ORIGINAL ARTICLE

UDC: 617.7
DOI: 10.2298/VSP121208018K

The prevalence of pseudoexfoliation syndrome and possible systemic associations in patients scheduled for cataract surgery at the Military Medical Academy in Belgrade

Prevalencija pseudoeksfolijativnog sindroma i moguća udruženost sa sistemskim oboljenjima kod bolesnika predviđenih za hirurgiju katarakte u Vojnomedicinskoj akademiji u Beogradu

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Abstract

Background/Aim. Pseudoexfoliation syndrome (PEX) is an age-related systemic degenerative disorder characterized by the production and progressive accumulation of extracellular fibrillar eosinophilic material in the anterior segment of the eye. The aim of the study was to evaluate several clinical aspects of PEX, such as frequency of PEX and pseudoexfoliation glaucoma (PEXG), intraocular pressure (IOP), the type of lens opacity, and the possible relationship of PEX and systemic diseases. **Methods**. All 674 cataract patients had a comprehensive eye examination, including slitlamp biomicroscopy before and after mydriasis, IOP measurement, and fundus examination. The patients were classified into two groups: the PEX and the non-PEX group. **Results**. The overall prevalence of PEX syndrome was found to be 17.5% (118 patients). The mean age of PEX patients (79.7 ± 6.1 years) was significantly higher when compared with those without PEX (73.5 ± 9.1 years) (p = 0.000). The prevalence of PEX syndrome was found to increase with age, from 7.3% in the 7th decade of life to 27% in patients older than 80 years ($p < 0.001$). The most common cataract type in the PEX patients was mature cataract observed in 40.7% of patients. The rest of the patients had mixed (30.5%), nuclear (25.4%), cortical (1.7%) and hypermature cataract (1.7%). Among the PEX patients 44 (37.2%) had glaucoma. Intraocular pressure was significantly higher in eyes with pseudoexfoliations than in eyes without it (17.8 ± 3.2 mmHg and 15.8 ± 2.8 mmHg, respectively; p = 0.001). Moreover, the prevalence of coronary heart disease was found to be higher in PEX patients. **Conclusion**. PEX syndrome is a common problem among Serbian patients scheduled for cataract surgery. It represents one of the major glaucoma risk factors and probably associated with ischemic heart disease, intraoperative and postoperative problems in cataract surgery.

Key words:
exfoliation syndrome; cataract; glaucoma; prevalence; coronary artery disease, intraoperative complications; postoperative complications.

Apstrakt

Uvod/Cilj. Pseudoeksfolijativni sindrom (*pseudoexfoliation syndrome* – PEX) je starosni sistemski degenerativni poremećaj koji karakteriše produkcija i progresivna akumulacija vanćelijskog vlaknastog eozinofilnog materijala na spoljašnjim segmentima oka. Cilj ove studije bio je da ispita određene kliničke aspekte PEX, kao što su: učestalost PEX, pseudoeksfolijativni glaukom (PEXG), intraokularni pritisak (IOP), tipovi katarakte i moguća vezu PEX-a sa sistemskim bolestima. **Metode**. Svi bolesnici (n = 674) obuhvaćeni studijom detaljno su oftalmološki pregledani, uključujući pregled na biomikroskopu sa procepnom lampom, pre i posle midrijaze, merenje IOP i pregled očnog dna. Bolesnici su bili podeljeni u dve grupe: sa PEX-om i bez PEX-a. **Rezultati**. Ukupna prevalencija PEX-a bila je 17,5% (118 bolesnika). Prosečna starost bolesnika sa PEX-a bila je (79,7 ± 6,1 godina), što je statistički značajno više u odnosu na bolesnike bez PEX-a (73,5 ± 9,1 godina). Nađeno je da prevalencija PEX-a raste sa starenjem, od

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7,3% u sedmoj deceniji života do 27% kod starijih od 80 godina ($p < 0,001$). Učestalost pojedinih tipova katarakte kod bolesnika sa PEX-om bila je: maturna kod 40,7%, mešovita kod 30,5%, nuklearna kod 25,4%, kortikalna kod 1,7% i hipermaturna kod 1,7% bolesnika. Od 118 bolesnika sa PEX, 44 (37,2%) imalo je glaukom. Vrednosti IOP kod bolesnika sa PEX-om (bez glaukoma) bile su 17,8 ± 3,2 mmHg, što je statistički značajno više ($p = 0,000$) u odnosu na 15,8 ± 2,8 mmHg kod bolesnika bez PEX (bez glaukoma). Prevalencija koronarne bolesti bila je statistički značajno viša kod bolesnika sa PEX. **Zaključak**. PEX je čest kod bolesnika sa kataraktom u našoj populaciji. On predstavlja jedan od glavnih rizika od pojave glaukoma, udružen je sa ishemijskom bolešću srca, kao i intraoperativnim i postoperativnim problemima u hirurgiji katarakte.

