 subjects with microscopically positive faeces on Entamoeba histolytica.

Results: Out of the total number of subjects in the EIA group, negative (n = 50), 27 (54.0%) were male and 23 (46.0%) were female. Of the total number of subjects in the EIA group, positive (n = 50), 26 (52.0%) were male and 24 (48.0%) were female.

Conclusions: There was no statistically significant difference in the frequency of male and female respondents between the observed groups [$\chi 2$ (1) = 0.841, p = 0.841].

Key words: Amebiasis, Entamoeba histolytica, microscopy, enzyme immunoassay (EIA).

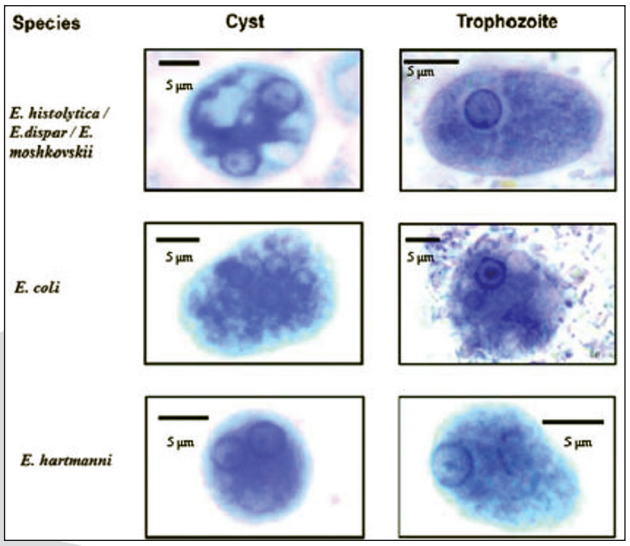
1. Introduction

Although several types of amoebae can parasitize in the human digestive tract, only Entamoeba histolytica causes amoebiasis. Other intestinal amoebae (Entamoeba coli, Endolimax nana, Jodamoeba butschlii) are apatogenic and should not be related to pathological processes in the gut (1). Of particular importance to humans is Entamoeba histolytica as a pathogen and Entamoeba coli as a non-pathogenic species (2). Amebiasis is an acute or chronic disease caused by E. histolytica in the form of symptomatic or asymptomatic colon infestations, with possible localization to other organs. The route of infection is fecal-oral, whereby a person becomes infected by entering cysts through contaminated food and water, but transmission is also possible through direct contact. In its vegetative form, Entamoeba histolytica can be found in the intestine from the ileocecal region to the rectum, where it densely inhabits the ileocecal region, colon flexure and its sigmoid

part (3). In the cytoplasm of the trophozoite, whose size is 10-60 micrometers, the outer transparent ectoplasm responsible for respiration, nutrition, movement and protection is clearly distinguished from the internal granular endoplasm responsible for digestion, as evidenced by the remains of undigested glucose. In the endoplasm, in addition to the phagocytosed material, there is a vesicular nucleus, erythrocytes, granules (2). The amoebae move characteristically fast, ejecting annular pseudopods (false legs) in one direction. In the native preparation, the sail is not visible, the colored iron-hematoxylin according to Heidenheim shows a bubbly structure with a fine centrally located cariosis and a cornice of tiny chromatin beads properly distributed around the periphery (3). When the trophozoites reach the distal portions of the colon with a peristaltic wave, they are converted to cysts. In the case of accelerated peristalsis (as in diarrhea), cysts are not created, but trophozoites emerge into the external environment, where they perish rapidly. Cysts are only present in a mushy or formed stool (2). Man is infected by the ingestion of histolytic amoeba cysts . After ingestion, amoeba cysts pass the stomach and in the small intestine, by the process of excision it releases the trophozoites, which reach the colon (4). In the lumen of the colon, amoebae are most often apatogenic. If under certain conditions (bacterial and viral infections, protein-poor diet, amount of ingested cysts), the mucosal natural protection of the mucosa is weakened, the histolytic properties of amoeba (4,5) will be expressed.

The epidemiology of parasitosis of E. histolytica, E. dispar and E. moshkovskii remains uncertain, since most of the existing data have been obtained by methods incapable of distinguishing three morphologically identical species. Entamoeba dispar seems to be about 10 times more common than E. histolytica, with most of the 500 million people infected with E. histolytica / E. dispar carrying E. dispar. Little is known about the epidemiology and incidence of E. moshkovskii infections, as only a few studies have used molecular methods to identify this parasite.

The existence of these morphologically indistinguishable Entamoebe species has led the World Health Organization (WHO) to recommend the development and application of improved methods for the specific diagnosis of E. histolytica infection.



2. Material and methods

The study was realized in Department of Clinical Microbiology University of Sarajevo. The study included all subjects suspected of amoebiasis of age group, of whom feces samples were tested by direct microscopy, as well as antigen detection on Entamoeba histolytica. The study included 100 subjects with microscopically positive faeces on Entamoeba histolytica.

All patients were taken with a solid (formed) stool that was transported in separate vials

Diagnosis of microscopic preparation from a solid (formed) stool was done by the following by the method: direct examination of native preparations, preparations stained by Lugol and MIFC methods and we examined cysts and trophozoites of protozoa by microscopy under medium magnification (10x40).

Antigen detection was performed using an EIA enzyme immunoassay for the recognition of Entamoeba histolytica antigens from stool (Serazym commercial kit)

To perform this test, it is necessary on admission to place the patient's stool to a temperature of 2-8 ° C and to do it within 72 hours, otherwise it should be placed at a temperature of -20 ° C.

3. Results

Out of the total number of subjects in the EIA negative group (n = 50), 27 (54.0%) were male and 23 (46.0%) were female. Of the total number of subjects in the EIA positive group (n = 50), 26

Table 1. Gender structure of subjects by groups and gender

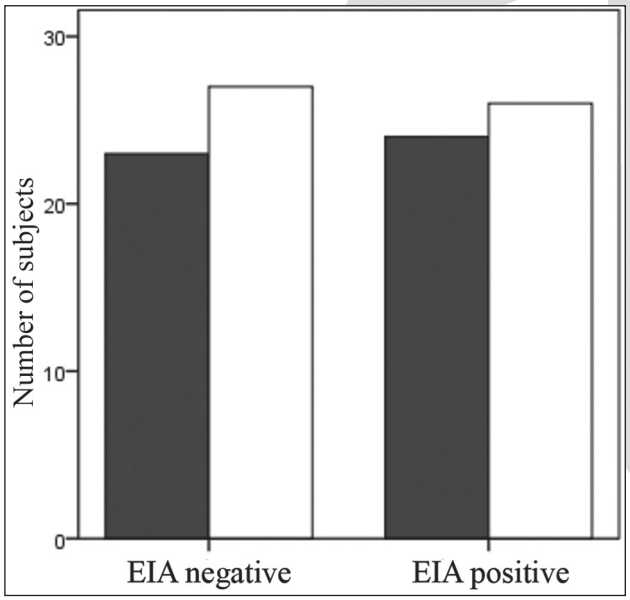
			gender		total
			female	male	
Group	EIA negative	N	23	27	50
		%	46.0%	54.0%	100.0%
	EIA positive	N	24	26	50
		%	48.0%	52.0%	100.0%
Total		N	47	53	100
		%	47.0%	53.0%	100.0%

Table 2. Shows the absolute and relative frequencies of the respondents by gender and group

Group		N	M	Percentiles			Min.	Max.
				25.	50.	75.		
EIA negativan	female	23	39.5	23.0	41.0	55.0	4	83
	male	27	48.0	34.0	49.0	67.0	15	78
	total	50	44.1	23.0	45.5	63.3	4	83
EIA pozitivan	female	24	55.2	35.5	62.5	80.0	10	91
	male	26	51.1	38.0	53.0	69.0	3	90
	total	50	54.2	36.5	56.5	77.8	3	91

N-number of subjects; M-average; Q1 -25. percentile; Q2 (Me) - 50 percentile; Q3 -75. percentile; Min.-minimum value; Max. - the largest value

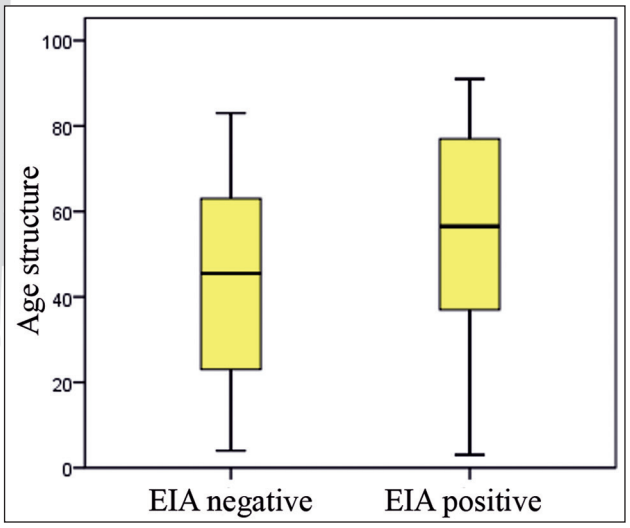
(52.0%) were male and 24 (48.0%) were female. There was no statistically significant difference in the frequency of male and female subjects between the observed groups [$\chi 2$ (1) = 0.841, p = 0.841].



Graph 1. Respondents' gender structure by groups

The median age of subjects in the EIA negative group was (n = 50), 45.5 years (IQR = 23.0 to 63.3), while in the EIA positive group (n = 50) was 56.5 years (IQR = 36.5 to 77.8), (U = 932,000 , z = - 2.193, p = 0.028).

