

Association between Single Nucleotide Polymorphisms in Connective Tissue Genes and Obstetric Anal Sphincter Injury

Eyal Rom^{1,*}, Nada Danial-Farran², Hedi Benyamini Raischer³, Nitzan Dana Sela⁴, Jonia Alshiek^{3,4} and Raed Salim^{1,3,4}

¹Department of Obstetrics and Gynecology, Emek Medical Center, Afula, Israel

²The Genetic Institute, Emek Medical Center, Afula, Israel

³Department of Obstetrics and Gynecology, Holy Family Hospital, Nazareth, Israel

⁴Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

***Corresponding Author:** Eyal Rom, Department of Obstetrics and Gynecology, Emek Medical Center, Afula, Israel, Tel: +97249897434, E-mail: eyal_rom@hotmail.com

Received Date: January 01, 2026 **Accepted Date:** January 08, 2026 **Published Date:** January 10, 2026

Citation: Eyal Rom, Nada Danial-Farran, Hedi Benyamini Raischer, Nitzan Dana Sel, Jonia Alshiek, et al. (2026) Association between Single Nucleotide Polymorphisms in Connective Tissue Genes and Obstetric Anal Sphincter Injury. 13: 1-9

Abstract

Introduction and hypothesis: Obstetric anal sphincter injuries (OASIs), similarly to pelvic organ prolapse (POP), may result from mechanical forces on the same pelvic muscles and connective tissue. Family history is a known risk factor for both disorders, and associations between POP and single nucleotide polymorphisms (SNPs) have been reported. We aimed to examine the occurrence of a subset of known SNPs associated with POP among women with OASIs.

Methods: In a prospective case-control study conducted between October 2020 and December 2023, primiparous women with spontaneous vaginal delivery who experienced OASI were included. The control group did not experience OASI. After DNA extraction from both groups, ten SNPs previously associated with POP were selected, and their prevalence in each group was examined.

Results: The study cohort included 90 women: 30 and 60 in the study and control groups, respectively. Demographic and obstetric variables were similar between groups. No differences were observed in the frequency of each SNP or the overall SNP average between groups. A total of 19 (63.3%) women in the study group and 42 (70.0%) women in the control group were homozygous for one or more SNPs. The distribution of the ten SNP types, and the numbers of homozygous and heterozygous SNPs, did not differ by OASI severity.

Conclusions: In this novel study, we did not find an association between the ten examined SNPs and the occurrence of OASI.

Keywords: Obstetric Anal Sphincter Injuries; Single Nucleotide Polymorphisms

Introduction

Obstetric anal sphincter injuries (OASIs) are a severe complication of vaginal delivery that can lead to considerable morbidity and severely diminished quality of life in a substantial

0.1% and 34.9% among studies and countries, depending on the population number of women [1]. Despite surgical repair, a considerable number of women continue to experience some degree of anal incontinence that may lead to distressing and disabling complaints, and accompanying social and hygienic problems, isolation, lowered self-esteem, negative effects on sexual function, and diminished quality of life [1-4].

The prevalence of OASI varies between examined, parity, type of episiotomy used, and incidence of operative vaginal delivery [5-8]. Although most risk factors are associated with the mechanical forces encountered during vaginal birth, OASI is usually unpredictable and is currently unpreventable, because it is associated primarily with non-modifiable risk factors [9, 10].

A tendency toward OASI occurrence, unrelated to mechanical forces, had been reported within families. The Medical Birth Registry of Norway has reported that OASI risk increases if a woman's mother or sister experienced OASI during a vaginal birth [11], thus suggesting that a genetic tendency might predispose individuals to this complication. However, the genetic predisposition to OASI, if any, had not been investigated.

Pelvic organ prolapse (POP), a connective tissue disorder, has been associated with a subset of single-nucleotide polymorphisms (SNPs) in connective tissue genes [12-19]. OASI, similarly to POP, results from the same mechanical forces during vaginal birth on the same pelvic muscles and connective tissue, thereby potentially affecting the pelvic floor and leading to similar symptoms of anal incontinence. The hypothesis in this study was based on the assumption that the genetic variations in connective tissue identified in women with POP might also contribute to OASI development. Accordingly, we selected ten SNPs known to have the strongest associations with POP, prioritizing those located within genes involved in extracellular

matrix remodeling and connective tissue integrity. By examining the frequency of these specific variants among women who experienced OASI, we aimed to bridge the genetic gap between pelvic floor relaxation and acute birth trauma. Identifying these associations may improve OASI risk stratification prior to a trial of labor, potentially facilitating targeted prevention strategies in high-prevalence regions.

