

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 May 14; 23(18): 3195-3378



### EDITORIAL

- 3195 Liver transplantation for intermediate hepatocellular carcinoma: An adaptive approach

*Biolato M, Marrone G, Miele L, Gasbarrini A, Grieco A*

- 3205 Immune response to vaccines in children with celiac disease

*Anania C, Olivero F, Spagnolo A, Chiesa C, Pacifico L*

### REVIEW

- 3214 Inflammatory bowel disease in liver transplanted patients

*Filipec Kanizaj T, Mijic M*

- 3228 Platelets in liver disease, cancer and regeneration

*Kurokawa T, Ohkohchi N*

### ORIGINAL ARTICLE

#### Basic Study

- 3240 Thiopurine use associated with reduced B and natural killer cells in inflammatory bowel disease

*Lord JD, Shows DM*

- 3252 Hepatitis B virus X protein induces hepatic stem cell-like features in hepatocellular carcinoma by activating KDM5B

*Wang X, Oishi N, Shimakami T, Yamashita T, Honda M, Murakami S, Kaneko S*

- 3262 Artificial liver support in pigs with acetaminophen-induced acute liver failure

*He GL, Feng L, Cai L, Zhou CJ, Cheng Y, Jiang ZS, Pan MX, Gao Y*

- 3269 Effects of sleeve gastrectomy plus trunk vagotomy compared with sleeve gastrectomy on glucose metabolism in diabetic rats

*Liu T, Zhong MW, Liu Y, Huang X, Cheng YG, Wang KX, Liu SZ, Hu SY*

- 3279 Wall shear stress in portal vein of cirrhotic patients with portal hypertension

*Wei W, Pu YS, Wang XK, Jiang A, Zhou R, Li Y, Zhang QJ, Wei YJ, Chen B, Li ZF*

#### Case Control Study

- 3287 Risk of progression of Barrett's esophagus in patients with cirrhosis

*Apfel T, Lopez R, Sanaka MR, Thota PN*

**Retrospective Study**

- 3295** Clinical significance of hypoechoic submandibular gland lesions in type 1 autoimmune pancreatitis  
*Takano S, Fukasawa M, Kadokura M, Shindo H, Takahashi E, Hirose S, Fukasawa Y, Kawakami S, Sato T, Enomoto N*
- 3301** Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma  
*Jung JH, Lee HJ, Lee HS, Jo JH, Cho IR, Chung MJ, Park JY, Park SW, Song SY, Bang S*
- 3309** Ling classification describes endoscopic progressive process of achalasia and successful peroral endoscopy myotomy prevents endoscopic progression of achalasia  
*Zhang WG, Linghu EQ, Chai NL, Li HK*

**Observational Study**

- 3315** Disruptive behavior in the workplace: Challenges for gastroenterology fellows  
*Srisarajivakul N, Lucero C, Wang XJ, Poles M, Gillespie C, Zabar S, Weinshel E, Malter L*
- 3322** Correlation of endoscopic disease severity with pediatric ulcerative colitis activity index score in children and young adults with ulcerative colitis  
*Kerur B, Litman HJ, Stern JB, Weber S, Lightdale JR, Rufo PA, Bousvaros A*
- 3330** Stress and sleep quality in doctors working on-call shifts are associated with functional gastrointestinal disorders  
*Lim SK, Yoo SJ, Koo DL, Park CA, Ryu HJ, Jung YJ, Jeong JB, Kim BG, Lee KL, Koh SJ*

**Prospective Study**

- 3338** *In vivo* and *ex vivo* confocal endomicroscopy of pancreatic cystic lesions: A prospective study  
*Krishna SG, Modi RM, Kamboj AK, Swanson BJ, Hart PA, Dillhoff ME, Manilchuk A, Schmidt CR, Conwell DL*
- 3349** Chronological age when healthcare transition skills are mastered in adolescents/young adults with inflammatory bowel disease  
*Stollon N, Zhong Y, Ferris M, Bhansali S, Pitts B, Rak E, Kelly M, Kim S, van Tilburg MAL*

**Randomized Controlled Trial**

- 3356** Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease  
*Pedersen N, Ankersen DV, Felding M, Wachmann H, Végh Z, Molzen L, Burisch J, Andersen JR, Munkholm P*

**EVIDENCE-BASED MEDICINE**

- 3367** Antimicrobial susceptibility testing before first-line treatment for *Helicobacter pylori* infection in patients with dual or triple antibiotic resistance  
*Cosme A, Montes M, Ibarra B, Tamayo E, Alonso H, Mendarte U, Lizasoan J, Herreros-Villanueva M, Bujanda L*

**CASE REPORT**

3374 Severe esophageal injury after radiofrequency ablation - a deadly complication

*Katz-Agranov N, Nevah Rubin MI*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Ballarin Roberto, PhD, Assistant Professor, Doctor, Surgeon, Hepatobiliarypancreatic Oncologic Surgery and Liver Transplant Center, University of Modena, Modena 41100, Italy

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. The 2015 edition of Journal Citation Reports<sup>®</sup> released by Thomson Reuters (ISI) cites the 2015 impact factor for *WJG* as 2.787 (5-year impact factor: 2.848), ranking *WJG* as 38 among 78 journals in gastroenterology and hepatology (quartile in category Q2).