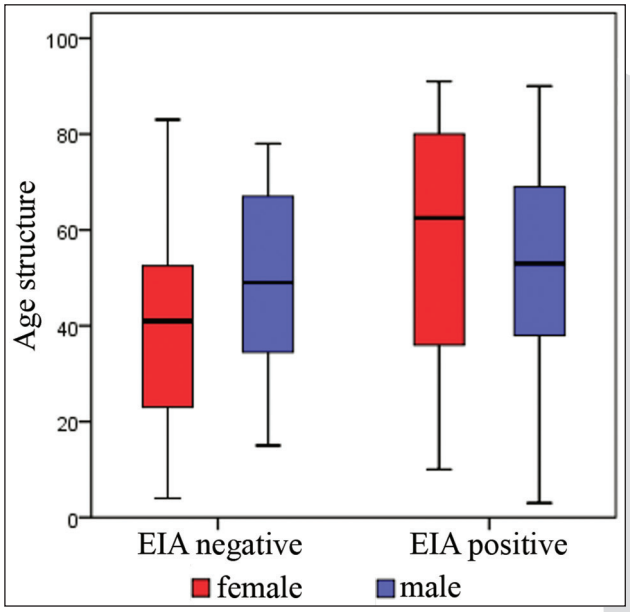
The median age of the female subjects in the EIA negative group was 41.0 years (IQR = 23.0 to 55.0), while in the EIA positive group was 62.5 years (IQR = 35.5 to 80.0), (U = 159.000, z = - 2.491, p = 0.013)



Data are presented as median and interquartile ranges; NS - not significant;

Graph 2. Age structure of respondents by groups and sex of respondents

The median age of male subjects in the EIA negative group 49.0 years (IQR = 34.0 to 67.0), while in the EIA positive group was 53.0 years (IQR = 38.0 to 69.0), (U = 314,000, z = - 0.659, p = 0.510).



Data are presented as median and interquartile ranges; NS - not significant;

Graph 3. Age structure of respondents by groups and sex of respondents

The EIA negative subjects were statistically significantly younger compared to the EIA positive subjects, that is, the EIA negative female respondents were statistically significantly younger compared to the EIA positive subjects, whereas there was no statistically significant difference in the male EIA subjects, age between the two observed groups.

4. Discussion

Amebiasis has been associated with humans since ancient times and it is easy to understand that, until the discovery of the causative agent of the disease, it could not be differentiated from other bowel diseases accompanied by diarrhea (6). Entamoeb histolytic infection has spread worldwide, especially in tropical and subtropical regions and in countries with low hygiene standards. However, the infection is also spread in other regions (7). In the epidemiology of amoebiasis, man plays a major role. Amebiasis is only transmitted via cysts, beacuse the vegetative forms of Entamoebae in the external environment immediately decay. Asymptomatic parasites are a major source of infection. Therefore, as a source of infection, only people who excrete cysts via stool or who are chronic carriers can be considered. Patients with an acute form of the disease are not infectious because they secrete only the vegetative forms of Entamoebae histolyticae (8,9).

Ameb has infected about 10% of the world population, with a prevalence of about 50% in Central and South America, Africa and Asia. About 40000-100000 people die each year from amoebic abscess and dysentery. The World Health Organization estimates that around 50 million people are infected in the world annually, of which 70,000 die. Mexico, Central and South America are endemic areas primarily due to limited hygiene and sanitary conditions and warm-humid climates, but infections and deaths are reported worldwide (10,11).

Amoebiasis is equally affectes women and men, the disease rarely occurs in children under the age of five, and amoebic liver abscess is more common in men. Risk groups include male homosexuals, travelers from endemic areas, alcoholics, pregnant women, the elderly, and HIV-positive persons. The causative agent reaches into the body after the ingestion of contaminated food or water containing cystic amoebae (relatively resistant to chlorine, heat and drying). The causative agent reaches human body through a contact of mucous membrane of a oral cavity with feaces of contaminated objects, and much less frequently by oral-anal contact during sexual intercourse (11,12). Within one year, about 50 million people get affected by amoebiasis, and about 100,000 die, and it is second after malaria due to protozoal infections. The prevalence of the disease is 4%, although this prevalence is much higher in risk groups (1,13,14).

The epidemiology of parasitosis of E. histolytica, E. dispar and E. moshkovskii remains uncertain, since most of the existing data have been obtained by methods incapable of distinguishing three morphologically identical species. The existence of these morphologically indistinguishable Entamoebe species has led the World Health Organization (WHO) to recommend the development and application of improved methods for the

specific diagnosis of E. histolytica infection. Epidemiological studies of amoebiasis should include tools for diagnosing E. histolytica and E. dispar individually, simultaneously and accurately. Techniques developed to identify E. histolytica include the detection of specific antigen in stools and other clinical specimens, developed for the diagnosis of E. histolytica, E. dispar, and E. moshkovskii by clinical laboratories.

5. Conclusions

1. Of the 100 subjects tested with microscopically positive faecal findings on Entamoeba histolytica, 50 subjects were EIA positive and 50 EIA negative.

2. In the EIA group, 52.0% are male, 48.0% are female. In the EIA group, 54.0% were male, 46.0% were female.

3. The EIA negative subjects were statistically significantly younger compared to the EIA positive subjects. Female respondents from the EIA negative group were statistically significantly younger compared to those from the EIA positive group.

4. Enzymatic immunological recognition of Entamoeba histolytica antigens from the stool is a more reliable and alternative diagnostic test than microscopic examination.

5. Identification of E. histolytica remains an important goal of the clinical parasitology laboratory and diagnostics is an important confirmatory diagnostic step in the treatment of patients who may be infected with E. histolytica and require specific therapy.

References

1. *Ravdin JI. Infections by Entamoeba, Parasites and Parasitic Diseases, Clinic for Enteritic Diseases Dallas, 2001;689-693.*
2. *Bašić F, Bešlagić E. Morfološki aspekti sa dijagnostikom, Medicinski fakultet Sarajevo 1998; 113-121.*
3. *Bešlagić Edina i saradnici. Medicinska mikrobiologija, Medicinski fakultet Univerziteta u Sarajevu, 2010; 362-366.*
4. *Mihaljević F, Fališevac J, Bezjak B, Mravunac J. Specijalna klinička infektologija, Medicinska naklada Zagreb, 1994; 385-390.*
5. *Larson DE, Farnell MB. Amoebiasis, Upper Gastrointestinal Haemorrhage, Mayo Clinic Proc, 2000; 371-378.*
6. *Velisavljev M, Korać D, Juretić M. Bolesti uzrokovane protozoama, Klinička pedijatrija, Medicinska knjiga Beograd; 1987; 235-239.*
7. *Sakai Y. Amebic Colitis, Etiology and Treatment of Inflammatory Bowl Diseases, Nippon Naika Gakkai Zassi, 1993; 694-703.*
8. *Patel AS, Derridder PH. Amebic Colitis, Amebic Colitis Masquerading as Acute Inflammatory Bowel Disease, Ugsekr Laeger 4 th Edition, 1998; 356-368.*
9. *Lysy J, Zimmerman J, Sheman Y, Feigin R, Ligumsky M. Crohn s Colitis Complicated by Superimposed Invasive Amoebic Colitis, Enteric Diseases, University of Sttutgart 1978; 291-298.*
10. *Luis S, Diamond D. A new Medium for the Axenic Culivation of Entamoeba histolytica and other Entamoeba, Diseases Caused by Protozoa, Clinic for Gastroenterology Harlow University 2002; 96-111.*
11. *Dugdalle DC. Amebiasis, Parasitic Diseases, University of Washington School of Medicine, Department of Infectiology, 2007; 76-81.*
12. *LS Diamond Clark CG, Amebiasis, The Journal of microbiology, Clinic for Gastroenterology Harlow university 2002; 96-111.*
13. *Merk S. Amebiasis, Intestinal Protozoa, University of Texas, Online Medical Library 2006; 35-44.*
14. *Hamzić S, Bešlagić E, Pejić-Rodinis I, Kamberović-Avdić F. Microscoping method in microbiological diagnostic of amoebiasis and cyst-bearing Entamoeba histolytica, HealthMED, 2011; Volume 5/Number3: 604-608.*

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The importance of physical activity in reducing falls in Brazilian older adults

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Abstract

The number of falls increases over the years, especially in older adults more than 80 years of age. Considering this, the focus of this study was to observe, in the scientific literature, studies related to the importance of physical activity in the reduction in falls of the older population. The research was carried out from the Scielo and Bireme databases. Analysis of the studies involved reading the titles, abstracts, and full texts. Studies written in Portuguese, carried out with older adults (> 60 years), and published between 2011 and 2015 were included. Review articles and publications presented at conferences and symposia were excluded. The majority of the articles selected (63%) presented positive and significant results regarding the importance of the habitual practice of physical activity in the prevention of falls. Institutionalized older adults, those who were frail, and who presented recurrent falls demonstrated an increased risk of falls. The habitual practice of physical activity may provide older adults with a lower risk of falls. In addition to the prevention of falls, physical activity acts on some of the theories of aging, minimizing the risks of chronic diseases, and increasing self-esteem and self-concept.

Key words: Aged, Exercise, Risk Factors

1. Introduction

In Brazil, demographic data reveal a gradual transformation of the age pyramid, bringing it closer to that observed in developed countries, with narrowing of the base, showing a decrease in birth rates, and progressive enlargement of the body and apex, revealing a decrease in mortality rates and, consequently, an increase in life expectancy (CARVALHO and WONG, 2008). These modifications result in population aging. In this group (≥ 60 years old), the population that increases most significantly is that of long-lived adults (≥ 80 years old) (CARVALHO and WONG, 2008). In Brazil there is a prevalence of older adults of approximately 14% and it is estimated that by 2050, Brazil will have the 6th largest elderly population in the world (IBGE, 2014).

Worldwide, from 1951 to 2001, the number of older people grew by an average of eight million a year, with 66% residing in developing countries such as Brazil. It is estimated that by 2050 this percentage will reach 80% (UNITED NATIONS, 2001).

The increase in the elderly population has been accompanied by social, cultural, and epidemiological implications (VERAS, 2007; NOGUEIRA, et al., 2008), such as an increase in the prevalence of diseases and chronic conditions (VERAS, 2007) that affect older adults themselves, their family, the community, and the health system, as these conditions may be accompanied by greater vulnerability and dependence, contributing to the reduction in well-being and quality of life of the affected person and those around them (ALVES, 2007).

Although not a rule, the aging process leads to the loss of several factors such as decreased flexibility, slow and progressive decrease in muscle mass, gait, muscle strength, especially fast twitch fibers, and bone mass and ligaments, making mobility and agility increasingly difficult and having consequences in the life of older adults, such as an increased risk of falls (BECK, et al., 2011).

In Brazil, approximately 32% of older adults between 65 and 75 years fall at least once a year, 35% from 75 to 84 years, and 51% over 85 years. Worldwide these figures are approximately 40%. Although only 2.5% of falls result in hospitalization, half the fallers do not survive the following year (CRUZ et al., 2012).

Most often, as a consequence of these falls, fractures occur that, due to the time of immobilization, potentiate the decline in functional capacity, limiting the performance of physical activity, leading to fear of suffering further falls, and social isolation, loss of autonomy, and independence for execution of activities of daily living, social isolation, depression, etc. The highest frequencies of falls are in females, due to their higher prevalence of weaknesses, illnesses, medication use, and a lower amount of lean muscle mass and strength (NETO and GUIMARÃES, 2012).

