Original Research Paper

Volume-8 | Issue-5 | May-2018 | PRINT ISSN No 2249-555X

Gastroenterology

GASTROINTESTINAL SYMPTOMS AND QUALITY OF LIFE IN RENAL TRANSPLANT RECIPIENTS: A POST-HOC GENDER ANALYSIS OF THE CETRA (COMPLICATIONS RELATED TO GASTROENTERIC SYMPTOMS IN RENAL TRANSPLANT PATIENTS) STUDY

Delia Colombo	Patient Access, Novartis Farma S.p.A., Origgio (VA), Italy
Zagni Emanuela*	Patient Access, Novartis Farma S.p.A., Origgio (VA), Italy *Corresponding Author
Alessandra Ori	MediNeos Observational Research, Modena, Italy
Guido Basilisco	Gastroenterology Unit, IRCCS-Fondazione Policlinico, Mangiagalli, Regina Elena, Milano, Italy
Claudio Ponticelli	Past Director Nephrology and Dialysis Unit, Ospedale Maggiore, Milano, Italy

ABSTRACT The CETRA study assessed in renal transplant recipients the prevalence of gastrointestinal (GI) symptoms and their impact on quality of life (QoL). This post-hoc analysis evaluated gender differences in GI symptoms and QoL over 12 months after kidney transplantation. Symptom impact on QoL was assessed by GI QoL index. 857 patients were analyzed (64% males). At 12 months all symptoms were reported with higher frequency at self-assessment that in physicians' interviews. Physicians reported overall GI symptoms, dyspepsia, constipation, abdominal pain and gastro-esophageal reflux in significantly more women, while at self-assessment men reported significantly more diarrhea and women more constipation. Postmenopausal women had also significantly more dyspepsia. The impact of GI symptoms on QoL was slightly higher in women, but with no statistical or clinical significance. Sex hormone influence on peripheral and central regulatory mechanisms of the brain-gut axis may have a role in the observed gender differences.

KEYWORDS : kidney transplantation, gender differences, gastrointestinal symptoms, quality of life.

Introduction

Gastrointestinal (GI) complications are frequent in renal transplantation recipients, possibly involving any segment of the digestive tract [1,2]; causes may include stress, pre-existing GI disorders, infections or immunosuppressive treatment [1-3].

The CETRA (Complications related to gastroEnteric symptoms in renal TRAnsplant patients) study assessed patient- and physician-reported prevalence of GI symptoms and their impact on quality of life (QoL) in over 1000 Italian kidney transplant recipients with stable graft function and without underlying diseases that could cause GI symptoms [4]. The results showed that GI symptoms in the patients' perspective occurred in almost 90% of stable renal transplant recipients, with a significant impact on QoL), whereas physicians significantly underestimated the occurrence of GI problems in their patients. No significant association between the presence of GI symptoms and a specific immunosuppressant regimen was found.

Despite the recognized importance of considering gender in evaluating clinical manifestations of diseases and treatment effects [5-8], little is known about gender differences in renal transplantation outcomes, especially in terms of GI complications. It has only been reported that female sex is a major factor associated with increased risk of unspecified non-infectious post-transplant diarrhea [9].

Much more evidence has been accumulated about gender differences in GI symptoms and disorders in the general population. Gender differences have been reported in the prevalence of symptoms of functional GI disorders [10] and upper GI symptoms [11]. Twice as many women than men are affected by irritable bowel syndrome (IBS) in developed countries, and sex hormone-dependent mechanisms have been hypothesized [12]. Moreover, among IBS patients, women experience more psychological and somatic symptoms than men [13]. In patients with gastro-esophageal reflux disease, females were reported to have more frequent/intense heartburn and extra-esophageal symptoms and more frequent episodes of abdominal pain, indigestion and constipation than men [14]. In kidney transplant recipients, female gender was one factor associated with increased incidence of *Clostridium difficile* colitis [15]. Data about gender differences in QoL in kidney transplant recipients are scarce. A study of QoL following kidney transplant in end-stage renal disease found a significant improvement in all QoL parameters, with no gender differences [16]. Another study evaluating the correlation between sexual function and QoL after renal transplantation showed that quality and frequency of sexual intercourse had a greater impact on QoL in men than in women [17].