**FLYLEAF**

**I-IX** Editorial Board

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** *Xiang Li*  
**Responsible Electronic Editor:** *Cui-Hong Wang*  
**Proofing Editor-in-Chief:** *Lian-Sheng Ma*  
**Responsible Science Editor:** *Yuan Qi*  
**Proofing Editorial Office Director:** *Jin-Lei Wang*

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
 ISSN 1007-9327 (print)  
 ISSN 2219-2840 (online)

**LAUNCH DATE**  
 October 1, 1995

**FREQUENCY**  
 Weekly

**EDITORS-IN-CHIEF**  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
 All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
 Jin-Lei Wang, Director  
 Yuan Qi, Vice Director  
 Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501,  
 Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501,  
 Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

**PUBLICATION DATE**  
 May 14, 2017

**COPYRIGHT**  
 © 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
 Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Observational Study

**Stress and sleep quality in doctors working on-call shifts are associated with functional gastrointestinal disorders**

Soo-Kyung Lim, Seung Jin Yoo, Dae Lim Koo, Chae A Park, Han Jun Ryu, Yong Jin Jung, Ji Bong Jeong, Byeong Gwan Kim, Kook Lae Lee, Seong-Joon Koh

Soo-Kyung Lim, Seung Jin Yoo, Chae A Park, Han Jun Ryu, Yong Jin Jung, Ji Bong Jeong, Byeong Gwan Kim, Kook Lae Lee, Seong-Joon Koh, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Boramae Hospital, Seoul 156-707, South Korea

Dae Lim Koo, Department of Neurology, Seoul National University Boramae Hospital, Seoul National University College of Medicine, Seoul 156-707, South Korea

**Author contributions:** Lim SK and Koh SJ have contributed equally to this article; Lim SK, Yoo SJ, Koo DL and Koh SJ were the guarantors and designed the study; Lim SK, Park CA and Ryu HJ participated in the acquisition, analysis, and interpretation of the data; Lim SK and Koh SJ participated in the interpretation of the data, and drafted the Initial manuscript; Lim SK, Jung YJ, Jeong JB, Kim BG and Lee KL and Koh SJ revised the article critically for important intellectual content.

**Institutional review board statement:** The present study was reviewed and approved by Institutional Review Boards of Seoul National University Boramae Hospital.

**Informed consent statement:** All respondents submitted informed written consent prior to study enrollment.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

Correspondence to: Seong-Joon Koh, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Boramae Hospital, 5 Gil 20, Boramae-Road, Dongjak-Gu, Seoul 156-707, South Korea. [jel1206@snu.ac.kr](mailto:jel1206@snu.ac.kr)  
Telephone: +82-2-8702234  
Fax: +82-2-870-3866

Received: January 24, 2017  
Peer-review started: February 1, 2017  
First decision: February 23, 2017  
Revised: March 8, 2017  
Accepted: April 12, 2017  
Article in press: April 12, 2017  
Published online: May 14, 2017

**Abstract****AIM**

To investigate the role of sleep quality and psychosocial problems as predictors of functional gastrointestinal disorders (FGIDs) in doctors that work 24 hour-on-call shifts.

**METHODS**

In this cross-sectional observation study, using the Rome III Questionnaire and Pittsburgh Sleep Quality Index (PSQI), we analyzed 170 doctors with 24 hour-on-call shifts.

**RESULTS**

Among the participants that had experienced a 24 hour-on-call shift within the last 6 mo, 48 (28.2%) had FGIDs. Overall prevalence of irritable bowel syndrome (IBS) and functional dyspepsia (FD) were 16.5% and 17.1%, respectively, with 5.3% exhibiting both. Sleep scores (PSQI) ( $8.79 \pm 2.71$  vs  $7.30 \pm 3.43$ ,  $P = 0.008$ ), the presence of serious psychosocial alarm (83.3%

*vs* 56.6%,  $P = 0.004$ ), and the proportion of doctors who experienced over two months of recent on-call work (81.2% *vs* 68.9%,  $P = 0.044$ ) were significantly different between individuals with or without FGIDs. Multivariate analysis revealed that presenting serious psychosocial alarm was an independent risk factor for prevalence of FD (OR = 5.47, 95%CI: 1.06-28.15,  $P = 0.042$ ) and poor sleep quality (PSQI  $\geq 6$ ) was a predictor of IBS (OR = 4.17, 95%CI: 1.92-19.02,  $P = 0.016$ ).