Some factors are related to a decreased recurrence of falls in older adults, among them balance and strengthening of the muscles, both of which can be improved through physical activity. Thus, performing physical activity, including resistance exercises, seems to be able to improve mobility, static and dynamic balance, and muscle strength, reducing the risk of falls in elderly Brazilians. Studies indicate that adolescents and young adults who practice habitual physical activity have a lower risk of falling when older than non-practitioners. In addition, the practice of physical activity in adolescents and adults decreases the occurrence of osteoarticular problems, metabolic and cardiovascular diseases, and problems related to decreased functional capacity when reaching old age (MESSIAS and NEVES, 2009).

Thus, the aim of the present study was to observe, through a literature review, the importance of physical activity in reducing falls in elderly Brazilians.

2. Methodology

This study is a literature review to deepen the knowledge about the importance of physical ac-

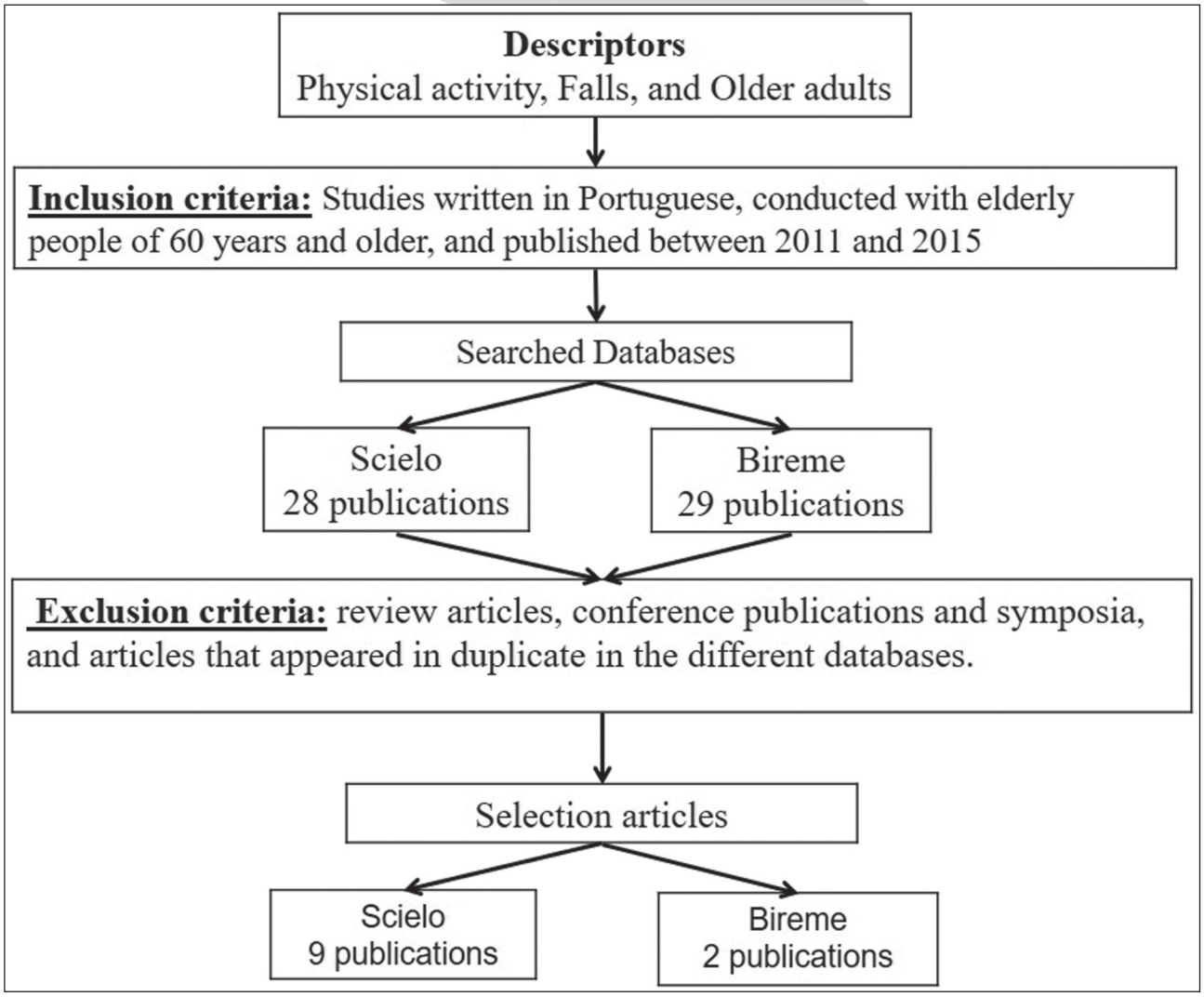

Figure 1. Flowchart of the selection of the articles included in this review.

tivity to decrease falls in Brazilian older adults. The bibliographic survey took place in the Bireme and Scielo databases from November 2015 to April 2016. The descriptors were used together and in the following order: physical activity, falls, and older adults.

Table 1. Importance of physical activity in reducing falls in elderly Brazilians

Author/Year	Methods	Importance of Physical Activity
Lima et al., 2011	**n=** 42 older adults (60 – 75 years) **Falls:** Self-Report **Balance:** Berg balance scale **Physical Activity:** IPAQ (long version)	In the three years of follow-up, the older adults reduced the distance covered in the 6MWT, but the balance of active individuals did not change during this period.
Miguel et al., 2012	**n=** 58 older adults (74 ± 5.50 years) **Falls:** Self-report and *Falls Efficacy Scale*– FES-I Brazil **Physical Activity:** Evaluated by the *Minnesota Leisure Time Activities Questionnaire*	The sedentary frail older adults fell more than the active non-frail older adults.
Albino et al., 2012	**n=** 22 older adults, 60 to 75 years **n=** 7 strength and **n=** 15 flexibility. **Falls:** Berg balance scale	With training there was improvement in muscle strength and flexibility and an association with body balance in the older adults, which may reduce the risk of falls.
Antero-Jacquemin et al., 2012	Fallers: **n=** 25, non-fallers: **n=** 56 (65 years or over) **Physical Activity:** Human physical activity profile questionnaire **Muscle Strength:** Isokinetic Dynamometer.	The level of physical activity did not differ between groups (Fallers vs. non-fallers). The fallers group presented lower knee joint strength.
Couto and Perracini, 2012	**n=** 150 older adults, (71.9 ±5.6) **Falls:** Self-report **Physical Activity:** Determined through questions about frequency and duration of physical activity.	Lack of physical activity may explain approximately 54% of falls and recurrent falls in elderly participants of social groups.
Cavalcante et al., 2012	**n=** 50 older adults (64% m) **Falls:** Self-report **Physical Activity:** Self-report (yes or no)	60% of the older adults practiced regular physical activity and among the sedentary 90% self reported falls.
Freitas et al., 2013	**n=** 77 women (60 to 75 years) **Physical Activity:** IPAQ long **Balance:** Unipodal Support Test - static balance, and TUG - dynamic balance.	The level of physical activity of the elderly improved body balance, reducing falls.
Fernandes et al., 2012	**n=** 8 older adults (3M and 5W), ≥ 60 years, **Protocol:** 6 month intervention: **Balance:** TUG.	The exercise program directed at strength training, balance, and proprioception improved the physical performance of the elderly, reducing the risk of falls.
Lobo, 2012	**n=** 49 institutionalized older adults and 63 non-institutionalized older adults. **Postural stability:** *Functional Reach Test* **Physical Activity:** Baecke questionnaire	Institutionalized older adults were more sedentary and had a higher chance of recurrent falls than non-institutionalized older adults.
Antes et al., 2013	**n=** 266 older adults (≥ 60 years) **Falls:** Fear of falling (yes or no) **Physical Activity:** IPAQ long	Leisure physical activity was not associated with fear of falling in the elderly.
Valim-Rogatto et al., 2011	**n=** 291 older adults **Falls:** Self-report (falls in the previous 12 months) **Physical Activity:** IPAQ	The occurrence of falls demonstrated no association with the level of physical activity in the elderly.

Legend: *IPAQ = International Physical Activity Questionnaire, 6MWT = 6-Minute Walk Test, TUG = Timed up and go.*

Studies written in Portuguese, conducted with elderly people of 60 years and older, and published between 2011 and 2015 were included. The articles were selected by abstract and then read in full. In the present work, review articles, conference publications and symposia, and articles that appeared in duplicate in the different databases were excluded.

The initial search in the Scielo database resulted in 28 publications, while in the platform of the virtual health library (Bireme), 29 publications were found. After applying the exclusion criteria, 11 articles remained, 9 published in the Scielo database and 2 in Bireme. Figure 1 presents the flowchart of the selection of articles included in this review. Subsequently, the selected articles were arranged in a spreadsheet in Microsoft Excel® 2010 and categorized according to authors, year of publication, sample, methods used to evaluate physical activity and falls, and main results.

3. Results

The importance of physical activity for the prevention or association of falls is presented in Table 1.

Among the 11 articles observed, seven showed significant results regarding the importance of habitual physical activity in preventing falls, three articles reported no relationship between habitual physical activity and falls, and in one article (LIMA et al., 2011), after three years of follow-up, the active elderly presented no change in static balance, thus reducing the risk of falls.

4. Discussion

Falls can be defined by an unintentional displacement of the body to a level below the initial position, being unable to be timely corrected, and determined by multifactorial circumstances that include instability (RIBEIRO, 2008).

The present study observed, through a literature review, that the majority of the articles analyzed presented positive and significant results regarding the importance of habitual physical activity in preventing falls in the elderly. The main associated factors were: obesity, strength, balance, mobility, and institutionalization.

With the aging process, the chance of older people with lower mobility increases due to postural instability and gait alteration, consequently increasing the risk of falls. Alterations in mobility may occur due to motor dysfunctions, sense of perception, balance, or cognitive impairment. The locomotor apparatus undergoes alterations, causing a reduction in range of motion, modifying walking with shorter and slower steps with a tendency to drag the feet. The range of motion of the arms also decreases, tending to remain closer to the body. The base of support expands and the center of body gravity tends to advance, seeking greater balance (ANTUNES, 2011).

Aging is known to produce natural alterations throughout the body, and its biological process translates into a decline in the whole body, becoming faster from the age of 70 (DANERES and VOSER, 2013). These changes are different in men and women, in women the aging process occurs earlier, between 45 - 60 years (FERREIRA, 2005).