Material and Methods

This prospective case-control study was conducted at a university teaching hospital from October 2020 to December 2023. The institutional review board approved the trial protocol on August 31, 2020 (#0147-19-EMC). Informed consent was obtained from all participants in the study. The study was registered at ClinicalTrials.gov (identifier NCT04047433).

The study cohort included primiparous women with a vaginal delivery. The study group comprised women diagnosed with 3rd or 4th degree perineal tear (OASI) after a vaginal birth, whereas the control group comprised women who had a vaginal birth without OASI. The control group was matched to the study group by age and date of delivery in a 1:2 ratio. OASIs were diagnosed and graded according to a standardized classification of perineal lacerations [20] by a physician in the delivery ward. The diagnosis and grade of the tears were confirmed in all cases by a senior physician specializing in pelvic floor surgery or by an obstetrician specializing in suturing tears of this nature. The exclusion criteria included patients who were multiparous, had a known metabolic or connective-tissue disorder (e.g., Ehlers-Danlos syndrome), or had known neurologic disorders. Patients who underwent episiotomy or assisted vaginal delivery (e.g., vacuum or forceps delivery) were also excluded.

After delivery, peripheral blood samples (5 mL) were obtained from eligible cases and controls who agreed to participate and provided signed informed consent. All blood samples were transferred to the institutional genetic laboratory facility for DNA extraction and storage. DNA was extracted with a Qiagen kit according to the manufacturer's protocol and stored at a temperature of -20°C. The DNA samples were examined for ten SNPs in genes encod-

ing proteins associated with extracellular matrix structure. A pair of primers amplified approximately 250 base pairs including the SNP site of interest. Amplification of the products was performed with Sanger sequencing on an Applied Biosystems 3500 machine.

Demographic and obstetric variables and outcomes were collected from each patient records at admission, delivery, and discharge.

The primary outcome was the incidence of the selected SNPs among women diagnosed with OASI compared with those in the control group.

Sample Size Calculation

The sample size was calculated based on published data indicating a 60% SNP prevalence in women with POP compared to 30% in healthy controls [17]. To detect this specific 30% difference—representing a large genetic effect—with 80% power and a two-sided alpha of 0.05, a sample size of 93 women (1:2 ratio; 31 study, 62 control) was required. Consequently, this study was designed to identify substantial differences in genotype frequency rather than subtle genetic variations.

Statistical Analysis

The associations between the demographic variables and the two groups were tested via independent t-tests for continuous variables and the χ^2 test or Fisher's exact test in the case of small cell size for categorical variables. The associations of SNPs with OASI were tested at the allele and genotype levels, with the χ^2 test or Fisher's exact test in the case of small cell size. Genotype and allele frequencies in cases and controls were analyzed for associations with the χ^2 test on 2×2 and 2×3 contingency tables. The overall SNPs and the heterozygote and homozygote averages between groups were tested with independent t-tests. Tree analysis revealed no combinations of SNP types appearing more distinctly in the study group versus the control group. The associations among demographic variables, the ten types of SNPs, and the degree of OASI (3rd or 4th degree) were tested

with the χ^2 test or Fisher's exact test in the case of small cell size for categorical variables. Statistical analysis was performed in SPSS v. 27 software (IBM). The threshold for significance was set at $p < .05$ (two tailed).

Results

Overall, 93 eligible women provided informed consent to participate. Three were excluded from the final analysis because of logical issues. The final analysis included 30 and 60 women in the study and control groups, respectively.

Basic demographic, obstetric, and intrapartum variables are presented in Table 1. All variables were comparable between groups, except for neonatal birthweight, which was significantly higher in the study group than the control group ($p=0.007$).