### CONCLUSION

Physicians should recognize the role of sleep impairment and psychological stress in the development of FGIDs and a comprehensive approach should be considered to manage patients with FGIDs.

**Key words:** Psychosocial stress; Sleep; 24 hour-on-call shift; Doctors; Functional gastrointestinal disorders

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The aim of this study is to investigate the role of sleep quality and psychosocial stress as predictors of functional gastrointestinal disorders (FGIDs) in doctors that work 24 hour-on-call shifts. Our study showed a higher prevalence of FGIDs in doctors with 24 hour-on-call shifts. This is the first attempt to provide evidence of the interplay between sleep impairment, psychosocial stress, and higher workload in the pathogenesis of FGIDs. Our survey data is trustworthy, as doctors were enrolled as subjects, rather than the general population.

Lim SK, Yoo SJ, Koo DL, Park CA, Ryu HJ, Jung YJ, Jeong JB, Kim BG, Lee KL, Koh SJ. Stress and sleep quality in doctors working on-call shifts are associated with functional gastrointestinal disorders. *World J Gastroenterol* 2017; 23(18): 3330-3337 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i18/3330.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i18.3330>

### INTRODUCTION

Functional gastrointestinal disorders (FGIDs), as disorders of gut-brain interaction include functional dyspepsia (FD) and irritable bowel syndrome (IBS). FGIDs are recognized by symptom-based diagnostic criteria, which are published by the Rome foundation. Since 2006, the Rome III has played an important role in the research and diagnosis of FGIDs<sup>[1]</sup>. Stress may aggravate symptoms of FGIDs through effects on the central nervous system (CNS), with life-threatening situations, and acute or chronic stress possibly resulting in sensory-motor disturbances of gastrointestinal tract<sup>[2]</sup>. Although psychosocial factors

are not required for diagnosis of FGIDs, they influence physiological functioning of the GI tract via the brain-gut axis<sup>[3,4]</sup>.

Psychosocial stress and physical stress, such as infection, trauma, and excessive work, may contribute to symptoms and development of FGIDs<sup>[5,6]</sup>. It is well known that altered sleep patterns are also linked to the FGIDs and altered intestinal sensitivity. A report demonstrated that poor sleep quality is associated with functional gastrointestinal symptoms in the general population<sup>[7]</sup>. Interestingly, insufficient sleep with reduced sleep quality could be a severe stress factor and results in emotional, cognitive, and somatic effects<sup>[8]</sup>. Our previous study showed that psychological stress in nurses that participated in shift work was associated with FGIDs<sup>[9]</sup>. Taken together, poor sleep quality, psychological stress, and excessive work load are closely linked with each other, which may contribute to the development of FGIDs. However, little research is available investigating the interaction among sleep quality, psychological factors, and excessive work in the pathogenesis of FGIDs.

The prevalence of FD and IBS using the Rome III criteria in the Korean general population were 13.2% and 3.9%, respectively<sup>[10]</sup>. However, an increasing prevalence of IBS among individuals in stressful conditions, such as university and medical college students, has also been reported<sup>[11,12]</sup>. One such study found, among medical students in Malaysia, a prevalence of IBS of 15.8%<sup>[13]</sup>. Additionally, a previous study revealed high prevalence of IBS among medical students and interns<sup>[14]</sup>. These studies suggested that stress plays a key role in the development of FGIDs.

In the present study, we selected interns, residents, and fellow doctors who worked 24 hour-on-call shifts as study population. These individuals may have duties every other day, or once in every three days, followed by routine daytime work. Therefore, sleep deprivation and poor sleep problems are frequent among this population. Further, these individuals also often suffer from excessive work and psychological stress. Through this population, we investigated the interplay between poor sleep quality and psychosocial stress in the pathogenesis of FGIDs.

### MATERIALS AND METHODS

#### Study design and setting

We conducted a cross-sectional observational survey of a population consisting of 240 subjects including doctors, who had experienced 24 hour-on-call shifts. The subjects were doctors employed at Seoul National University Boramae Hospital, a referral hospital in a major metropolitan area in Korea. The subjects were recruited for this study on a voluntary basis, and completed structured self-reported, paper-based questionnaires between July 2015 and July 2016.