Ključne reči:
eksfolijativni sindrom; katarakta; glaukom; prevalenca; koronarna bolest; intraoperativne komplikacije; postoperativne komplikacije.

Introduction

Pseudoexfoliation syndrome (PEX) is an age-related systemic degenerative disorder characterized by production and progressive accumulation of extracellular fibrillar eosinophilic material in the anterior segment of the eye. This material may be found in many ocular tissues including ciliary processes, zonules, anterior lens surface, pupillary margin, corneal endothelium, trabecular meshwork, and conjunctiva. Ocular PEX has been associated with the development of open- and closed-angle glaucoma and cataract with zonular instability [1–3]. It has already been reported that PEX syndrome is a major risk factor in modern extracapsular cataract surgery and phacoemulsification. The risk of intraoperative problems (such as a poorly dilating pupil) zonular weakness with or without lens instability, capsular break and vitreous loss) and postoperative complications (including fibrinoid reaction, posterior synechias, cell deposits and capsule contraction-phimosis) is higher in eyes with this syndrome [4–5]. Currently, PEX is regarded as a systemic disorder, since pseudoexfoliation material has also been identified in the skin and connective tissue portions of various visceral organs. In this regard, previous studies have shown a relationship between PEX and various systemic disorders, such as hypertension, coronary heart disease, stroke, abdominal aortic aneurysm, Alzheimer's disease, asymptomatic myocardial dysfunction, diabetes, and sensorineural hearing loss [6–16]. It is estimated that 60–70 million people worldwide are affected by PEX. The prevalence of PEX increases with age, but shows significant variations between geographical regions. In cataract surgery patients, the PEX prevalence ranges from 0.4% in Chinese to 39.3% in Ethiopian population [17–19]. To our knowledge, the prevalence of PEX in Serbian patients scheduled for cataract surgery has not yet been investigated. Therefore, the aim of our study was to evaluate several clinical aspects of PEX, such as frequency of PEX and pseudoexfoliation glaucoma (PEXG), intraocular pressure (IOP), the type of lens opacity, and the relationship of PEX and systemic diseases.

Methods

This retrospective study included 674 consecutive patients scheduled for cataract surgery (phacoemulsification) with intraocular lens implantation, in the Eye Clinic of Military Medical Academy (MMA) in Belgrade from January to Octobre 2011. The MMA as a 1200-bed tertiary care facility admits around 30,000 patients and performs about 30,000 surgical procedures (more than 4,000 in the Eye Clinic) and more than half a million specialist examinations each year.

All the patients were examined independently by two investigators, with the same instruments, in a dark examination room. A diagnosis of PEX was made after mydriasis with 1% tropicamid and 10% phenylephrine hydrochloride. Slitlamp examination was performed before and 30–40 min after the dilation of the pupils. Secondary cataracts related to trauma, uveitis and steroid use, congenital cataracts, and patients younger than 50 years of age were excluded from the study. Data were collected on the basis of an interview with the patient and from the records of patient files. The data included age, gender, history and duration of any eye and systemic disease, and use of ocular or systemic medications. The study included only the patients who had detailed internal diseases specialist examination in the last six months.