The occurrence of SNPs in the study cohort is presented in Table 2. No significant differences in the frequencies of each SNP or the overall SNP average were observed between groups. Of the 90 women included, 61 (67.8%) were homozygous for one or more SNPs: 19 of the 30 women in the study group (63.3%) and 42 of 60 (70.0%) women in the control group. No significant differences were observed in the distribution of the number of homozygous SNPs between groups ($p=0.56$) or the average in each group (mean difference: -0.003, $p=0.83$). The women were heterozygous for zero to six SNPs, and no significant difference was observed in the average number of heterozygous SNPs between groups (mean difference: -0.023, $p=0.48$).

Tree analysis revealed that no combinations of SNP types appeared more prominently in the study group than the control group. Furthermore, the number of branches without a patient did not differ significantly between groups.

Of the 30 women with OASI, eight (26.7%) had 4th degree OASI. The distribution of the ten SNP types did not significantly differ according to tear severity. The distribution of homozygotes and heterozygotes was also not significantly different between groups.

Table 1: Maternal baseline characteristics of the study cohort

Characteristic	Study (N=30)	Control (N=60)	p value
Maternal age, years	25 (4)	26 (4)	0.13
Body mass index, kg/m ²	22.8 (4.5)	22.8 (5.2)	0.99
Gestational age at birth, weeks	39.2 (1.0)	39.1 (1.3)	0.63
Pregnancy number	1.1 (0.4)	1.2 (0.7)	0.36
Gestational diabetes mellitus	0	6 (10%)	0.17
Gestational hypertension	0	4 (6.6%)	0.3
Epidural analgesia	17 (56.6)	38 (63.3%)	0.65
Second stage length, min	87 (88)	61 (66)	0.12
Neonatal weight at birth, gr	3411 (388)	3170 (389)	0.007
Male sex	19 (63.3%)	28 (46.7%)	0.12
Data are presented as mean (standard deviation) or n (%)			
Characteristic	Study (N=30)	Control (N=60)	p value
Maternal age, years	25 (4)	26 (4)	0.13
Body mass index, kg/m ²	22.8 (4.5)	22.8 (5.2)	0.99
Gestational age at birth, weeks	39.2 (1.0)	39.1 (1.3)	0.63
Pregnancy number	1.1 (0.4)	1.2 (0.7)	0.36
Gestational diabetes mellitus	0	6 (10%)	0.17
Gestational hypertension	0	4 (6.6%)	0.3
Epidural analgesia	17 (56.6)	38 (63.3%)	0.65
Second stage length, min	87 (88)	61 (66)	0.12
Neonatal weight at birth, gr	3411 (388)	3170 (389)	0.007
Male sex	19 (63.3%)	28 (46.7%)	0.12
Data are presented as mean (standard deviation) or n (%)			

Table 2: Occurrence of single nucleotide polymorphisms in the study cohort

Gene (SNP number)	Genotype	Study	Control	p value	Odds ratio (95% CI)
		(n=30)	(n=60)		
Fibulin 5 (rs2018736)	AA (normal)	13 (43.3)	16 (26.7)	0.25 ^a	1.0 (reference)
	AC	14 (46.7)	34 (56.7)		0.5 (0.2–1.3)
	CC	3 (10)	10 (16.7)		0.3 (0.08–1.7)
Fibulin 5 (rs12589592)	GG (normal)	19 (63.3)	36 (60)	0.93 ^b	1.0 (reference)
	GA	10 (33.3)	20 (33.3)		0.9 (0.3–2.4)