Identifying aspects of life that remain impaired after kidney transplantation may help in the development of interventions aimed at improving patients' QoL. Therefore we performed this post-hoc gender analysis of the CETRA study, aimed at describing the prevalence of GI symptoms and QoL during 12-month after kidney transplantation.

Patients and methods

The CETRA study had enrolled 1,130 adult kidney transplant recipients of either gender (63.5% men), with their allograft functioning for >6 months and stable serum creatinine level <2.5 mg/dl [4], excluding patients with a history of severe GI complications before transplantation. Patients and methods of the CETRA study are reported in detail elsewhere [4]. Patients who had completed the 12-month follow-up visit within 9.5-14.5 months from basal visit and had the evaluation of GI symptoms (by physician and self-assessment) available at study visits were included in this analysis.

Presence or absence of GI symptoms had been assessed at each study visit by physicians using the GSRS [18,19], a 15-question scale assessing the pattern and severity of the following GI symptom domains: abdominal pain, reflux syndrome, diarrhea, indigestion syndrome and constipation. Presence of GI symptoms by physicians' evaluation was based on the affirmative answer of the patients to the question whether each single symptom was present or not in the last week before the control visit. Presence of GI symptoms by patients' self-assessment was based on a score >1 assigned for the level of discomfort for each symptom in a self-administered questionnaire.

The impact of GI symptoms on patients' QoL had been assessed at each study visit by means of the GIQLI, a 0-4 scale including 36 items grouped in five domains: GI symptoms, emotion, physical function, social function, and medical treatment [20]. A higher score indicated better QoL. Ongoing therapies were recorded at each study visit: medications for GI complications (antacids, nonsteroidal anti-inflammatory drugs, bile acid sequestrants) and type of immunosuppressive regimen (azathioprine, cyclosporine, mycophenolate sodium, mycophenolate mofetil, everolimus, sirolimus, tacrolimus, corticosteroids). To evaluate the impact of menopause on prevalence of GI symptoms and on QoL, since menopausal status had not been recorded in the CETRA study, it was estimated that women >50 years were post-menopausal.

Baseline socio-demographic and clinical features are described by gender. Continuous variables are presented as mean ± SD, and qualitative variables as absolute and relative frequencies. The

prevalence of GI symptoms (according to patient's and physician's point of view) was assessed at each study visit as number of patients affected by each symptom over the total number of patients included in the analysis at study visit. Comparisons between women and men were performed by Student's t-test (for continuous variables), χ^2 test or Fisher's exact test (for categorical ones). As post-hoc analysis, the significance threshold was set at 0.05 (all p-values presented are exploratory). Patients with missing data in selected parameters were not excluded from analysis but were simply not evaluated for these parameters.

Results

The patients evaluable for this analysis were 857, 64% males. Patients' demographics and baseline clinical characteristics are summarized in **Table 1**. Men and women had similar mean age, and 53% of women compared to 48% of men had <50 years. No significant gender differences in duration of dialysis, years since transplantation and frequency of rejection episodes before basal visits were recorded. No significant gender differences were observed in baseline medications, either immunosuppressive or non-immunosuppressive. The overall number of daily pills was also similar in men and women.

At baseline, no differences in GI symptoms were reported by physicians, whereas at the self-assessment questionnaire a significantly higher percentage of women complained abdominal pain/dyspepsia. At 12 months, physicians recorded a higher prevalence in women than in males of overall GI symptoms (33.0% vs 26.6%; Chi-square p =0.0484), and specifically of constipation, abdominal pain, dyspepsia, and reflux (**Table 2**). At the GSRS questionnaire, all GI symptoms in both genders were reported much more frequently than in the physicians' interview; at 12 months, significantly more diarrhea was reported by men, while significantly more constipation was reported by women (**Table 2**). At the 12-month final visit, post-menopausal women (aged ≥50) reported to physicians significantly less diarrhea (2.1% vs 8.4%; p = 0.0103), but significantly more dyspepsia (4.8% vs 1.0%; p = 0.0353) than men ≥50 years. Gender differences in both physician-recorded and self-reported symptoms in the <50-year group substantially mirrored those observed in the overall population.