The patients had a comprehensive eye examination including visual acuity testing, refractive work-up, slit-lamp biomicroscopy before and after mydriasis, IOP measurement with Goldmann applanation tonometry, and fundus examination. Clinical diagnosis of PEX was made on the basis of the presence of typical fibrogranular pseudoexfoliation material on the anterior capsule surface and the pupillary margin (Figure 1–3). Pupil size was measured before and after dilation with a specially designed ruler under the same lighting conditions. In pseudophakic and aphakic fellow eyes pseudoexfoliation material was sought in locations other than the

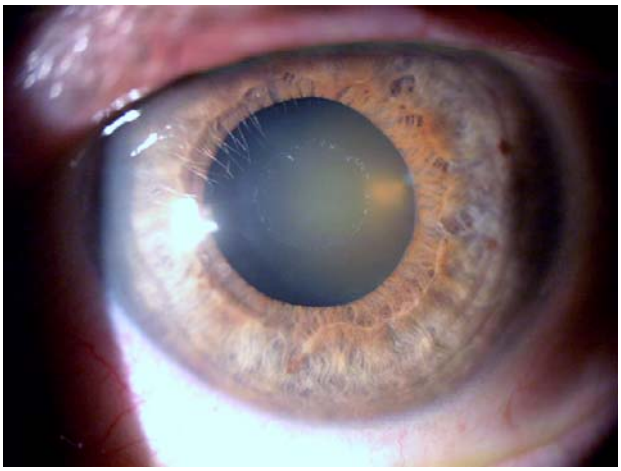

Fig. 1 – A 74-year-old woman with pseudoexfoliation of the anterior lens surface and poorly dilatated pupil.

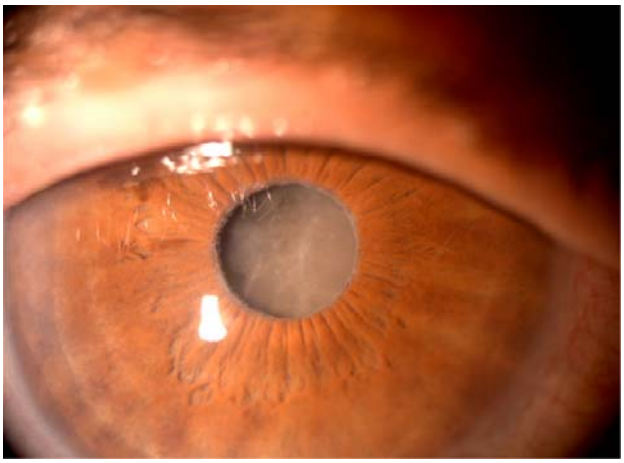

Fig. 2 – A 76-year-old woman with pseudoexfoliation on the pupillary margin and hard mature cataract.

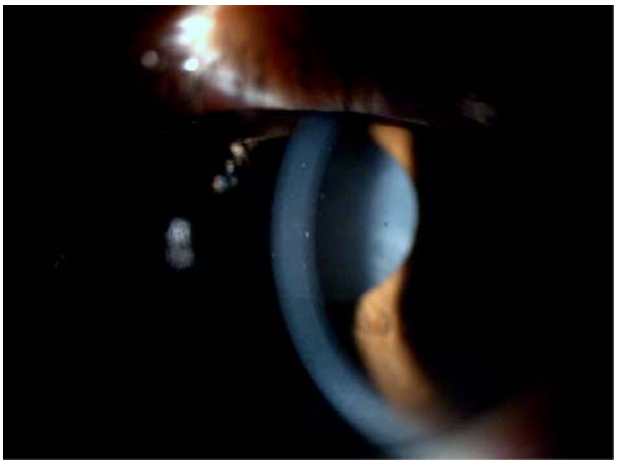

Fig. 3 – A 80-year-old man with pseudoexfoliation on the corneal endothelium.

lens. Other diagnostic features included endothelial pigmentation, loss of pupillary ruff, moth-eaten iris transillumination, Sampaoelesi line, and pigment deposition in the trabecular meshwork. Type of cataract was classified as nuclear, cortical, subcapsular, mixed-nonmature, mature, and hypermature based on slit-lamp biomicroscopy. Gonioscopy was performed only in those patients who had previously established glaucoma or patients who were suspected to have glaucoma based on raised IOP and suspicious optic nerve head findings. The diagnosis of glaucoma was made if the patient had a history of glaucoma surgery or was using glaucoma medication, when IOP was >21 mmHg with glaucomatous optic disc cupping, and visual field defects. Optic nerveheads were considered glaucomatous on biomicroscopical examination with the Volk (90D) lens in the presence of focal or generalized narrowing or disappearance of the neuroretinal rim with an enlarged amount of cupping or pallor. Ocular hypertension (OHT) was defined as IOP > 21 mmHg without optic nervehead changes or visual field defects. Study protocol was in adherence to the tenets of the Declaration of Helsinki.