**Study subjects**

Doctors including interns, residents, and fellows, who experienced 24 hour-on-call shifts during the past 6 mo at Seoul National University Boramae Hospital, received self-report questionnaires. A doctor with 24 hour-on-call shifts is defined as doctors who experienced night on call duties, followed by routine daytime work. All doctors enrolled in our study experienced a 24 hour-on-call shift every other day, or once in every three days, for at least 6 mo. Agreed participants completed questionnaires that were composed of an assessment of their gastrointestinal symptoms, sleep time, sleep quality, psychosocial stress, and demographic characteristics. Dividing FGIDs into FD and IBS was performed through questions about bowel habits. Subjects with past medical history of FGIDs, inflammatory bowel disease, or colorectal surgery, as well as individuals who were pregnant, or were taking medication for hypertension, asthma, hypothyroidism, gastrointestinal symptoms, or psychological symptoms were excluded from the study. Furthermore, incomplete questionnaires were also excluded from subsequent analysis. The present study was reviewed and approved by Institutional Review Boards of Seoul National University Boramae Hospital and all respondents submitted informed consent.

**Questionnaires and outcome measures**

Rome III criteria and a validated Korean version of Bowel Disease Questionnaire (BDQ-K) was used for the assessment of FD and IBS<sup>[15]</sup>. To diagnose FD, subjects must have one or more of following symptoms for at least 3 mo, with symptom onset in at least the previous 6 mo: bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning with no evidence of structural disease. FD was classified into postprandial distress syndrome (PDS) and epigastric pain syndromes (EPS) subtypes. Diagnosis for IBS was based on the presence of abdominal pain or discomfort for at least 3 mo in the previous 6 mo with the presence of 2 of the following symptoms: pain improved after defecation or, symptoms associated with a change in the form of stool. IBS subtypes were divided by using questions related to hard or lumpy stools, or loose or watery stools. Subtypes of IBS are IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)<sup>[16,17]</sup>. The BDQ-K contains 31 gastrointestinal (GI) items and additional 14 questions. Items referring to GI symptoms, medical visits, sociodemographic data, body mass index, family history, and surgical history were also included<sup>[18]</sup>. We used the Pittsburgh Sleep Quality Index (PSQI) for measuring sleep quality<sup>[19]</sup>. Additionally, the Rome III Psychosocial Alarm Questionnaire was used for assessment of psychosocial problems<sup>[20]</sup>. The Rome III Psychosocial Alarm Questionnaire consists of the

following questions: (1) in the last week, have you felt tense, or wound up? (2) in the last week, have you felt downhearted and low? (3) have you recently felt so low that you felt like hurting or killing yourself? (4) during the last 4 wk, how much bodily pain have you had? (5) during the last 4 wk, how much did pain interfere with your normal activities? (6) when I have pain, I say to myself "it is terrible, and I feel it will never get better"; and (7) it is quite common for people to have been emotionally, physically, or sexually victimized at some time in their lives, and this can affect how people manage their medical conditions. Has this ever happened to you? Through the Rome III Psychosocial Alarm Questionnaire, anxiety, depression, suicidal ideation, and other psychosocial problems of participants could be assessed. Age, sex, height, weight, marital status, income, medical history, family history, alcohol history, smoking history, working period, occupational position, and total duration of on-call work during the last 6 mo were also included.

**Statistical analysis**

Statistical analysis was performed with SPSS version 20 (IBM, New York, United States). Using an independent *t* test, continuous variables showed baseline characteristics of subjects. A  $\chi^2$  test for univariate associations was used, with a Fisher exact test for categorical variables in this analysis. Logistic regression analysis to assess the predictive factor for IBS and FD was used. A *P* value of 0.05 was considered statistically significant. Each variable having a *P* value < 0.20 in univariate analysis by binary logistic regression analysis model was entered into the multivariate analysis, with adjustments for age and sex.

**RESULTS****Prevalence of functional gastrointestinal disorders and baseline characteristics of the study subjects**

Of 240 doctors, 70 doctors met exclusion criteria such as incompleteness of questionnaire, history of disease or medication, or refusal to be involved in the study. After exclusions, 170 doctors participated voluntarily and submitted the self-report questionnaire.

The subjects were divided into a FGIDs group and a non-FGIDs group to compare their baseline characteristics according to the presence or absence of FGIDs. Among the 170 subjects, 48 (28.2%) subjects had FGIDs [28 (16.5%) had IBS and 29 (17.1%) had FD]. Nine (5.3%) subjects had both IBS and FD. The most frequent IBS subtypes in doctors was mixed IBS (57.1%) and the second subtype was diarrhea predominant IBS (35.7%). The prevalence of EPS and PDS as subtypes of FD were 24.1%, 34.5%, respectively. Prevalence of individuals with both EPS and PDS was 41.4% (Table 1).