	GG	1 (3.3)	4 (6.7)		0.4 (0.04–4.5)
ZFAT (rs1036819)	AA (normal)	24 (80)	46 (76.7)	0.90 ^b	1.0 (reference)
	AC	6 (20)	12 (20)		0.9 (0.3–2.8)
	CC	0	2 (3.3)		NA
Collagen 3 alpha 1 (rs1800255)	GG (normal)	15 (50)	30 (50)	0.43 ^b	1.0 (reference)
	GA	12 (40)	28 (46.7)		0.8 (0.3–2.1)
	AA	3 (10)	2 (3.3)		3 (0.4–19.9)
Collagen 3 alpha 1 (rs1801184)	GG (normal)	10 (33.3)	23 (38.3)	0.891	1.0 (reference)
	GA	17 (56.7)	31 (51.7)		1.2 (0.5–3.2)
	AA	3 (10)	6 (10)		1.1 (0.2–5.5)
MMP9 (rs17576)	AA (normal)	18 (60)	26 (43.3)	0.31 ^a	1.0 (reference)
	AG	9 (30)	24 (40)		0.5 (0.2–1.4)
	GG	3 (10)	10 (16.7)		0.4 (0.1–1.8)
MMP9 (rs3918253)	TT (normal)	5 (16.7)	18 (30)	0.30 ^a	1.0 (reference)
	TC	14 (46.7)	27 (45)		1.8 (0.5–6.1)
	CC	11 (36.7)	15 (25)		2.6 (0.8–9.3)
MMP10 (rs17435959)	GG (normal)	30 (100)	55 (91.7)	0.39 ^b	1.0 (reference)
	GC	0	4 (6.7)		NA
	CC	0	1 (1.7)		NA
Laminin gamma-1 (rs10911193)	CC (normal)	25 (83.3)	54 (90)	0.53 ^b	1.0 (reference)
	CT	5 (16.7)	5 (8.3)		2.1 (0.5–8.1)
	TT	0	1 (1.7)		NA
Laminin gamma-1 (rs10911241)	AA (normal)	26 (86.7)	52 (86.7)	1 ^b	1.0 (reference)
	AG	4 (13.3)	7 (11.7)		1.1 (0.3–4.2)
	GG	0	1 (1.7)		NA

Data are presented as n (%) or OR (95 CI) Chi square test Fisher's exact test first row, normal/heterozygote; second row, normal/homozygote ZFAT, Zinc-Finger gene in Autoimmune Thyroid disease; MMP; Matrix Metallo-Proteinase

Discussion

Herein, the incidence of known POP-associated SNPs in women who experienced OASI after a vaginal birth was comparable to that in a control without OASI. This find-

ing also applied to both the heterozygous state and the homozygous state. Additionally, the distribution of the ten SNP types did not differ according to OASI severity. Neonatal birthweight was higher among women who experienced OASIs than those who did not. This outcome was largely expected.

OASI is an unpredictable and unpreventable complication. To date, no evidence is available to counsel women regarding the probability of such an event before a trial of vaginal birth. Although understanding of a genetic basis

might improve counseling, the association between OASI and a specific genetic origin remains uncertain.

POP, similarly to OASI, occurs in the same anatomic region, and both disorders result from similar mechanical forces leading to symptoms associated with anal incontinence [21]. These aspects, combined with the known associations between several SNPs and POP, suggest that a similar genetic basis might underlie both disorders. Diminished elastin content and expression have been observed in vaginal and supportive pelvic tissues in women with POP [22–27]. Polymorphisms in matrix metalloproteinases (MMPs) genes, such as MMP-9 [28], have been associated with POP. Fibulin-5, an inhibitor of MMP-9 and a major contributor to elastic fiber assembly, has been reported to protect against POP in a murine model [29] but has been associated with POP among Russian women [30]. Elevated presence of polymorphisms in type 3 collagen has been reported among Dutch and Chinese women with POP [14,15], but not in a mixed Brazilian population [16]. Another polymorphism in type 3 collagen has been associated with elevated risk of POP among Korean women [17]. POP has also been associated with laminin, a glycoprotein in the extracellular matrix [18].

In the current study, we examined SNPs previously shown to have the strongest association with POP, but the findings did not support associations with OASI. Our findings might be simply explained by the absence of a genetic basis associated with OASI, despite prior reports of a familial relationship and suggestions of a possible genetic link [11]. Alternatively, although these SNPs were previously established to be associated with POP, they might have weaker effects on OASI. Because our study was specifically designed to detect only large genetic differences, it is possible that we did not identify more modest genetic effects that contribute to OASI risk in a multi-factorial manner. The interplay between genetic predisposition and mechanical birth forces suggests that while these specific SNPs do not show a large effect size here, they may still play a subtle role within a larger polygenic framework.

Additionally, we emphasize that the current study did not evaluate several additional SNP variants encoding extracellular matrix proteins, which might potentially be linked to OASIs. Finally, as previously described [14–16],

the absence of a relationship in one geographic region does not preclude a positive association in another region of the world.