One of the factors that has been related to falls is obesity, although not simply weight gain, but excess body fat. Aging is closely linked to this increase and changes in its distribution pattern. Over the last few decades, overweight has already risen past 50% in the Brazilian adult population and there is a growing trend, with a higher prevalence of obesity among women, as well as in both sexes, from 50 years of age (DANERES and VOSER, 2013).

Another factor of fundamental importance for the risk of falls in older adults is the decrease in muscle mass and strength (sarcopenia). This occurs, among other factors, due to urinary creatinine excretion that reflects the creatine content in muscles and total muscle mass, decreasing by about 50% between 20 and 50 years of age. After age 30 there is a decrease in muscles and intramuscular fat content. The number of muscle fibers in the elderly is 20% lower than in adults, this being more pronounced in fast twitch fibers (FERREIRA, 2005), thus reflecting in a reduction in basic tasks of daily living which further reduces the levels of physical activity, in turn potentiating the worsening of sarcopenia, becoming a cycle of decreased functionality in this population, which leads to increased falls.

Although no studies were found addressing osteoporosis, physical activity, and falls, it is already documented in the literature that decreasing bone mass, which begins to occur around 30 years of

age, increases the risk of falling in older people. In the case of older adults with osteoporosis, there may be a reversal of the order in which the facts related to the fall occur, since usually the older person falls, and due to the fall the bone fracture occurs. In the case of older adults with severe osteoporosis, there is a chance that the individual will suffer a fracture during gait movement and then fall. These falls, due to osteoporosis, cause limitation, pain, and immobility. Functional disability arising from falls due to osteoporosis can reach 60% (MENDES, 2014).

Balance may be affected by various systems of our body, among which the visual system can be considered the most important in the prevention or risk of falls, as it can supply the lack of other sensory stimuli. Through this the body obtains information on location and distance of objects in a given environment and the positioning of the body in relation to the center of gravity. With aging, decreased visual acuity, increased sensitivity to light changes, and reduced depth perception occur (FIEDLER AND PERES, 2008).

As the muscle mass decreases and the visual system is compromised, the vestibular system is also affected, since it works in conjunction with the previous two, being divided into three parts: a sensory component (detecting head movements and their orientation in space), a central processor (the cerebellum receives and integrates these signals and sends them to the motor component which is responsible for the eye and spinal cord muscles), and a motor control component (SIQUEIRA, 2007).

Falls do not occur in only one way, so it is not always simple to define what leads to falls in older adults. According to Aragão (2004), falls occur due to instability and lack of ability to correct body displacement during movement and in the elderly this instability is greater than in adults or adolescents. Falls are not always the result of sudden or violent contact with the furniture or the floor, in some cases they are preceded by faltering movements, where the older adult tries to hold on to the furniture or the wall before falling to the floor.

The greatest likelihood of falls affecting older adults are in those with a disease, especially if it leads to alterations in mobility, balance, and postural control, as the occurrence of falls is directly linked to decreased mobility and functional disability of older adults (GUIMARÃES et al, 2004).

All articles selected for this review used control variables known to be associated with the risk of falls in the elderly, such as: advanced age, female gender, impaired neuromuscular function, presence of chronic diseases, previous history of falls, polypharmacy, use of antidepressants, inadequate physical environment, and functional disability. The risk of falls is known to increase with the accumulation of these factors (FIGUEIREDO et al, 2007).

5. Conclusion

Unfortunately, the majority of older adults fall at least once in their lifetime. This occurrence generates a number of factors that demotivate the individuals and lead to insecurity for displacement and performing basic activities of daily living, besides being a major cause of morbidity and mortality in old age.

The habitual practice of physical activity can provide older adults with a lower risk of falling and improved quality of life. In contrast, sedentary people may present a greater chance of decreased mobility and loss of autonomy.

Thus, after observing the results of the articles selected for this review, physical activity is important as a non-medication measure to improve the overall health of older adults and prevent falls. In addition to the prevention of falls, physical activity acts on some of the theories of aging, such as: theory of wear, social life, free radicals, and immunity, minimizing the risks of chronic diseases and increasing self-esteem and self-concept, thus favoring a good physical and mental condition, ensuring improvement in the performance of functional activities, as well as promoting independence and quality of life for older adults.

References

1. *Alves LC, Leimann BCQ, Vasconcelos MEL, Carvalho MS, Vasconcelos AGG et al. A influência das doenças crônicas na capacidade funcional dos idosos do município de São Paulo, Brasil. Cadernos de Saúde Pública, 2007; v.23, n.8: 1924-1930.*

2. *Antunes MJM. Envelhecimento e saúde da pessoa idosa. Universidade Federal do Maranhão. UNASUS/UFMA. São Luís, 2011; 19.*

3. *Aragão FA, Navarro FM. Influências do Envelhecimento, do tempo de Evolução da Doenças e do Estado Cognitivo sobre os Episódios de Quedas, em uma População Parkinsoniana. Revista FisioBrasil. São Paulo, 2004; n.67.*

4. *Carvalho JAM, Rodriguez-Wong LL. A transição da estrutura etária da população brasileira na primeira metade do século XXI. Caderno de Saúde Pública, 2008; v.24, n.3: 597-605.*

5. *Cruz DT, Ribeiro LC, Vieira MT, Teixeira MTB, Bastos RR, Leite ICG. Prevalência de quedas e fatores associados em idosos. Rev Saúde Pública, 2012; v.46, n.1: 138-46.*

6. *DANERES PS, VOSER RC. A atividade física na terceira idade. Benefícios aos seus praticantes. EFDeportes – revista digital, 2013; v.18, n.179.*

7. *Ferreira, Telles M. O papel da Atividade Física na Composição Corporal de Idosos. Revista Brasileira de Ciências da Saúde, v.1, n.1, Janeiro/Junho, 2005.*

8. *Fiedler, Mariarosa M, Peres KG. Capacidade funcional e fatores associados em idosos do Sul do Brasil? Um estudo de base populacional. Revista Saúde Publica, Rio de Janeiro, 2008; v.24, n.2: 409-415.*

9. *Figueiredo KMOB, et al. Instrumentos de avaliação do equilíbrio corporal em idosos. Revista Brasileira Cineantropometria& Desempenho humano. Rio Grande do Norte, 2007; v.9, n.4: 408-413.*

10. *Guimarães LHCT, et al. Comparação da propensão de quedas entre idosos que praticam atividade física e idosos sedentários. Revista Neurociências. São Paulo, 2004; v.12, n.12: 68-72.*

11. *Mendes TAM. Manuais de especialização: Geriatria e Gerontologia. 1 edição – Barueri, SP: Manole, 2014.*

12. *Messias MG, Neves RF. A influência de fatores comportamentais e ambientais domésticos nas quedas em idosos. Rev. Bras. Geriatr. Gerontol, 2009; v.12, n.2: 275-282.*

13. *Neto AFL, Guimarães RF. Atividade física e incidência de quedas em idosos. Revista saúde e desenvolvimento, 2012; v.1 n.2: 792-796.*

14. *Nogueira SL, Geraldo JM, Machado JC, Ribeiro RC. L. Distribuição espacial e crescimento da população idosa nas capitais brasileiras de 1980 a 2006: um estudo ecológico. Revista Brasileira de Estudos de População, 2008; v.25, n.1: 195-198.*

15. *Ribeiro AP, et al. A influência das quedas na qualidade de vida de idosos. Ciência e Saúde Coletiva. São Paulo, 2008; v. 13, n.4: 1265-1273.*

16. *Siqueira Fernando V, et al. Prevalência de quedas em idosos e fatores associados. Revista Saúde Publica,Rio Grande do Sul, 2007; v.41, n.5: 749-756.*

17. *United Nations New York – Population division – Department of economic and social affairs. World populationageing: 1950-2050. Disponível em: www.un.org/esa/population/publications/worldageing19502050, 2001.*

18. *Veras R. Fórum Envelhecimento populacional e as informações de saúde do PNAD: demandas e desafios contemporâneos. Introdução. Cadernos de Saúde Pública, 2007; v.23, n.10: 2. 463-2.466.*

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SSRI Antidepressant Side Effects in Depression Patients in the first 6 months of treatment

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Abstract

Introduction: Treatment with antidepressants is associated with the risk of a poor response to treatment and lifelong depression. The aim of this study is to evaluate success and treatment of the most common l prescribed antidepressants Paroxetine, Sertaline and Flusetine in relation to adverse reactions and relapse symptoms of the clinical picture of depression.

Methods and Respondents: The research was designed as a prospective, transient study voluntarily on a voluntary basis and with respect to anonymity, during 2013-2014. The study was included patients treated for depression without psychological symptoms. The research instruments were the Hamilton scale for the evaluation of depression (12) and the Toronto scale of adverse reactions to antidepressants (13). In the overall sample of respondents (n = 349), respondents were continuously treated with one of the 3 SSRI the most frequently prescribed antidepressants (Paroxetin, Sertalin or Flusetin) in the current episode of depression, lasting up to 6 months. The spinal focus group consisted of n = 176 subjects.

The average age of the subjects is 48.55 ± 9.74 years, and the female is 62%.

Results: The average values of Σ depression 20.27 ± 8.396 reveals that respondents are mostly suffering from a serious episode of depression. Success in withdrawal of symptoms and achievement of remission in the first 6 months is achieved with the following frequency: 8% during treatment with Paroxetine (Seroxat); 0% during treatment with Sertraline (Zoloft); and 6% during treatment with Flusetine. The failure to treat depression and the inability to achieve remission of the disease is statistically significantly correlated with the selected antidepressant (Speraman correlation factor = -0.141, P = 0.008). If you treat depression with Sertalin, then it might appear suicidal intentions in 12 % of responedents.

Conclusion: The outcomes of treatment most commonly prescribed by SSRI antidepressants in the first 6 months are very poor. It seems appropriate to control the adherence of SSRI antidepressants and improve pharmacotherapy with psychotherapy.

Key Words: treatment of SSRI antidepressants in the first 6 months, Paroxetine, Sertalin, Flusetin, failure of treatment due to the inability to achieve symptoms remission.