The baseline characteristics of the 170 doctors

**Table 1** Prevalence of irritable bowel syndrome and functional dyspepsia according to the subsets of functional gastrointestinal disorders *n* (%)

Subtypes of IBS and FD	
IBS	28/170 (16.5)
IBS-C	1/28 (3.6)
IBS-D	10/28 (35.7)
IBS-M	16/28 (57.1)
IBS-U	1/28 (3.6)
FD	29/170 (17.1)
EPS	7/29 (24.1)
PDS	10/29 (34.5)
Both EPS and PDS	12/29 (41.4)

IBS: Irritable bowel syndrome; IBS-C: Constipation predominant IBS; IBS-D: Diarrhea predominant IBS; IBS-M: Mixed IBS; IBS-U: Un-subtyped IBS; FD: Functional dyspepsia; EPS: Epigastric pain syndromes; PDS: Postprandial distress syndromes.

are shown in Table 2. Between FGIDs and non-FGIDs groups, there were significant differences in sleep score (PSQI) ( $8.79 \pm 2.71$  vs  $7.30 \pm 3.43$ ,  $P = 0.008$ ), the presence of serious psychosocial alarm (83.3% vs 56.6%,  $P = 0.004$ ), and the proportion of doctors that experienced over 2 mo in recent duration of on call work (81.2% vs 68.9%,  $P = 0.044$ ).

### Sleep quality and psychosocial alarm

In Table 3, IBS was significantly more common in individuals with poor sleep (PSQI  $\geq 6$ ) than in individuals with relatively normal sleep (PSQI  $< 6$ , 20.2% vs 6.5%,  $P = 0.033$ ). In addition, FD was also more prevalent in individuals with poor sleep than in those that reported normal sleep quality (21.8% vs 4.3%,  $P = 0.007$ ). The relationship between the severity of psychosocial alarm and the prevalence of FGIDs is presented in Table 4. Among 109 of subjects with signs of serious psychosocial alarm, 26 (23.9%) had FD, resulting in a statistically significant difference ( $P = 0.007$ ). However, there was no significant difference found among IBS ( $P = 0.416$ ).

### Risk factors for irritable bowel syndrome and functional dyspepsia

Risk factors for the prevalence of FD and IBS are shown in Tables 5 and 6, respectively. Univariate analysis showed marital status and alcohol drinking were associated with an increased risk of FD. However, after adjusting for variables, including age, sex, occupational position, and psychosocial alarm in a multivariate analysis, marital status (OR = 2.73, 95%CI: 1.08-6.39,  $P = 0.039$ ), alcohol drinking ( $\geq 1$  d/wk) (OR = 5.96, 95%CI: 1.08-10.22,  $P = 0.025$ ), and serious psychosocial alarm (OR = 5.47, 95%CI: 1.06-28.15,  $P = 0.042$ ) were associated with an increased risk of FD. The occupational position of resident was associated with a decreased risk of FD when compared to interns (OR = 0.28, 95%CI: 0.12-0.68,  $P = 0.005$ ).

In univariate analysis, poor sleep quality (PSQI  $\geq 6$ ) was associated with IBS. After adjusting age, sex, and variables which could possibly effect the development of IBS, such as occupational position and psychosocial alarm, female gender (OR = 2.33, 95%CI: 1.25-14.00,  $P = 0.020$ ), occupational position of resident (OR = 4.29, 95%CI: 1.25-14.73,  $P = 0.021$ ), and poor sleep quality (PSQI  $\geq 6$ ) (OR = 4.17, 95%CI: 1.92-19.02,  $P = 0.016$ ) were associated with an increased risk of IBS.

## DISCUSSION

In the present study, we evaluated the prevalence of FGIDs among doctors who experienced 24 hour-on-call duties for more than 6 mo. The prevalence of FD and IBS was 16.5% and 17.1%, respectively, representing a higher prevalence of these issues than in the Korean general population<sup>[10]</sup>. These results suggest that the effect of a doctor's excessive workload and 24 hour-on-call shifts induced psychosocial problems, and disrupted normal circadian rhythm, possibly leading to the development of FGIDs.

Insufficient sleep with reduced sleep quality can be a severe stress factor and results in emotional, cognitive, and somatic effects<sup>[8]</sup>. Although a previous study examining abnormal gut function during the day following poor sleep revealed the effect of sleep deprivation on intestinal sensitivity, the association between sleep and intestinal sensitivity has not yet been fully evaluated<sup>[21]</sup>. In the present study, we provide evidence that doctors with night on-call duties have poor sleep quality, which is associated with an increased risk of IBS. In relation to this, a higher proportion of doctors with IBS had poor sleep quality. A previous study reported that sleep disturbance influenced gastrointestinal symptoms in subjects with FGIDs, and that this relationship persisted even when psychological distress and stress were controlled<sup>[22]</sup>. Based on the current results combined with those of previous studies, we believe that poor sleep quality is one of the important factors in the pathogenesis of IBS. Further studies are needed to elucidate a causal relationship between poor sleep quality and IBS.