QoL at baseline was slightly better in men than in women in terms of total score and emotional status, physical, and social function, but the difference was not statistically significant (except physical function); at 12 months, slight, non-significant differences remained for GIQLI total score, emotional status and social function domains (**Table 3**). Very similar results were also obtained among patients <50 years, whereas in the ≥50-year group there were no differences at all.

Discussion

Based on clinical history recorded by physicians, overall GI symptoms at 12 months were significantly more frequent in women than men. Interestingly, at the patients' self-evaluation, all GI symptoms were reported with much higher frequency than in the physicians' interview and this may be due to a greater freedom felt by patients in reporting symptoms in a self-administered questionnaire than to a doctor and/or to physician's underestimation of patients' symptoms. Gender differences were also quite different at the self-assessment questionnaire. At 12 months, gender differences emerged in bowel function, with men reporting significantly more diarrhea and women reporting significantly more constipation. Females are more commonly affected by constipation than males [21,22], possibly due to the influence of sex hormones on peripheral and central regulatory mechanisms of the brain-gut axis, that may contribute to the alterations in visceral sensitivity, motility, intestinal barrier function, and to the immune activation of intestinal mucosa. Gender differences have also been reported in stress response of the hypothalamic-pituitary-adrenal axis [23-28]. Also in postmenopausal women, altered bowel function and laxative usage have been reported to be rather common [29]. Conversely, we are not aware of a major prevalence of diarrhea in the male general population. A paper by Herman et al reported that, among subjects with IBS, diarrhea was predominant among men, while constipation was predominant in women [22]. In our study, the female population aged >50 years, presumably prevalently composed by post-menopausal women, had again significantly less diarrhea than age-matched men, but significantly more dyspepsia. As with other functional GI disorders, some gender-specific features have been reported in "functional" dyspepsia, a heterogeneous disorder characterized by relapsing and remitting symptoms, that seems to be of greater concern in women [30]. Specifically, gender-related differences have been observed in both the prevalence of individual dyspepsia symptoms, and in gastric emptying and proximal gastric motor function. The impact of GI symptoms on QoL was lower in men than women both at baseline and after 12 months, in terms of overall score and specific domains, such as emotional status and social function, but the difference between genders did not reach statistical significance. Differences in the ways male and female patients cope with their illness were previously reported, though in a different disease setting, i.e. following cardiac surgery [31]. Denial was significantly more common among men, while women showed more dysphoria, anxiety, and depression. These findings seem to be rather consistent with our observation of a slightly greater impact of clinical GI symptoms on women's compared to men's QoL. However, the importance to recognize the minimal clinically important difference in health-related QoL (in GI QoL in particular) has been discussed in the literature [32-36].

GI symptoms in renal transplant recipients are thought to be possibly related not only to stress, infections and/or exacerbation of pre-existing gastrointestinal pathology, but also to potential GI side effects of immunosuppressive treatments. Women are generally more prone to suffer from side effects of medication [8,37]. However, CNIs and mycophenolates are based on plasma levels and are thus related, at the same bioavailability, to the weight of the individual. This might reduce the risk of a different side effect profile between genders.

Our study has some limitations. The study had not been designed for a between-gender comparison, therefore the sample size had not been calculated to detect gender differences and genders were not properly balanced. Some data (such as therapies) were collected retrospectively; however, prevalence of GI symptoms and QoL were assessed prospectively for 12 months. Lastly, major outcome measures are based on subjective evaluations; however, this is consistent with the focus of this analysis on patients' symptoms and QoL.

In conclusion, some statistically significant and clinically relevant gender differences in bowel and digestive function emerged among kidney transplant recipients. The influence of sex hormones on peripheral and central regulatory mechanisms of the brain-gut and the hypothalamic-pituitary-adrenal axes may account for such differences. Whereas females have been often reported to be more prone to develop drug side effects [8,37], in this clinical setting, the patient's tailored immunosuppressant dosage may explain the reduced gender differences.