χ^2 test was used to compare the qualitative variables and Student's *t*-test to compare the means of the continuous quantitative variables. *p*-values under 0.05 were taken to indicate a statistical significance.

Results

The mean age of the patients (318 or 47.2% male, 356 or 52.8% female) was 74.6 ± 8.9 years (range 50–92 years). The mean age of women was 74.7 ± 7.9 years and of men was 74.6 ± 9.8 years ($p > 0.05$). The overall prevalence of PEX syndrome was found to be 17.5% (118 patients). No statistically significant difference in PEX prevalence was found between men (45.8%) and women (54.2%), but a statistically significant difference was observed between the age groups ($p \leq 0.05$). The prevalence of PEX syndrome was found to increase with age, from 7.3% in the 7th decade of life to 27% in patients older than 80 years ($p < 0.001$). The most common cataract type in all the groups was nuclear 36.2%, followed by mixed and mature in 23.1% of the patients, posterior subcapsular in 11.3%, cortical in 5.9%, and hypermature in 0.3% of the patients. In the PEX patients the most comon cataract type was mature 40.7% (Figure 2) mixed 30.5%, nuclear 25.4%, cortical 1.7% and hypermature also 1.7% (Table 1). There was a high statistical diference between the type of cataract in the PEX and non-PEX patients ($p < 0.001$). The mean age of PEX patients (79.7 ± 6.1 years) was significantly higher when compared with all the subjects without PEX (73,5 ± 9,1 years) ($p = 0.000$). PEX was unilateral in 35.4% of the subjects and bilateral in 74.6%. The mean age of the bilateral PEX patients (81.5 ± 10.3 years) was significantly higler when compared with the unilateral PEX patients (74.2 ± 7.5 years). No subjects within 50–59 years age group had PEX at all, whereas 89.9% of the subjects with PEX were older than 70 (Table 2). The most common type of glaucoma was PEXG (6.5%), primary open angle glaucoma (POAG) (5.0%), angle closer glaucoma (2.4%), normal tension glaucoma (1.2%) and ocular hypertension (0.6%). Among the PEX patients 44 of 118 (37.2%) had glaucoma. In eyes scheduled for cataract surgery, IOP

Table 1

The estimated predominant type of cataract in patients with and without pseudoexfoliation syndrome (PEX) scheduled for cataract surgery

Type of cataract	PEX +*	PEX-**	Total	*p* value
Nuclear	30 (25.4)	214 (38.5)	244 (36.2)	> 0.05
Posterior subcapsular	0 (0)	76 (13.7)	76 (11.3)	< 0.05
Cortical	2 (1.7)	38 (6.8)	40 (5.9)	> 0.05
Mixed	36 (30.5)	120 (21.6)	156 (23.1)	> 0.05
Mature	48 (40.7)	108 (19.4)	156 (23.1)	< 0.001
Hypermature	2 (100)	0 (0)	2 (0.3)	< 0.05

Note: The results are expressed as n (%); *Patients with PEX; **Patients without PEX.

Table 2

Prevalence of pseudoexfoliation syndrome (PEX) according to ages, sex, and mean intraocular preasure (IOP)

Parameters	PEX +*	PEX-**	Total	*p* value
Mean age (years)	79.7 ± 6.1	73.5 ± 9.1	76.6 ± 8.9	< 0.001
Mean IOP (mmHg)	17.8 ± 3.2	15.8 ± 2.8		< 0.001
Sex				
male	54 (45.8)	264 (47.5)	318 (47.2)	> 0.05
female	64 (54.2)	292 (52.5)	356 (52.8)	> 0.05
Age groups (years)				
50–59	0 (0)	56 (10.1)	56 (8.3)	
60–69	8 (6.8)	102 (18.3)	110 (16.3)	
70–79	48 (40.7)	248 (44.6)	256 (43.9)	< 0.001
80–89	58 (49.2)	150 (27.0)	208 (30.9)	
> 90	4 (3.4)	0 (0.0)	4 (0.6)	

Note: The results are expressed as means ± SD or n (%); *Patients with PEX; **Patients without PEX.