In our study, a high proportion of doctors reported serious psychosocial alarm, which was associated with an increased risk of FD. This prevalence was higher than in general population showing serious psychosocial alarm<sup>[23]</sup>. A previous report showed that doctors had higher rates of psychological stress, depression, and attempted suicide<sup>[24,25]</sup>. Sleep deprivation due to 24 hour-on-call shifts negatively affects both physiological and psychological distress, which may impact clinical performance<sup>[26]</sup>. Making an effort to help individual vulnerability to stressful conditions in work environments and interventions to support emotional stress, would be an important step towards reducing the prevalence of FD<sup>[27]</sup>. Therefore, physicians should

**Table 2 Baseline characteristics of study subjects according to functional gastrointestinal disorders *n* (%)**

	With FGIDs ( <i>n</i> = 48)	Without FGIDs ( <i>n</i> = 122)	<i>P</i> value
Age (yr)	27.48 ± 2.70	28.44 ± 3.23	0.069
BMI (kg/m <sup>2</sup> )	21.80 ± 3.03	21.65 ± 3.79	0.804
Gender (female)	24/48 (50.0)	58/122 (47.5)	0.773
Occupational position (intern)	23/48 (47.9)	43/122 (35.2)	0.300
Marriage (married)	11/48 (22.9)	28/122 (23.0)	0.996
Smoking	3/48 (6.3)	9/122 (7.4)	0.796
Drinking (≥ 1 d/wk)	31/48 (64.6)	54/122 (44.3)	0.292
Working period (yr)	1.35 ± 1.18	1.66 ± 1.35	0.176
Duration of recent on-call work (≥ 2 mo)	39/48 (81.2)	84/122 (68.9)	0.044
Psychosocial alarm (Serious)	40/48 (83.3)	69/122 (56.6)	0.004
Length of sleep (h)	5.35 ± 0.86	5.48 ± 0.86	0.377
Sleep quality score (PSQI)	8.79 ± 2.71	7.30 ± 3.43	0.008
Poor sleeper (PSQI ≥ 6)	43/48 (89.6)	81/122 (66.4)	0.002

FGIDs: Functional gastrointestinal disorders; PSQI: Pittsburgh Sleep Quality Index; Data presented as mean ± SD.

**Table 3 Prevalence of irritable bowel syndrome and functional dyspepsia according to the sleep quality *n* (%)**

	PSQI < 6 (Non-poor sleeper) ( <i>n</i> = 46)	PSQI ≥ 6 (Poor sleeper) ( <i>n</i> = 124)	<i>P</i> value
IBS	3/46 (6.5)	25/124 (20.2)	0.033
FD	2/46 (4.3)	27/124 (21.8)	0.007

IBS: Irritable bowel syndrome; FD: Functional dyspepsia; PSQI: Pittsburgh sleep quality index.

be made aware of the relationship between on-call shift work, poor sleep quality, and psychological distress in the development of FD.

FD and IBS are considered as different aspects of a unifying spectrum of disease, as they often appear together as overlapping syndromes<sup>[28,29]</sup>. In addition, IBS and FD belong to the same categorical concept as FGIDs, and may share common pathophysiology such as visceral hypersensitivity<sup>[30]</sup>. However, they are somewhat different in aspects of risk factors<sup>[31]</sup>. In the present study, marital status, alcohol drinking, and serious psychosocial alarm were risk factors of FD, and female gender, occupational position of resident, and poor sleep quality were risk factors of IBS. Furthermore, poor sleep quality was associated with IBS but not associated with FD. A previous study also has demonstrated that sleep disturbance was independently associated with the prevalence of IBS, but not FD<sup>[32]</sup>. Our previous study showed that IBS had a relationship with poor sleep quality rather than psychosocial stress, and FD showed an association with psychosocial stress<sup>[9]</sup>. Unfortunately, the effect of sleep disturbance in IBS and FD remains still obscure. Recently, there are major advances in our understandings with the identification of subtype of FGIDs. There exist the differences in genetics, microbiota, brain-gut axis, and stress susceptibility between FD and IBS<sup>[30,33]</sup>. The interplay among these factors may contribute to the development of

different gastrointestinal symptoms. This is a plausible explanation that sleep disturbance has a different role in FD and IBS. Further mechanistic studies are needed to elucidate the role of sleep disturbance in the development of FGIDs.

We believe that this study is valuable to readers for the following reasons. Primarily, our study was performed among 24 hour-on-call shift doctors and showed a higher prevalence of FGIDs. This is the first attempt to provide evidence of the interplay between sleep impairment, psychological stress, and higher workload in the pathogenesis of FGIDs. Our survey data is trustworthy, as doctors were enrolled as subjects, rather than the general population. We analyzed risk factors of FD and IBS including diverse confounding factors. However, the present study also had limitations. For instance, this study was performed in a single referral hospital setting, which may have contributed to the development of selection bias. Additionally, problem of discerning organic gastrointestinal disease can also be raised, as the presence or absence could not be verified via endoscopy. Moreover, because our present study enrolled only doctors with 24 hour-on-call shift, it would be helpful to include doctors without 24 hour-on-call shift as future study subjects for identifying the role of on-call shift work in development of FGIDs by comparing with doctors who experienced 24 hour-on-call shift.