Limitations

Our study has several limitations. We examined the ten most relevant SNPs. Because other POP-associated SNPs were not examined, possible associations cannot be ruled out. Additionally, we included only women with spontaneous vaginal deliveries. Women who had an episiotomy or operative vaginal birth were excluded, to lessen the influence of both factors on OASI occurrence; thus, the results might not be applicable to this group of women. Finally, because the study was conducted at a single facility, the results might not be generalizable. The lack of operative deliveries or episiotomies in our cohort, while reducing confounding variables, limits our ability to generalize these findings to all clinical settings. Furthermore, variations in obstetric practices and the specific ethnic makeup of our population may influence the prevalence of these SNPs, potentially affecting the reproducibility of this research in different geographic regions or healthcare systems.

Conclusion

OASI is influenced by a combination of mechanical factors during vaginal birth and obstetric practices (e.g., episiotomy and operative vaginal delivery). These environmental and procedural factors are likely to play a more direct role in OASI than POP, a condition that tends to develop in older women. Nonetheless, the absence of a difference in the incidence of SNPs examined between women with versus without OASI, does not necessarily and unambiguously rule out actual associations. The findings of this novel study may pave the way to future genetic research on OASI, such as searching for other related SNPs, or the use of other genetic technology, such as next-generation sequencing, to identify novel rare genetic variants that disrupt the normal function of extracellular components.

Acknowledgments

We thank Paula S. Herer, biostatistician, MSc., MPH, for statistical guidance and assistance, and Isabelle Espanioli for dedicated work in performing the genetic testing and analysis.

References

1. Sultan AH, Kamm MA, Hudson CN, Bartram CI (1994) Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair. *BMJ*. 308: 887-91.
2. Walter S, Hallböök O, Gotthard R, Bergmark M, Sjö-dahl R (2002) A population-based study on bowel habits in a Swedish community: prevalence of faecal incontinence and constipation. *Scand J Gastroenterol*. 37: 911-6.
3. Boreham MK, Richter HE, Kenton KS, Nager CW, Gregory WT, et al. (2005) Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. *Am J Obstet Gynecol*. 192: 1637-42.
4. Memon H, Handa VL (2012) Pelvic floor disorders following vaginal or cesarean delivery. *Curr Opin Obstet Gynecol*. 24: 349-54.
5. Cheng YW, Hopkins LM, Caughey AB (2004) How long is too long: Does a prolonged second stage of labor in nulliparous women affect maternal and neonatal outcomes? *Am J Obstet Gynecol*. 191: 933-8.
6. Räisänen S, Vehviläinen-Julkunen K, Gissler M, Heinonen S (2010) Up to seven-fold inter-hospital differences in obstetric anal sphincter injury rates: a birth register-based study in Finland. *BMC Res Notes*. 3: 345.
7. Zafran N, Salim R (2012) Impact of liberal use of mediolateral episiotomy on the incidence of obstetric anal sphincter tear. *Arch Gynecol Obstet*. 286: 591-7.
8. Salim R, Peretz H, Molnar R, Braverman M, Hatokay A, et al. (2014) Long-term outcome of obstetric anal sphincter injury repaired by experienced obstetricians. *Int J Gynaecol Obstet*. 126: 130-5.
9. Garmi G, Peretz H, Braverman M, Berkovich I, Molnar R, et al. (2016) Risk factors for obstetric anal sphincter injury: To prolong or to vacuum? *Midwifery*. 34: 178-2.
10. Pergialiotis V, Vlachos D, Protopapas A, Pappa K, Vlachos G, et al. (2014) Risk factors for severe perineal lacerations during childbirth. *Int J Gynaecol Obstet*. 125: 6-14.
11. Baghestan E, Irgens LM, Børdahl PE, Rasmussen S (2013) Familial risk of obstetric anal sphincter injuries: registry-based cohort study. *BJOG*. 120: 831-7.
12. Skorupski P, Król J, Starega J, Adamiak A, Jankiewicz K, et al. An alpha-1 chain of type I collagen Sp1-binding site polymorphism in women suffering from stress urinary incontinence. *Am J Obstet Gynecol*. 194: 346-50.
13. Skorupski P, Miotła P, Jankiewicz K, Rechberger T (2007) Polymorphism of the gene encoding alpha-1 chain of collagen type I and a risk of pelvic organ prolapse – a preliminary study. *Ginekol Pol*. 78: 852-5.
14. Kluivers KB, Dijkstra JR, Hendriks JC, Lince SL, Vierhout ME, et al. (2009) COL3A1 2209G>A is a predictor of pelvic organ prolapse. *Int Urogynecol J*. 20: 1113-8.
15. Chen HY, Chung YW, Lin WY, Wang JC, Tsai FJ, et al. (2008) Collagen type 3 alpha 1 polymorphism and risk of pelvic organ prolapse. *Int J Gynaecol Obstet*. 103: 55-8.
16. Martins KF, de Jármy-DiBella M (2011) Evaluation of demographic, clinical characteristics, and genetic polymorphism as risk factors for pelvic organ prolapse in Brazilian women. *Neurourol Urodyn*. 30: 1325-8.
17. Jeon MJ, Chung SM, Choi JR, Jung HJ, Kim SK, et al. (2009) The relationship between COL3A1 exon 31 polymorphism and pelvic organ prolapse. *J Urol*. 181: 1213-6.
18. Nikolova G, Lee H, Berkovitz S, Nelson S, Sinsheimer J, et al. (2007) Rodríguez LV. Sequence variant in the laminin gamma1 (LAMC1) gene associated with familial pelvic organ prolapse. *Hum Genet*. 120: 847-56.
19. Giri A, Wu JM, Ward RM, Hartmann K (2015) Genetic determinants of pelvic organ prolapse among African American and Hispanic women in the Women's Health Initiative. *PLoS One*. 10: e0141647.
20. Committee on Practice Bulletins-Obstetrics (2018) ACOG Practice Bulletin No. 198: Prevention and management of obstetric lacerations at vaginal delivery. *Obstet Gynecol*. 132: e87-102.
21. Heilbrun ME, Nygaard IE (2010) Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and