Table 1 – Patients' demographics and clinical characteristics

	Males		Females	
Age	49.6 ±12.2	n=548	48.1 ± 11.6	n=309
<50 years	261, 47.6		163, 52.8	
≥50 years	287, 52.4		146, 47.2	
Years on dialysis prior to transplant	3.6 ±3.7	n=494	3.4 ±3.2	n=281
Years since transplant	5.7 ±5.2	n=548	6.1 ±5.7	n=309
Rejection phenomena	108, 20.3		47, 14.6	
Serum creatinine (mg/dl)	1.5 ± 0.4	n=475	1.3 ± 0.4	n=279
Creatinine clearance (ml/min)	62.9 ± 20.2	n=473	55.9 ±19.2	n=276
Serum blood urea nitrogen (mg/dl)	59.2 ± 26.1	n=454	52.6 ±26.7	n=249
Serum albumin (mg/dl)	4.3 ± 0.4	n=309	4.2 ±0.4	n=244
Serum glucose (mg/dl)	95.2 ± 25.2	n=452	94.1 ± 26.2	n=247
Hemoglobin (g/dl)	13.6 ± 1.6	n=513	12.5 ±1.4	n=291

Continuous variables are reported as mean ± standard deviation; categorical variables as relative and absolute frequencies.

Percentages computed out of patients without missing answers.
All comparisons between males and females were non-significant (p-value>alpha=0.05).

Table 2 – Prevalence of gastrointestinal symptoms as reported by physician's interview

	Physician's interview				Patients' self-administered GSRS			
	Baseline		12-month visit		Baseline		12-month visit	
	Males n=548	Females n=309	Males n=548	Females n=309	Males n=548	Females n=309	Males n=548	Females n=309
Overall GI symptoms°	202 (36.9)	125 (40.5)	**146 (26.6)**	**102 (33.0)***	485 (88.5)	273 (88.3)	446 (81.4)	254 (82.2)
of moderate to high intensity°°					195 (35.6)	118 (38.2)	142 (25.9)	89 (28.8)
Diarrhea	76 (13.9)	39 (12.6)	44 (8.0)	14 (4.5)	206 (37.6)	110 (35.6)	**226 (41.2)**	**101 (32.7) ***
Abdominal distension	133 (24.3)	78 (25.2)	97 (17.7)	60 (19.4)				
Indigestion syndrome					439 (80.1)	233 (75.4)	413 (74.4)	220 (71.2)
Constipation	61 (11.1)	45 (14.6)	**46 (8.4)**	**45 (14.6)****	286 (52.2)	165 (53.4)	**254 (46.4)**	**165 (53.4) ***
Abdominal pain	44 (8.0)	34 (11.0)	**25 (4.6)**	**27 (8.7)***	**291 (53.1)**	**202 (65.4)** §	277 (50.5)	175 (56.6)
Dyspepsia	27 (4.9)	22 (7.1)	**9 (1.6)**	**22 (7.1)** §				
Gastro-esophageal reflux	59 (10.8)	45 (14.6)	**33 (6.0)**	**33 (10.7)***	160 (29.2)	103 (33.3)	183 (33.4)	118 (38.2)

Chi-square test patients with GI symptoms (overall and domains) based on physicians' interview or patients' self-administered GSRS (males vs females) was performed.

* Prob < 0.05; ** Prob < 0.01; § Prob < 0.001

In physician's interview diarrhea includes increased passage of stools, loose stools, bowel urgency; abdominal distension includes borborygmi, abdominal distension, eructation, increased flatulence; indigestion domain includes rumbling, bloating, belching, and breaking wind; constipation includes reduced passage of stools, hard stools, incomplete bowel emptying; abdominal pain includes abdominal pain/discomfort; dyspepsia includes epigastrial discomfort, nausea and vomiting; gastro-esophageal reflux includes heartburn and acid regurgitation.