In conclusion, our study targeting doctors working 24 hour-on-call shifts showed a higher prevalence of sleep impairment and psychological stress in this population. Furthermore, we demonstrated the role of sleep impairment and psychological stress in the pathogenesis of FD and IBS. These results suggest that physicians should recognize the role of sleep impairment and psychological stress in the development of FGIDs, and that a comprehensive approach should be considered to manage patients with FGIDs.

**Table 4 Prevalence of functional gastrointestinal disorder according to the psychosocial alarm *n* (%)**

	Alarm absent ( <i>n</i> = 37)	Alarm present ( <i>n</i> = 24)	Alarm serious ( <i>n</i> = 109)	<i>P</i> value
IBS	4/37 (10.8)	3/24 (12.5)	21/109 (19.3)	0.416
FD	2/37 (5.4)	1/24 (4.2)	26/109 (23.9)	0.007

IBS: Irritable bowel syndrome; FD: Functional dyspepsia.

**Table 5 Risk factors for functional dyspepsia in univariate and multivariate analysis**

	Univariate analysis		<i>P</i> value	Multivariate analysis		<i>P</i> value
	OR	95%CI		OR	95% CI	
Age (yr)	0.91	0.79-1.03	0.136	1.166	0.96-1.42	0.131
Sex (female)	2.35	1.02-5.42	0.045	2.07	0.77-5.58	0.151
BMI (kg/m <sup>2</sup> )	1.00	0.96-1.02	0.686			
Occupational position						
Intern	Reference			Reference		
Resident	0.37	0.16-0.85	0.019	0.28	0.12-0.68	0.005
Fellow	0.48	0.05-4.28	0.511	1.42	0.12-17.58	0.783
Marriage	2.18	1.05-3.36	0.001	2.73	1.08-6.39	0.039
Smoking	0.33	0.15-2.33	0.099	3.07	0.610-15.45	0.174
Drinking (≥ 1 d/wk)	2.38	1.02-3.60	< 0.0001	5.96	1.08-10.22	0.025
Duration of recent on-call work (mo)	0.32	0.28-0.67	0.001	0.64	0.31-2.94	0.076
Psychosocial alarm						
None	Reference			Reference		
Present	0.76	0.07-8.88	0.827	0.69	0.05-9.11	0.780
Serious	5.48	1.23-24.36	0.025	5.47	1.06-28.15	0.042
Length of sleep (h)	0.88	0.56-1.43	0.453			
Poor sleep quality (PSQI ≥ 6)	0.28	0.04-0.72	< 0.0001	1.10	0.47-1.36	0.076
Working period (yr)	0.94	0.69-1.28	0.690			

For the occupational position, the intern is the reference group. For the psychosocial alarm, the absence of psychosocial alarm is the reference group. BMI: Body mass index; PSQI: Pittsburgh Sleep Quality Index; OR: Odds ratio.

**Table 6 Risk factors for irritable bowel syndrome in univariate and multivariate analysis**

	Univariate analysis			Multivariate analysis		
	OR	95%CI	<i>P</i> value	OR	95%CI	<i>P</i> value
Age (yr)	0.92	0.81-1.06	0.239	1.03	0.88-1.20	0.696
Sex (female)	0.54	0.23-1.25	0.151	2.33	1.25-14.00	0.020
BMI (kg/m <sup>2</sup> )	1.00	0.97-1.01	0.206			
Occupational position						
Intern	Reference			Reference		
Resident	0.99	0.43-2.29	0.977	4.29	1.25-14.73	0.021
Fellow	0.87	0.09-7.63	0.872	2.29	0.95-3.90	0.460
Marriage	1.19	0.45-2.94	0.778			
Smoking	0.42	0.05-3.38	0.411			
Drinking (≥ 1 d/wk)	0.79	0.58-3.14	0.478			
Duration of recent on-call work (mo)	0.92	0.88-2.78	0.125	1.45	0.40-5.26	0.576
Psychosocial alarm						
None	Reference			Reference		
Present	1.18	0.24-5.80	0.840	1.81	0.44-4.62	0.817
Serious	1.97	0.63-6.17	0.245	1.53	0.42-5.64	0.523
Length of sleep (h)	1.11	0.45-1.17	0.934			
Poor sleep quality (PSQI ≥ 6)	3.16	1.04-12.63	0.002	4.17	1.92-19.02	0.016
Working period (yr)	0.72	0.51-1.02	0.601			

For the occupational position, the intern is the reference group. For the psychosocial alarm, the absence of psychosocial alarm is the reference group. BMI: Body mass index; PSQI: Pittsburgh Sleep Quality Index; OR: Odds ratio.