Introduction

Depression is an episodic disorder, and in 50% to 80% of people who has the first depressive episode, a new, repeated depressive episode will appear definitely. Depression is a disease accompanied by a reduced mood, which changes the overall thinking, observation, physical condition, behavior and social function of a person (1). The untreated depressive episode lasts between 6 and 13 months on average, and most are treated for two to three months (2.3). The most frequently prescribed SSRI antidepressants are: Paroxetine (Seroxat) 57.3%, Sertalin (Zoloft) 11% and Fluoxetin (Flusetin) 41.15% (4.5). Typical symptoms in the clinical picture are: depressed mood, loss of interest and satisfaction in everyday and early activities, reduced energy and reduced self-esteem. Often, there are outbursts of cry or inability of a person to cry and feel emotions (6). Almost 80% of patients report sleeping problems, most commonly with difficulty sleeping or early morning awakening. In addition to sleeping problems, there is a decrease in appetite in many patients with a

consequent loss of body weight (7). Other common symptoms of depression include a reduction in the interest in sexual activity, which may sometimes result by referring person to spouse therapy, and sometimes it that depression is not recognized or treated beforehand (8).

Antidepressants are a group of drugs that primarily improve depression, stimulate vital dynamisms and act anxiolytic (6). Their effect is based on the knowledge of the functional disadvantage of "monoamine" in depressive disorder. Thus, antidepressants are synthesized that increase the concentration of monoamines at the receptor sites in the brain. They affect the change in the number and sensitivity of monoamine energetic receptors. *Noradrenaline* and *serotonin* are the most important monoamines.

Thus, the increase in serotonin leads to mood enhancement, and noradrenaline affects at motor skills and behavior (9). The role of the third neurotransmitter, *dopamine*, is not insignificant. It is significant at the stage of transition of depression to mania. Having in mind all this knowledge about neurotransmitters, a large number of drugs with selective action on a certain subtype of the receptor have been synthesized. Antidepressants are usually given to patients for 2-3 months. More often in practice we have the situation that after the withdrawal of symptoms of the patient's disease, the same dose is administered for another 3-6 months, as this procedure has been shown to prevent recurrence of the disease (2, 3,11).

The aim of this study is to evaluate the success and treatment most commonly prescribed by antidepressants Paroxetine, Sertaline and Flusetine in relation to adverse reactions and the relapse symptoms of the clinical picture of depression.

Methods and respondents

The research was designed as a prospective, transient study by volunteering on a voluntary basis and with respect to anonymity, during 2013-2014. The study included patients treated with a mild and moderate form of depression without psychological symptoms, and receiving antidepressant medication in pharmacies in Tuzla. The research instruments were Hamilton's scale for assessing depression (12) and the Toronto scale of adverse reactions to antidepressants (13). The study was approved by the Commission for Ethical Issues of the Pharmaceutical Chamber.

The total sample included 349 respondents of 500 involved (response to the survey 69.8%). Including the factor for the respondents was: diagnosed depressive disorder without psychotic symptoms; respondents aged 19-65 years. In the overall sample, respondents who are continuously treated with one of the 3 SSRIs are the most frequently prescribed antidepressants (Paroxetine, Sertalin or Flusetin) in the current episode of depression, for up to 6 months as respondents. The respondent focus group consisted of n = 176 respondents.

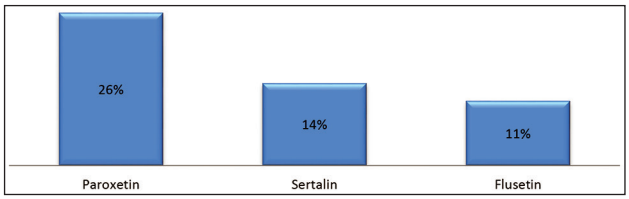
Statistical data processing

For the analysis of results, the standard Statistical Package for Social Research (SPSS) version 19.0 was used. Statistical processing of the results was carried out using standard methods of descriptive statistics. X2-test and t-test were used to test the statistical significance of the difference in the selected variables. A non-parametric Sperman test correlation was used for multivariate correlation analysis.

Results

The average age of the subjects is 48.55 ± 9.74 years, the average height is 171.66 ± 8.689cm and the average weight is 77.18 ± 15.824kg. Mean value Σ of depression 20.27 ± 8.396 reveals that respondents mostly suffer from a serious episode of depression.

The highest number of respondents is female 217 out of a total of 349 (62%), and they are 41 to 60 years of age (67%). Depressive disorder is most commonly represented in the most educated, with 59% of those with a university degree and 36% with a completed secondary school (Table 1)



Picture 1. Distribution of respondents according to selected SSRI antidepressants

Table 1. Structure of respondents according to individual characteristics and demographic data

Characteristics of respondents	No= 349 Number of respondents n	Frequency %
Gender		
Male	132	38
Female	217	62
Age group (years)		
<30	11	3
31-40	51	15
41-50	116	33
51-60	120	34
>60	51	15
Activities		
Administrative, health care service and others unproductive	427	94
All productive	22	6
Educational level		
Elementary school	2	0.6
Professional education	17	4.4
High school	125	36
Higher education	205	59

Most respondents were treated with antidepressants only 239 (68%) of 349 patients. N = 175 were treated with the most commonly prescribed SSRI antidepressants: Paroxetine 26% (n = 89), Sertaline 14% (n = 50) and Flusetine 11% (n = 36) (Picture 1).

In general, failure while treating patients with antidepressants in the first 6 months is unexpectedly high. The most difficult remission of depressive episode symptoms is achieved by treatment of the most frequently used by antidepressant (Picture 1). It may be a problem byneglecting the etiological factors of depression in treatment, inadequately determined diagnose during initial drug choice, inadequate treatment approach, and inadequate evaluation of the effects of treatment in time or drug resistance.

During the treatment by the most commonly prescribed antidepressants in the first 6 months, the success in withdrawing symptoms and achieving remission in general is possible with the following frequency: 8% during treatment with Paroxetine (Seroxat); 0% during treatment with Sertaline (Zoloft); and 6% during treatment with Flusetin (Figure 2).

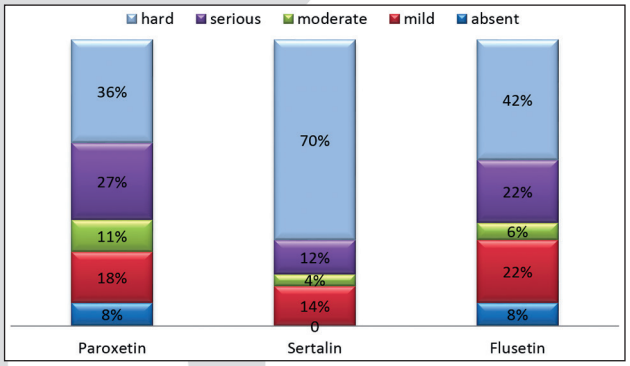


Figure 2. Comparative structure of suicide cases at respondents according to selected SSRI antidepressants

A severe episode of depression as the most difficult clinical form of the disease and the biggest symptoms that present failure during treatment was found at patients who were treated by: Paroxetine 36%, Sertaline 70% and Flusetine 42%. The rate of severity of a serious episode of depression was distributed in: 37% of Paroxetine treated patients, 14% of patients treated with Sertraline and 22% of patients treated with Flusetine. The unexpected results was treatment by Sertaline

(Zoloft) because 70% of the treated patients suffer from a severe episode of depression, 14% serious, 4% moderate, and 12% mild episode (Figure 2). A complete remission treatment with Sertalin was not achieved by any respondent. There is statistically significant difference in the different outcome of the treatment failure in relation to the different choice of the antidepressant ($\chi 2$ test = 49.943, P = 0.000, P <0.001).

The failure of treating depression and the inability to achieve remission of the disease significantly correlates with the selected antidepressant (Speraman correlation factor = -0.141, P = 0.008).

In Figure 3, the comparative structure of suicide is shown according to the most prescribed SSRI antidepressant. The prevalence of perception that life is not worthwhile is almost uniformly frequent and without significant differences compared to the choice of SSRI antidepressant: Sertaline 28% and Fluxetine 28% and Paroxetine 27%. It can be assumed that is the usual occurrence of SSRI treatment by antidepressants in the first months. Similar situation exists in estimating the rate of suicide reports: Sertaline 5% and Fluxetine 4% and Paroxetine 5%.

It is deeply concerned the fact of perception the suicidal intentions during treatment by Sertalin with the rate of prevalence of 12%.The level of suicide is statistically related with the chosen antidepressant (Speraman correlation factor = -0.141, P = 0.008).

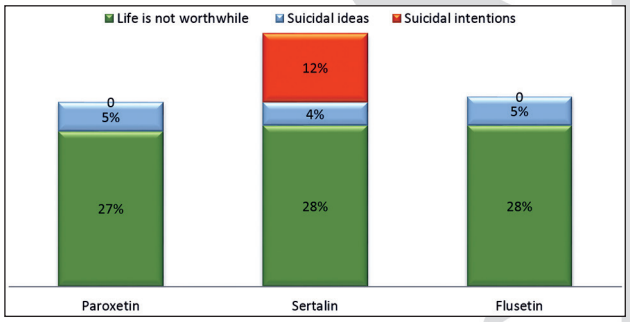


Figure 3. Comparative structure of suicide at respondents according to selected SSRI antidepressant

Discussion

Every treatment with antidepressants was followed by side effects, but the profile of the side effects with the new antidepressants changed significantly. After acute treatment of depressive disorder, the remaining symptoms are common. Patients with residual symptoms of depression have an increased risk of relapse and recidivism (14). Depression usually occurs at people who have had panic attacks or long-term anxiety for some time (1.15).

The improved tolerability of SSRI antidepressants in relation to other antidepressants is attributed to their selectivity and the absence of interaction with other receptors, such as histamine, cholinergic, dopaminergic and noradrenergic (16). However, serotonin receptors contain at least 7 classes that are further subdivided into the subreceptor level. These receptors mediate various non-mood functions including sleep, appetite, and sexual function, as well as symptoms such as pain, nausea, depression, and anxiety (8.17).

Selective serotonin inhibitors stored (SSRIs) are currently the first choice for depression therapy (19). In general, failure of treatment with SSRI antidepressants at our respondents in the first 6 months is unexpectedly high. The most difficult remission of symptoms of depressive episode has been achieved by treatment of the most recommended and used SSRI, Paroxetine and Sertalin. It should be noted that antidepressants have proven their effectiveness in the treatment of acute depressive episodes and the prevention of relapse for a long period of time (20). Research shows that psychotherapy can play an important role in enhancing the effects of antidepressant therapy, and can improve patients' long-term prognosis. Psychotherapy has certain goals related to the recurrence of symptoms of guilt, hopelessness, negativism and low self-esteem. It is known that antidepressants can not reduce the irritability that is most effectively enhanced by the management of stress. In this way, in the long term, health improves and stimulates cognitive changes. The results were confirmed in the modulation of critical common goals of treatment and facilitating depression remission during joint treatment with psychotherapy and pharmacotherapy in various parts of the cortical-limbic pathway. The use of ancillary psychotherapy in the acute phase of depression treatment seems to give only a modest increase in the rate of expected therapeutic responses. The simultaneous usage of pharmacotherapy and psychotherapy during the maintenance phase inconsistently gives

a clear advantage over maintenance ofpharmacotherapy (14).