was higher in eyes with PEX (but without glaucoma) than in those without PEX (17.8 ± 3.2 and 15.8 ± 2.8 mmHg, respectively; $p = 0.001$) (Table 2). The patients with PEX glaucoma had higher IOP compared with POAG patients, but there was no statistical significance (PEX 24.8 and POAG 23.2 mmHg, respectively; $p = 0.340$). The operative eyes with and without PEX did differ in pupil diameter before (3.7 ± 0.5 and 3.8 ± 0.4 mm, respectively; $p = 0.001$), and also after mydriasis (6.4 ± 0,7 and 7.5 ± 0.5 mm, respectively; $p = 0.000$). There was no stistically significant diference in the prevalence of arterial hypertension between the patients with and without PEX ($p = 0.641$). There was a stistically significant difference in the prevalence of ischemic heart disease between the patients with and without PEX ($p < 0.001$). Furthermore, in the patients with diabetes mellitus the prevalence of PEX was statistically significantly lower compared with the patients without PEX ($p < 0.030$). The group of patients with cerebrovascular disease included the patients who had sustaind one or more transient ischemic attacks and the patients with the history of stroke. There was no statistically significant difference in the prevalence of cerebrovascular disease between the patients with and those without PEX ($p = 0.239$) (Table 3).

Ethiopia [19], 42% in Sweden [20] and 16.4% in Turkey [8, 24]. This variationes depend on the examiner or other factors such as patients selection, the ethnic composition of the population, the clinical criteria for diagnosis, and the thoroughness of examination.

In the present study PEX syndrome was found in 17.5% of patients and there was an increase in the prevalence of PEX according to the age group, from 7.3% in the 60–69 years group up to 27.9% in the 80–89 years age group. Our results are comparable with earlier studies which have also shown that PEX is strongly age-dependent disorder, which seldom occurs before the age of 50 [8, 9, 18]. In the current study, patients with PEX were significantly older (79.7 ± 6.1 years) than patients without PEX (73.5 ± 9.1 years) ($p \leq 0.001$). This is in agreement with the results of previous reports, which found that the mean age of cataract patients with PEX was higher than those without PEX [3, 8, 10, 21]. In addition, we did not find any patient under 60 years of age with PEX, and we found only four patients with PEX in the 60–69 age group. Previous studies regarding the difference between the frequency and clinical significance of PEX in men and women are not consistent. Although Hietanen et al. [21] reported that PEX is more frequent in women, recent studies

Table 3

Associated systemic diseases in patietns with psudoexfoliation syndrome (PEX)

Systemic diseases	PEX group	Non PEX group	*p* value
Ischemic heart disease*	68 (57.6)	192 (34.5)	< 0.001
Hypertension	88 (74.6)	398 (71.6)	> 0.05
Diabetes mellitus	12 (10.2)	126 (22.7)	< 0.05
Cerebrovascular diseases	20 (17.0)	52 (8.4)	> 0.05
Heart arrhythmias	24 (20.4)	64 (10.6)	> 0.05

Note: The results are expressed as n (%); *angine pectoris and acute myocardial infarct.

Discussion

To our knowledge this is the first report on PEX among Serbian patients scheduled for cataract surgery. The reported frequency of PEX syndrome among candidates for cataract surgery varies extensively in different geographic regions even from place to place in the same country: 0.3% in Poland, 3% in France, 9% in North American Indians, 16% in Russia, 18% in Norway [20] 25.2% in Finland [21], 28% in Greece [9, 22], 28.7% in Spain [23], 35.4% in Estonia [18], 39.3% in including a larger number of PEX patients have reported opposite results [22, 23, 25]. Morover, Sekeroglu et al. [8] found no difference according to gender. Similarly, our results despite a higher number of women with PEX (54.2%) compared with men (45.8%), did not show a statistically significant difference between this two groups.

The most common cataract type in our PEX patients was mature cataract (40.7%) and nuclear cataract in non-PEX group (31.8%). In contrast, previous studies reported nuclear cataract as the most common type in PEX patients.