urinary incontinence in primiparous women. *Am J Obstet Gynecol.* 202; 488.e1-6.

22. Karam JA, Vazquez DV, Lin VK, Zimmern PE (2007) Elastin expression and elastic fibre width in the anterior vaginal wall of postmenopausal women with and without prolapse. *BJU Int.* 100: 346-50.

23. Goepel C (2008) Differential elastin and tenascin immunolabeling in the uterosacral ligaments in postmenopausal women with and without pelvic organ prolapse. *Acta Histochem.* 110: 204-9.

24. Ewies AA, Al-Azzawi F, Thompson J (2003) Changes in extracellular matrix proteins in the cardinal ligaments of post-menopausal women with or without prolapse: a computerized immunohistomorphometric analysis. *Hum Reprod.* 18: 2189-5.

25. Yamamoto K, Yamamoto M, Akazawa K, Tajima S, Wakimoto H, et al. (1997) Decrease in elastin gene expression and protein synthesis in fibroblasts derived from cardinal ligaments of patients with prolapsus uteri. *Cell Biol Int.*

21: 605-11.

26. Chen B, Wen Y, Polan ML (2004) Elastolytic activity in women with stress urinary incontinence and pelvic organ prolapse. *Neurourol Urodyn.* 23: 119-26.

27. Klutke J, Ji Q, Campeau J, Starcher B, Felix JC, et al. (2008) Decreased endopelvic fascia elastin content in uterine prolapse. *Acta Obstet Gynecol Scand.* 87: 111-5.

28. Wu JM, Visco AG, Grass EA, Craig DM, Fulton RG, et al. (2012) Matrix metalloproteinase-9 genetic polymorphisms and the risk for advanced pelvic organ prolapse. *Obstet Gynecol.* 120: 587-93.

29. Budatha M, Roshanravan S, Zheng Q, Weislander C, Chapman SL, et al. (2011) Extracellular matrix proteases contribute to progression of pelvic organ prolapse in mice and humans. *J Clin Invest.* 121: 2048-59.

30. Khadzhieva MB, Kamoeva SV (2014) Fibulin-5 (FBLN5) gene polymorphism is associated with pelvic organ prolapse. *Maturitas.* 78: 287-92.

Submit your manuscript to a JScholar journal and benefit from:

- ¶ Convenient online submission
- ¶ Rigorous peer review
- ¶ Immediate publication on acceptance
- ¶ Open access: articles freely available online
- ¶ High visibility within the field
- ¶ Better discount for your subsequent articles

Submit your manuscript at
<http://www.jscholaronline.org/submit-manuscript.php>