However, whether due to inexperience of the chronicity of depression or because of intolerable adverse effects or inappropriate fear of addiction, treatment with antidepressants is often interrupted after remission or recovery from an acute episode, which often leads to recidivism of the disease. This, however, increases the risk of poor response to treatment and lifelong depression (21). It may be a problem in neglecting the etiological factors of depression in treatment, inadequately diagnosed during initial drug choice, inadequate treatment approach, and inadequate evaluation of the effects of treatment in time or drug resistance. Social theories emphasize the role of stress, assuming that a series of stress staging predisposes a person for the development of depression. There are surely also the premorbid personality traits that can represent a good basis for the development of this disorder (22). What is confirmed suggests that the choice of a particular SSRI ($\chi 2$ test = 49.943, P = 0.000, P <0.001) is very important for the different outcomes and success for treatment with SSRI antidepressants.

Patients treated with SSRI antidepressants continuously without interruption in the first 3 months experience a lower risk of relapse and recidivism (risk ratio: OR = 0.42, 95% CI, 0.40 to 0.44). Also, patients who have three or more control visits to a psychiatrist or a selected physician in the first 3 months also reduce the risk of relapse / recidivism. Factors associated with a significant increase in relapse / recurrence are comorbidity chronic diseases, anxiety disorder and alcohol consumption (23).

Insomnia, irritability and anxiety occur occasionally in early stages of treatment. Several patients discontinued Flusetine treatment due to adverse reactions and the least treated Sertalin (24). Our results are contradictory. Unexpectedly, there is a poor therapeutic effect in our patients treated with Sertraline because 70% of the treated subjects suffer from a severe episode of depression, 14% serious, 4% moderate, and 12% mild episode (Figure 2). A complete remission of the treated Sertalin was not achieved by any respondent. The most common side effects of SSRI are gastrointestinal problems, headache and tremor. The evaluation revealed several side effects associated with the treatment of Flusetine in the treatment of other SSRI antidepressants. Flusetin, by other authors, may, however, be the first choice among medication for patients with rapid antidepressant effect (Mackay et al., 1997; Mather et al., 2002).

Continuous treatment SSRI with antidepressants and regular visit to psychiatrist or family doctor during an acute phase is associated with a significant reduction of recidivism or the recurrence of depression. Supervision and counseling of a pharmacist during this period can be invaluable (24). Clinicians should focus on suppressing of recidivism with long-term pharmacotherapy treatment of antidepressants with a combined psycho treatment which improves treatment outcomes, especially at patients with high risk of relapse (21).

Conclusion

Our respondents who are treated with the most prescribed SSRI antidepressants (Paroxetin, Sertalin, Flusetin) generally have poor treatment outcome, and despite treatment in the first 6 months they suffer from relapses of depressive symptoms and a very serious level of suicide.The most difficult remission of symptoms of depressive episode has been achieved by treatment of the most commonly recommended and used Paroxetine and Sertaline. Sertalin is solely responsible for suicide intentions in the first 6 months of treatment with a prevalence rate of 12%. It seems appropriate to control the adherence of SSRI antidepressants and improving pharmacotherapy with psychotherapy.

References

1. *McClanahan T, Antonuccio D. Depression. In: Thomas J, Hersen M (ur). Psychopatology in the workplace, recognition and adaptation. New York, Brunner- Routledge. 2004; 133-46.*

2. *Hotujac LJ. Poremećaji raspoloženja: afektivni poremećaji. U: Muačević V (ur). Psihijatrija. Medicinska naklada, Zagreb. 1995; 349-370.*

3. *Horwath E, Cohen RS, Weissman MM. Epidemiology of depressive and anxiety disorders. In: Tsuang MT, Tohen M (eds). Textbook in psychiatric epidemiology. 2nd edition. New York: Wiley-Liss. 2002; 389-426.*

4. *Trumić E, Pranjić N, Begić L, Bečić F, Aščerić M. Idiosyncratic Adverse Reactions of Most Frequent Drug Combinations Longterm Use Among Hospitalized patients with Polypharmacy. Med Arh. 2012; 66(4): 243-8.*

5. *Anonymous Izvještaj: Zdravstveno stanje stanovništva. Zavod za javno zdravstvo Federacije Bosne i Hercegovine, 2009.*

6. *Davidson JR, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? J Clin Psychiatry. 1999; 60(7): 4–9.*

7. *Nelson JC. Safety and tolerability of the new antidepressants. J Clin Psychiatry. 1997; 58(6): 26–31.*

8. *Brady KT, Clary MC. Affective and anxiety comorbidity in post- traumatic stress disorder treatment trials of sertraline. Compr Psychiatry. 2003; 44(5): 360-9.*

9. *Parker G. Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotype expression of depression. Acta Psychiatr Scand. 2002; 106(3): 168-70.*

10. *Sampson SM. Treating depression with selective serotonin reuptake inhibitors: a practical approach. Mayo Clin Proc. 2001; 76: 739-44.*

11. *Spijker J, Nolen WA. An algorithm for the pharmacological treatment of depression. Acta Psychiatr Scand. 2010; 121: 180-8.*

12. *Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23: 56-62.*

13. *Vanderkooy JD, Sidney H, Kennedy MD, Michael-Bagby R. Antidepressant Side Effects in Depression Patients Treated in Naturalistic Setting: A study of Bupropion, Moclobemide, Paroxetine, Sertaline, and Venflaxine. W Can J Psychatry. 2002; 47(2): 174-80.*

14. *Peterson TJ. Enhancing the efficacy of antidepressants with psychotherapy. J Psychopharmacol. 2006; 20(3): 19-28.*

15. *Hajjar ER, Cafiero AC, Hanion JT. Polypharmacy in eldery patients. Am J Geriatr. Pharmacother. 2007; 5(4): 314-6.*

16. *Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry. 2001; 3(1): 22-7.*

17. *Carroll R, Metcalfe C, Gunnell D. Hospital presenting self-harm and risk of fatal and nonfatal repetition: systematic review and meta-analysis. PLoS One. 2014; 28: 9(2).*

18. *Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders: tolerability, safety and pharmacoeconomics. J Psychopharmacol. 1998; 12 (B): S55-S87.*

19. *Cuijpers P, Dekker J, Hollon SD, Andersson G. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. J Clin Psychiatry. 2009; 70: 1219-24.*

20. *Mackay FJ, Dunn NR, Wilton LV, Pearce GL, Freemantle SN, Mann RD. A comparison of fluvoxamine, fluoxetine, sertaline and paroxetine examined by observational cohort study. Pharmacoeidemiol Drug Saf. 1997; 6(4): 235-46.*

21. *Nutt DJ. Rationale for barriers to, and appropriate medication for the long-term treatment of depression. J Clin Psychiatry. 2010; 71(E1:e02). doi:10.408813CP905se1c.02gry.*

22. *Labbate LA, Sonne SC, Randal CL, Anton RF, Brady KT. Does comorbid anxiety or depression affect clinical outcomes in patients with post- traumatic stress disorder and alcohol use disorders? Compr Psychiatry. 2004; 45(4): 304-10.*

23. *Cuijpers P, Reynolds CF 3rd, Donker T, et al. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depress Anxiety. 2012; 29: 855-93.*

24. *Kim KH, Lee SM, Paik JW, Kim NS. The effects of antidepresants treatment during the first 6 months on relapse or reccurence of depression. J Affect Disord. 2011; 132 (1-2): 121-9.*

25. *Mather A, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo ME. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder. The British Journal of Psychiatry. 2002; 180: 411-5.*

26. *Martin A, Sanderson K, Cocker F. Meta- analysis of health promotion intervention in the workplace on depression and anxiety symptoms. Scand J Work Environ Health. 2009; 35: 7-18.*

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'Renal Cell Carcinoma Complicated with Amyloidosis or vice versa'

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Abstract

Amyloidosis mostly complicate chronic inflammatory diseases. It is not common in clinical practice to diagnose amyloidosis A secondary to cancer cases. Here we present 68 years of male patient whom incidentally noticed resectable left kidney mass which come out as papillary renal cell carcinoma in partial nephrectomy material with amyloidosis A. With this case, importance in paying attention and detailed exploration of proteinuria and relation of amyloidosis A with cancer which is very rare were emphasized to the clinicians.

Key Words: Amyloidosis A, nephrotic syndrome, renal cell carcinoma.

Introduction

Amyloidosis A usually develops after 17 years of inflammation in 5 % of patients with chronic inflammatory diseases due to increased hepatic amyloid A protein synthesis during the course of inflammation (1). Even though malign neoplasms generate systemic inflammatory response, co-occurence with amyloidosis rarely reported (@%7) (2). The underlying etiology for this seldom co-occurence was thought to be the result of early deaths of cancer patients before the emergence of clinical status related to amyloid fibril deposition (3).

Here, a case whom nephrectomy due to renal cancer was performed and was followed up with diagnosis of nephrotic syndrome secondary to amyloid AA deposition was presented.