For instance, in the study by Kaljurand et Puska [18] nuclear sclerosis was predominated in eyes with PEX compared to those without PEX (57.6% and 36.9%, respectively). Reasons for this discrepancy might be explained by higher mean age of PEX patients in our study (79.7 ± 6.1 years) compared with previous studies (63.7 ± 10.5 in Ethiopia, 74.3 ± 7.0 in Turky and 77.1 ± 9.3 in Poland). Furthermore, the mean age of patints and consistently the most common cataract type in our study could be influenced by waiting lists for cataract surgery wich are among one and two years. The poor economic situation in Serbia could also partly explain higher percentage of mature cataracts in our patients.

The association between PEX and glaucoma is well established. In the eyes with PEX but without glaucoma, the mean IOP was higher than in the eyes without PEX and glaucoma. The reported prevalence of glaucoma in the PEX eyes has been found to vary in different populations: 7% in the United States [26], 7.5% in India [25], 13% in Iran [20], 13.3% in Ethiopia [19], 27.8% in Estonia [18], 28.8% in Crete [22], 30% in Norway [20], 32.1% in Turkey [8], 39.5% in Greece [9], 30% in Finland [21] and 37.2 % in our study. Our results are consistent with these findings. Moreover, PEX is the most common identifiable cause of open-angle glaucoma in the world [27]. The prevalence of PEX among patients with glaucoma has been reported as 1.4% in the United States [26], 26.7% in India [25], 30.5% in Turkey [8], 50% in Finland [21], 54.5% in Estonia [18], 60% in Norway [27], 75% in Sweden [10]. Consistent with previous reports, our results showed that PEXG represented 41.5% of all cases of glaucoma. Furthermore, in the PEX patients without glaucoma, the mean IOP was higher than in the non-PEX group wich is in agrement with previous studies [8–10, 18, 21]. On the basis of these findings, it could be assumed that PEX represents one of major risk factors for glaucoma development.

PEX is a systemic disorder of the extracellular matrix and exfoliation material has been found to be deposited in many organs of the body, including the heart, liver, lung, kidneys, and meninges [2, 4]. To date there are numerous studies regarding the association of ocular PEX syndrome and different systemic diseases. However, the results of the previous studies are not consistent. As elastin is a major component of the extracellular matrix of arterioles, PEX might be associated with vascular diseases [28]. Preliminary reports have suggested an association between PEX and transient ischemic attacks, stroke, heart disease, and cerebrovascular disease. However, our study did not find a stistically significant diference in the prevalence of arterial hypertension, cerebrovascular diseases, cardiac arrhythmias between patients with and without PEX [8–13]. Nevertheless, the prevalence of ischemic heart disease was statistically significantly higher in patients with PEX than in those without PEX. This finding might be explained by the fact that both PEX and ischemic heart disease occur more commonly in older patients. Earlier studies concerning the relationship between diabetes mellitus and PEX have shown that the incidence of PEX was significantly lower in diabetic compared to non-diabetic patients of similar age [29]. Consistently with these findings, our results showed the prevalence of diabetes mellitus in our PEX group was significantly lower than in non-PEX group. Other studies did not find a statisticaly significant difference of diabetes mellitus prevalence in PEX and non-PEX patients [8,12,30]. A possible explanation for differences in the prevalence of PEX in diabetic patients can be explained with geographical differences and environmental contributing factors in causing PEX.

One of the limitations of our study was its retrospective design. Furthermore the correlation of PEX syndrome and systemic disease in this study was evaluated only on the basis of information collected from medical records. In addition, a relatively small number of patients with PEX precludes generalized conclusions on the basis of the obtained results. Thus, further prospective studies are needed to assess the optimal prevalence of PEX syndrome and its association with systemic diseases.

Conclusion

On the basis of our results we could assume that PEX syndrome is a common problem among Serbian patients with age-related cataract. Moreover, it was shown that PEX syndrome is significantly associated with hypermature and mature cataract, reduced pupil dilatation, higher mean IOP, IOP of > 21 mmHg, glaucoma, and ischemic heart disease. Thus, in order to prevent potential ocular and systemic complications, patients who are candidates for cataract surgery should be thoroughly screened for PEX. However, many questions about PEX syndrome still remain obscure. Therefore, the true prevalence of PEX among the general population in Serbia, and its association with cataract, glaucoma and systemic dieases should be further studied through population-based surveys.

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Received on May 9, 2012.
Revised on December 8, 2012.
Accepted on June 21, 2013.
OnLine-First March, 2014.