In patients' assessment diarrhea domain includes diarrhea, loose stools, and urgent need to have a bowel movement; indigestion domain includes rumbling, bloating, belching, and breaking wind; constipation domain includes constipation, hard stools, and sensation of not completely emptying the bowels; abdominal pain/dyspepsia domain includes pain or discomfort in your upper abdomen or the pit of your stomach, hunger pain, nausea; reflux domain includes heartburn and acid reflux.

Categorical variables are reported as relative and absolute frequencies.
°In patients' assessment, GI symptoms were considered present in all patients having scored at least one item >1 at the GSRS questionnaire.

°°In patients' assessment, symptoms were considered of moderate to high intensity when scored ≥ 4 at the GSRS questionnaire.

Table 3 - Impact of GI symptoms on male and female patients' QoL, as measured by GIQLI

Domain	**Baseline**		**12-month visit**	
	Males n = 480	Females n= 264	Males n = 508	Females n = 277
GIQLI total score	124.4 ± 17.0	122.5 ± 17.8	125.2 ± 16.2	122.9 ± 17.9
GI symptom domain	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5
Emotional status domain	3.3 ± 0.7	3.2 ± 0.7	3.4 ± 0.6	3.3 ± 0.7
Physical function	**3.4 ± 0.6**	**3.3 ± 0.7***	3.4 ± 0.5	3.4 ± 0.6
Social function	3.6 ± 0.6	3.5 ± 0.6	3.4 ± 0.8	3.3 ± 0.8
Medical treatment	3.8 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	3.7 ± 0.5

T-test males vs females was performed.
* Prob < 0.05.
Results are presented as mean ± SD.

Acknowledgements

The study was supported by a grant from Novartis Farma S.p.A., Origgio (VA), Italy. The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all aspects of manuscript development. We are grateful to Renata Perego and Sara Rizzoli for helping in writing the manuscript.

References

1. Helderman JH, Goral S. Gastrointestinal complications of transplant immuno suppression. J Am Soc Nephrol. 2002;13:277-287.
2. Ponticelli C, Passerini P. Gastrointestinal complications in renal transplant recipients. Transpl Int. 2005;18:643-650.
3. Sarkio S, Halme L, Kyllonen L, Salmela K. Severe gastrointestinal complications after 1,515 adult kidney transplantations. Transpl Int. 2004;17:505-510.
4. Ponticelli C, Colombo D, Novara M, Basilisco G; CETRA Study Group. Gastrointestinal symptoms impair quality of life in Italian renal transplant recipients but are under-recognized by physicians. Transpl Int. 2010;23(11):1126-1134.
5. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44:499–523.
6. Schwartz JB. The influence of sex on pharmacokinetics. Clin Pharmacokinet. 2003;42(2):107–121.
7. Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. J Womens Health (Larchmt). 2005;14(1):19–29.
8. Franconi F, Campesi I, Occhioni S, Antonini P, Murphy MF. Sex and gender in adverse drug events, addiction, and placebo. Handb Exp Pharmacol. 2012;(214):107-126.
9. Bunnapradist S, Neri L, Wong W, et al. Incidence and risk factors for diarrhea following kidney transplantation and association with graft loss and mortality. Am J Kidney Dis. 2008;51(3):478-486.
10. Schmulson M, Adeyemo M, Gutiérrez-Reyes G, et al. Differences in gastrointestinal symptoms according to gender in Rome II positive IBS and dyspepsia in a Latin American population. Am J Gastroenterol. 2010;105(4):925-932.
11. Haag S, Andrews JM, Gapasin J, Gerken G, Keller A, Holtmann GJ. A 13-nation population survey of upper gastrointestinal symptoms: prevalence of symptoms and socioeconomic factors. Aliment Pharmacol Ther. 2011;33(6):722-729.
12. Meleine M, Matricon J. Gender-related differences in irritable bowel syndrome: potential mechanisms of sex hormones. World J Gastroenterol. 2014;20(22):6725-6743.
13. Cain KC, Jarrett ME, Burr RL, Rosen S, Hertig VL, Heitkemper MM. Gender differences in gastrointestinal, psychological, and somatic symptoms in irritable bowel syndrome. Dig Dis Sci. 2009;54(7):1542-1549.
14. Vakil N, Niklasson A, Denison H, Rydén A. Gender differences in symptoms in partial responders to proton pump inhibitors for gastro-oesophageal reflux disease. United European Gastroenterol J. 2015;3(5):443-452.
15. Helderman JH, Goral S. Gastrointestinal complications of transplant immunosuppression. J Am Soc Nephrol. 2002;13(1):277-287.
16. Das RC, Srivastava K, Tudu J, Hooda AK. Cross-sectional study of quality of life after renal transplant in end stage renal disease. Ind Psychiatry J. 2014;23(1):40–43.
17. Tavallaii SA, Fathi-Ashtiani A, Nasiri M, Assari S, Maleki P, Einollahi B. Correlation between sexual function and postrenal transplant quality of life: does gender matter? J Sex Med. 2007;4(6):1610-1618.
18. Kleinman L, Kilburg A, Machnicki G, et al. Using GI-specific patient outcome measures in renal transplant patients: validation of the GSRS and GIQLI. Qual Life Res. 2006;15:1223-1232.
19. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? Scand J Gastroenterol. 1993;28:681-687.
20. Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg. 1995;82:216-222.
21. Gonenne J, Esfandyari T, Camilleri M, et al. Effect of female sex hormone supplementation and withdrawal on gastrointestinal and colonic transit in postmenopausal women. Neurogastroenterol Motil. 2006;18(10):911-918.