Description of Case

68 years old male patient with a history of hypertension (duration of 8 years), coronary artery bypass surgery (2 vessels), atrial fibrillation, hypercholesterolemia, chronic kidney disease (G3b) and subtotal gastrectomy due to malignancy was diagnosed as nephrotic syndrome one and a half year ago on his first admission to our hospital. At that time under medications of isosorbid mononitrat 20 mg 2*1, atorvastatin 1*40 mg, amlodipine 1*10 mg, trimetazidine 2*1 and acetyl salicylic acid 1* 150 mg, his blood pressure was 110/60 mmHg (no difference between the arms was noticed) and pitting oedema was found. Biochemical tests revealed as follows: serum creatinine level: 1.77 mg/dL, hemoglobin (Hgb): 9.9 g/dL, albumin level: 1.7- 2.1 g/dL creatinine clearance (from a 24-hour urine collection): 34 mL/min, LDL-C: 277 mg/dL, density of urine: 1.006 and protein: 600 mg/dL in routine urinalysis, 24-hour urine protein excretion: 16.9 g/day, 24-hour urine albumin excretion: 4.7 g/day. Both kidneys were in normal size but parenchymal echogenicity was increased to grade 2 and irregular hypoechoic mass of 24*16 mm in left kidney was discovered in abdomen ultrasonography. The mass in left kidney was 8*8 mm in size and enhanced with contrast in computed tomography which showed high probability for renal cell carcinoma (figure 1). Renal cell carcinoma staging according to the American Joint Committee on cancer (AJCC)/union for international cancer control (UICC) TNM staging system (AJCC/UICC TNM classification) was T1a N0 M0 (4). As the mass was resectable stage 1 tumor, partial nephrectomy was performed. Nephrectomy specimen was evaluated histopathologically and papillary renal cell carcinoma with negative surgical margins, 8*7 mm in size, unifocal, without sarcomatoid and rhabdomyomatous differentiation, necrosis and lymphovascular invasion (figure 2) and amyloidosis A (figure 3) were diagnosed. After had

been treated and followed up for 8 months with diagnosis of CKD grade 4-5, the patient has been in hemodialysis programme for 4 months.

Figure 1. Computed axial tomography scan showing contrast enhanced irregularly shaped solid mass in left kidney

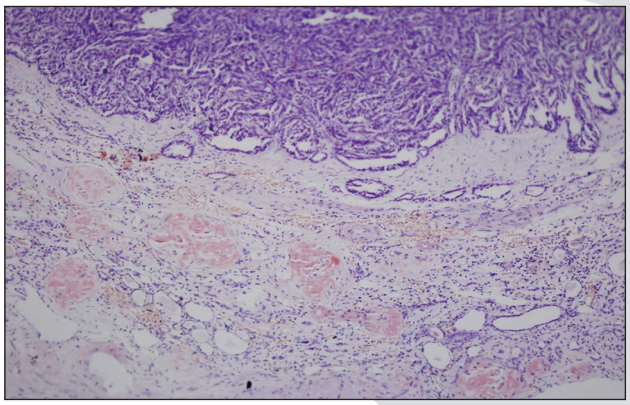

Figure 2. Nephrectomy material which display glomeruli with amyloid deposition around the papillary renal carcinoma H.E. ×100

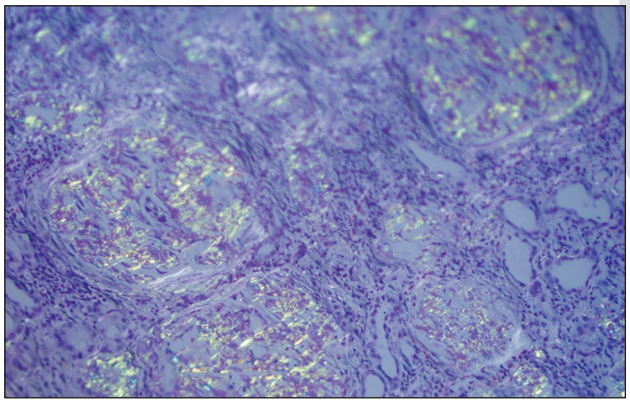

Figure 3. Green birefringence of congo red stain in polarised light pointing glomerular amyloid deposition C.R. (Congo Red) ×200

Discussion

AA amyloidosis can be observed mostly in familial Mediterranean fever (FMF) and chronic inflammatory rheumatic diseases (1,5,6). Rheumatoid arthritis underlies 40% of the cases (5). Besides to these diseases, inflammatory bowel diseases especially Crohn's disease, chronic infections such as bronchiectasis, decubitus ulcers, paraplegics, tuberculosis, intravenous drug users, osteomyelitis were reported to complicate with amyloidosis A (5,7). Neoplasms like renal cell carcinoma and Hodgkin Lymphoma might also be associated with amyloidosis A (5).

Amyloidosis co-occurrence with renal cell carcinoma (RCC) in the world was noticed by Ask-Upmark first time, 59 years ago with 18 cases. Over the years it was shown that malignities compose @ 7 % of the causes leading to amyloidosis AA. Among all these malignities, RCC constitute nearly 25-42% of cases. However only @ 2.1-3.2 % of RCC cases were observed to have amyloidosis AA deposition in autopsies (7). It has been known that there is a link between chronic inflammation and malignancy. Amyloidosis is regarded as a chronic inflammatory state which is a trigger for oncogenesis (8). So these patients with co-existance of amyloidosis and renal cell carcinoma might have had a disease leading to chronic inflammation which end up both amyloidosis and malignancy. As a result, renal manifestations of chronic systemic inflammation are not only amyloid nephropathy and kidney failure but also renal tumors. On the other side, renal cell tumors were demonstrated to secrete IL-6 which in turn increase serum amyloid A levels (7). By this mechanism, tumor itself can produce amyloidosis A without another disease. This effect might be non-endocrine paraneoplastic manifestation of RCC (8).

RCC consists of nearly 3% of all malignities (10). Clear cell RCC constitutes most of renal malign tumors (@ 75 %). Second most commonly found papillary RCC as in our case accounts @ 10 % of all RCC cases. Besides genetic mutations, hypercholesterolemia, obesity, hypertension, smoking habit, sedentary life, hyperglycemia and industrial agents were accused of RCC development (10). Our patient had the components of metabolic syndrome as a risk factor for RCC.

According to TNM classification, our patient had resectable stage 1 renal tumor. It was shown that in order to protect renal parenchyma as much as possible, nephron sparing surgery (partial nephrectomy) is recommended for local disease (<7 cm in size) treatment. With this approach, we were able to delay the need of dialysis initiation nearly 8 months for this patient. In the subsequent year, during surveillence after the operation, no recurrence of tumor was detected.

In conclusion, this case reminds us amyloidosis A as a nonendocrine paraneoplastic syndrome marker for RCC and also amyloidosis itself might trigger oncogenesis through chronic inflammation both of which are very rare.

References

1. *Ronco P, Aucouturier P, Moulin B. Renal amyloidosis and glomerular diseases with monoclonal immunoglobulin deposition. Eds; Feehally J, Floege J, Tonelli M, Johnson RJ. In Comprehensive Clinical Nephrology, Elseiver 2019 (Sydney); 320-332.*

2. *Babu A, Lachmann H, Pickett T, Boddana P, Ludeman L. Renal cell carcinoma presenting as AA amyloidosis: a case report and review of the literature. CEN Case Rep 2014; 3(1) : 68-74. doi: 10.1007/s13730-013-0088-8.*

3. *Nobata H, Suga N, Itoh A, Miura N, Kitagawa W, et al. Systemic AA amyloidosis in a patient with lung metastasis from renal cell carcinoma. Amyloid 2012; 19(4): 197-200. doi: 10.3109/13506129.2012.712926.*

4. *Rini BI, McKiernan JM, Chang SS, et al. Kidney. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), Springer, New York 2017; 739.*

5. *Cooper C, Bilbao JE, Said S, Alkhateeb H, Bizet J, et al. Serum amyloid A renal amyloidosis in a chronic subcutaneous ("skin popping") heroin user. J Nephropathol 2013; 2(3): 196-200. Doi.10.12860/JNP.2013.31.*

6. *Blank N, Hegenbart U, Lohse P, Beimler J, Röcken C, et al. Risk factors for AA amyloidosis in Germany. Amyloidosis 2015; 22(1): 1-7. Doi:10.3109/13506129.2014.980942.*

7. *Babu A, Lachmann H, Pickett T, Boddana P, Ludeman L. Renal cell carcinoma presenting as AA amyloidosis: a case report and review of the literature. CEN Case Rep 2014; 3(1): 68-74. Doi:10.1007/s13730-013-0088-8.*

8. *Su VY, Liu CJ, Hu YW, Chen YM, Lai SL, et al. Amyloidosis and the risk of cancer: a nationwide population-based study. Int J Clin Oncol 2015; 20(6): 1244-51. Doi:10.1007/s10147-015-0849-9.*

9. *Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996; 14(4): 216-22.*

10. *Petejova N, Martinek A. Renal cell carcinoma: review of etiology, pathophysiology and risk factors. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2016; 160(2): 183-94. Doi: 10.5507/bp.2015.050.*

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HsC-reactive protein as a predictor of mortality in patients with atrial fibrillation in heart failure

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Abstract

Background: To determine the predictive value of HSC-reactive protein level in mortality for patients in heart failure with atrial fibrillation.

Respondents and methods: Cross-section study analysed the predictive value of C-reactive protein in 200 patients with heart failure of all ages, both sexes. The study was conducted in the Department of Internal Medicine of Cantonal Hospital "Dr. Irfan Ljubijankić", Bihać, Bosnia and Herzegovina. Considering the leaders of the heart rate, respondents were divided into two equal groups: the first group were patients in heart failure with atrial fibrillation, and the second group were patients in heart failure with sinus rhythm. All patients with heart failure were clinically examined, with electrocardiogram, ultrasound of the heart, and the value of HsCRP in serum was determined. In the study, the value of HsCRP considered normal if <5.0 mg / l.

Results: The average age of patients in the first group was 65.0 (8.6) years, and in the second group 65.3 (9.1) (t = 0.215, df = 198, p = 0.83). The first group consisted of 47/100 (47%), while the second group had 41/100 (41%) of female respondents, (X 2 = 0.73, df = 1, p = 0.48). There were more male respondents in both groups. The average value of HsCRP in the entire sample was 5.75 (5.68) mg / L (range 0.0 to 28.0 mg / l). The frequency of respondents with elevated HsCRP in the first group was 40 (40%), while the second group was 44 (44%), (X2 = 0.18; df = 1; p = 0.67). In the first group there were 21 (21%) mortality, and 15 (15%) in the second group (X 2 = 0.85, df = 1, p = 0.36). Univariate regression analysis of the first group of respondents HsCRP shown the relation of chances (odds ratio - OR) of 1.13 (95% CI = 1.04 to 1.22; p = 0.003), and when a function of time (hazard ratio - HR) was taken into account, HsCRP as a predictor was 1.10 (95% CI = 1.04 to 1.17; p = 0.001). In the second group of respondents HsCRP showed OR = 1.07 (95% CI = 0.98 to 1.17; p = 0.13), and HR value was 1.06 (95% CI = 0.99 to 1, 14; p = 0.11).

Conclusion: HsC-reactive protein is a significant predictor of mortality in patients with atrial fibrillation in heart failure.