22. Herman J, Pokkunuri V, Braham L, Pimentel M. Gender distribution in irritable bowel syndrome is proportional to the severity of constipation relative to diarrhea. Gend Med. 2010;7(3):240-246.
23. Mulak A, Taché Y, Larauche M. Sex hormones in the modulation of irritable bowel syndrome. World J Gastroenterol. 2014;20(10):2433-2448.
24. Larauche M, Mulak A, Taché Y. Stress and visceral pain: from animal models to clinical therapies. Exp Neurol. 2012;233:49-67.
25. Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. Med Sci Monit. 2004;10:RA55-RA62.
26. Rybaczyk LA, Bashaw MJ, Pathak DR, Moody SM, Gilders RM, Holzschu DL. An overlooked connection: serotonergic mediation of estrogen-related physiology and pathology. BMC Womens Health. 2005;5:12.
27. Taché Y, Bonaz B. Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. J Clin Invest. 2007;117:33-40.
28. Cremon C, Gargano L, Morselli-Labate AM, et al. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. Am J Gastroenterol. 2009;104:392-400.
29. Triadafilopoulos G, Finlayson M, Grellet C. Bowel dysfunction in postmenopausal women. Women Health. 1998;27(4):55-66.
30. Flier SN, Rose S. Is functional dyspepsia of particular concern in women? A review of gender differences in epidemiology, pathophysiologic mechanisms, clinical presentation, and management. Am J Gastroenterol. 2006;101(12 Suppl):S644-653.
31. Modica M, Ferratini M, Spezzaferri R, De Maria R, Previtali E, Castiglioni P. Gender differences in illness behavior after cardiac surgery. J Cardiopulm Rehabil Prev. 2014;34(2):123-129.
32. Shi HY, Lee KT, Lee HH, et al. The minimal clinically important difference in the Gastrointestinal Quality-of-Life Index after cholecystectomy. Surg Endosc. 2009;23(12):2708-2712.
33. Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. Spine J. 2007;7:541–546.
34. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr Opin Rheumatol. 2002;14:109–114.
35. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol. 2003;56:395–407.
36. Hays RD, Farivar SS, Liu H. Approaches and recommendations for estimating minimally important differences for health-related quality-of-life measures. COPD 2005;2:63–67.
37. Miller MA. Gender-based differences in the toxicity of pharmaceuticals - the Food and Drug Administration's perspective. Int J Toxicol. 2001;20(3):149-152.