Key words: HsC-reactive protein, heart failure, atrial fibrillation

Objective

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmias. Heart failure is a condition characterised by structural or functional disorders of the heart leading to inability of the heart chambers to receive or displace the blood and thereby transporting oxygen to the body in an amount that body needs. The risk of ischemic stroke and other thromboembolic complications are significantly increased in patients with heart failure (SI) in the presence of atrial fibrillation (AF). Atrial fibrillation may worsen existing or to precipitate new heart failure, significantly affects the tolerance of physical activity and quality of life in general, and one-third of all hospitalisations due to cardiac arrhythmias consists of hospital admissions due to atrial fibrillation (Potpara and Polovina, 2011). The discovery of biomarkers has led to unprecedented opportunities to study cardiovascular diseases, early diagnosis and better ability for risk stratification, biomarkers targeted therapies and better specification of short-term and long-term prognosis of the disease. Dominant markers that reflect the process of inflammation were discov-

ered, as well as thrombosis / fibrinolysis, neurohormonal activity, intraplak instability; in other words, better imaging of vulnerable patients and vulnerable blood.

In order to solve all the above aspects, multimarker approach in the diagnosis and stratification of each patient is preferred (Ćirić-Zdravković et al., 2008). The significance of cardiac biomarkers is also revealed through new studies that are under way, and which speak in favour of using the very markers in the diagnosis, prognosis and treatment of heart failure. One of studies is conducted by Januzzi et al. where the results of successful research NT-proBNP to heart failure appear, and where therapy guided with values of NT-proBNP reduces clinical treatment of heart failure more than 50%.

C-reactive protein (CRP) is an acute phase reactant, which is growing in infections and inflammation. High CRP levels are associated with increased mortality due to cardiovascular diseases in the general population. Highly specific C-reactive protein might be a predictor of new cardiovascular episodes in patients with unstable angina pectoris and acute myocardial infarction, including death (Ross, 1999). So C-reactive protein is not only an indicator of systemic and vascular inflammation, but also reliable and well-standardised test that could be used in conjunction with troponin in cardiovascular risk stratification.

AIM

To determine the predictive value of the HSC-reactive protein level in mortality in patients with atrial fibrillation in heart failure.

Respondents and methods

A prospective study included 200 patients with heart failure, all ages, both sexes, which were treated clinically and as outpatients at the Department of Internal Medicine at the Cantonal Hospital "Dr. Irfan Ljubijankić" in Bihać. Subjects were divided into two equal groups of 100 subjects, considering the leaders of the heart rate: the first group consisted patients in heart failure with atrial fibrillation, and the other control group was consisted of patients with heart failure in sinus rhythm. All patients with heart failure had clinical examination, electrocardiogram, ultrasound of the heart, and value of HsCRP in serum was determined. In the study, the value of HsCRP is considered normal if HsCRP <5.0 mg / l. Analysis of the value of HsCRP was measured with Beckman Coulter AU 480, using imunoturbidimetric method.

Statistical analysis was performed in the SPSS 22.0 software package (Armonk, NY: IBM Corp.). The parameters of descriptive statistics were used to show the basic characteristics of the sample. The student's t-test for comparison of quantitative variables was used where possible, otherwise the Mann-Whitney test was used. Chi-square or Fisher's test was used to compare categorical variables.

Univariate regression analysis was used to test the predictive potential of variables which were point of interest. The Kaplan-Meier curves were created with determination of log-rank tests for the time to death, including comparison of the respondent groups. Cox's regression analysis was made for evaluation of the risk (hazard ratio), with the calculation of 95% reliability interval, in order to test the potential of predictive variables of interest, in the function of time. The level of statistical significance of 95% ($p < 0.05$) was considered as the limit of significance for all statistical tests.

Results

The average age of patients in the first group was 65.0 (8.6) years, and in the second group 65.3 (9.1) ($t = 0.215$, $df = 198$, $p = 0.83$). The portion of female respondents in the first group was 47/100 (47%), and 41/100 in the control group (41%), ($X2 = 0.73$, $df = 1$; $p = 0.48$). Median value of ejection fraction (EF) in the first group of subjects was 45% (IQ range: 36-50), while in the control group of respondents was 45% (IQ range: 35-50), ($p = 0.49$). The average value (SD) of HsCRP in the entire sample was 5.75 (5.68) mg / l, ranging from a minimum of 0.0 to a maximum of 28.0 mg / l. Taking into account the upper reference value limit, 84/200 (42.0%) subjects had elevated HsCRP (Figure 1).

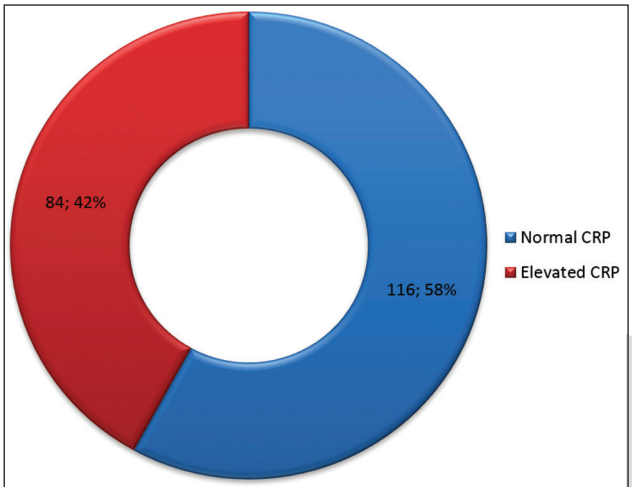

Figure 1. Representation of elevated CRP values in the sample

The average value (SD) of HsCRP in the first group of subjects was 5.82 (5.89), and 5.68 in the control group (5.48), (t = 0.17, df = 198, p = 0.86). The frequency of patients with lethal outcome during the follow-up period in the total sample amounted to 36/200 (18%). Comparing the incidence of death, the group one had 21 (21%), and the control 15 (15%), (X2 = 0.85, df = 1; p = 0.36). A separate analysis of the predictive potential of HsCRP was performed in the first group of patients, univariate regression analysis showed that HsCRP was not statistically significant predictor of mortality after 12 months in this first group of patients.

Namely, HsCRP Odds Ratio (odds ratio - OR) of 1.13 was shown (95% CI = 1.04 to 1.22; p = 0.003), i.e., for every increase of HsCRP to 1 mg / l, the chances of fatalities grew by 1.13 times. When the function of the time was taken into account, after the Cox Cox's regression analysis, proportional hazards model, it was obtained that the risk ratio (hazard ratio - HR) as a predictor for HsCRP was 1.10 (95% CI = 1.04 to 1.17; p = 0.001), and for every increase of the HsCRP 1 mg / l, the risk of fatalities was monthly increased for 1.10 times. So, also in the survival perspective in the function of time during the 12 months, HsCRP was a significant predictor of mortality. Analogously to afore-mentioned analysis, predictive potential of HsCRP was separately analysed in the control group of subjects. HsCRP was not statistically significant predictor of mortality OR = 1.07 (95% CI = 0.98 to 1.17; p = 0.13). When taking into consideration the function of time (HR = 1.06; 95% CI = 0.99 to 1.14; p = 0.11) HsCRP was not statistically significant predictor of mortality in the control group of subjects.

Discussion

Despite advances in the treatment of heart failure, mortality remains high, where the five-year mortality rate is almost 50% (Roger VL et al. 2004). Taking into account the significant number of patients with heart failure, high mortality and high cost of treating these patients, it is necessary to emphasise the importance of risk stratification in heart failure. Although early clinical studies examined the risk of mortality in patients with heart failure, it wasn't possible to assess the individual prognosis. Earlier studies showed that elevated levels of biomarkers, including C-reactive protein (CRP), B-type natriuretic peptide (BNP) and troponin, may be individually associated with an increased risk of mortality in patients with heart failure. CRP, BNP and troponin, which reflect the different pathophysiological mechanisms (i.e.. Inflammation, cardiac stress and myocyte necrosis), can improve the prediction of mortality in heart failure beyond the traditional, usual risk indicators. Establishment of multi-marker strategy as assistance in predicting risk for heart failure, can enhance the ability to accurately identify patients at high risk of mortality, and to obtain information that might be of critical use in clinical decision making in the treatment of patients (Dunlay SM et al. 2009). The values of inflammatory CRP parameters in heart failure have found an important place in both the diagnostics and monitoring of the course of treatment and prognosis of disease outcome. There is a close relation between the parameters of inflammatory interleukin 6 (IL 6) and CRP. There is increasing number of evidence that inflammation may be associated with the pathogenesis of atrial fibrillation and arrhythmias. C-reactive protein in the acute phase is produced in the liver as a response to stimuli that trigger inflammation, including interleukin such as IL-6. IL-6 and CRP are important markers of inflammation, and they are often studied within cardiovascular diseases and AF. Although there are deficiencies in some studies, most of them explain that the CRP and other inflammatory markers represent

independent risk factors for the incidence of AF in patients who in the early history did not have AF, and also for the development of SI. Results of recent studies confirm that CRP is independently associated with mortality and all causes of mortality, consisting of stroke / TIA, systemic embolism, acute coronary syndrome, acute heart failure and cardiac death (Hermida J et al. 2012).

Conclusion

HsCRP is a significant predictor of mortality in patients with atrial fibrillation in heart failure.

References

1. *Ćirić-Zdravković S, Apostolović S, Glasnović J et al. Markers of ischemia and myocardial necrosis. Acute Coronary Syndrome, Proceedings, Kopaonik 2008; 119-134.*

2. *Dunlay SM, Gerber Y, Weston SA et al. Prognostic value of biomarkers in heart failure: application of novel methods in the community. Circ Heart Fail. 2009; 2(5): 393-400.*

3. *Hermida J, Lopez FL, Montes R et al. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 1; 2012; 109(1): 95-99.*

4. *Potpara T, Polovina M. Contemporary Approach to Atrial Fibrillation In: Ostojić M, Kanjuh V, Beleslin B. Cardiology. Belgrade: Institute for Textbooks 2011; 839-849.*

5. *Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. JAMA 21; 2004; 292(3): 344-350.*

6. *Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999; 340: 115-126.*

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
Top margin	20 mm
Bottom margin	20 mm
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Right margin	18 mm
Column Spacing	5 mm

Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

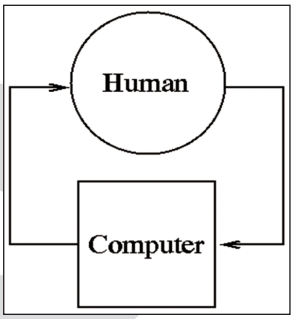

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

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