## COMMENTS

### Background

Stress may aggravate symptoms of Functional gastrointestinal disorders

(FGIDs) through effects on the central nervous system. Although psychosocial factors are not required for diagnosis of FGIDs, they influence physiological functioning of the gastrointestinal tract via the brain-gut axis. Little research exists examining the interaction among sleep quality, psychological factors, and

excessive work in the pathogenesis of FGIDs.

### Research frontiers

A previous report showed that doctors had higher rates of psychological stress and this prevalence was higher than in general population showing serious psychosocial alarm. Another study revealed that the effect of sleep deprivation on intestinal sensitivity, but the association between sleep and intestinal sensitivity has not yet been fully evaluated.

### Innovations and breakthroughs

A study from Korea with Korean general population recruited from a health-screening program revealed the point prevalence of functional dyspepsia (FD) and irritable bowel syndrome (IBS) of 13.2% and 3.9%, which is lower than our present study reporting the prevalence of FD and IBS of 16.5% and 17.1% in doctors who experienced 24 hour-on-call shifts. Difference between these study group suggest that the effect of a doctor's excessive workload and 24-hour-on-call shifts induced psychosocial problems, and disrupted normal circadian rhythm, possibly leading to the development of FGIDs.

### Applications

This study targeting doctors working 24 hour-on-call shifts showed a higher prevalence of sleep impairment and psychological stress and they demonstrated the role of sleep impairment and psychological stress in the pathogenesis of FD and IBS. Physicians should recognize the role of sleep impairment and psychological stress in the development of FGIDs, and a comprehensive approach should be considered to manage patients with FGIDs.

### Terminology

Twenty-four hour-on-call shift is duty every other day, or once in every three days, followed by routine daytime work.

### Peer-review

In this manuscript, the authors intend to evaluate whether the sleep disturbance, and psychosocial stress could act as a risk factor for development of FGIDs among doctors with 24 hour-on-call shifts. It is suggested that the sleep quality and psychosocial stress are significant predicting factors for FGIDs. In general, this paper is significant of clinical importance.

## REFERENCES

- Drossman DA**, Chang L, Bellamy N, Gallo-Torres HE, Lembo A, Mearin F, Norton NJ, Whorwell P. Severity in irritable bowel syndrome: a Rome Foundation Working Team report. *Am J Gastroenterol* 2011; **106**: 1749-1759; quiz 1760 [PMID: 21747417]
- Drossman DA**. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology* 2016; Epub ahead of print [PMID: 27144617 DOI: 10.1053/j.gastro.2016.02.032]
- Wilhelmsen I**. Brain-gut axis as an example of the bio-psychosocial model. *Gut* 2000; **47** Suppl 4: iv5-iv7; discussion iv10 [PMID: 11076893]
- Van Oudenhove L**, Demyttenaere K, Tack J, Aziz Q. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18**: 663-680 [PMID: 15324706 DOI: 10.1016/j.bpg.2004.04.010]
- Barry S**, Dinan TG. Functional dyspepsia: are psychosocial factors of relevance? *World J Gastroenterol* 2006; **12**: 2701-2707 [PMID: 16718756 DOI: 10.3748/wjg.v12.i17.2701]
- Nagao-Kitamoto H**, Kitamoto S, Kuffa P, Kamada N. Pathogenic role of the gut microbiota in gastrointestinal diseases. *Intest Res* 2016; **14**: 127-138 [PMID: 27175113 DOI: 10.5217/ir.2016.14.2.127]
- Cremonini F**, Camilleri M, Zinsmeister AR, Herrick LM, Beebe T, Talley NJ. Sleep disturbances are linked to both upper and lower gastrointestinal symptoms in the general population. *Neurogastroenterol Motil* 2009; **21**: 128-135 [PMID: 18823289 DOI: 10.1111/j.1365-2982.2008.0181.x]
- Roehrs T**, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006; **29**: 145-151 [PMID: 16494081]
- Koh SJ**, Kim M, Oh DY, Kim BG, Lee KL, Kim JW. Psychosocial stress in nurses with shift work schedule is associated with functional gastrointestinal disorders. *J Neurogastroenterol Motil* 2014; **20**: 516-522 [PMID: 25230903 DOI: 10.5056/jnm14034]
- Park H**. Functional gastrointestinal disorders and overlap syndrome in Korea. *J Gastroenterol Hepatol* 2011; **26** Suppl 3: 12-14 [PMID: 21443700 DOI: 10.1111/j.1440-1746.2011.06644.x]
- Dong YY**, Zuo XL, Li CQ, Yu YB, Zhao QJ, Li YQ. Prevalence of irritable bowel syndrome in Chinese college and university students assessed using Rome III criteria. *World J Gastroenterol* 2010; **16**: 4221-4226 [PMID: 20806442 DOI: 10.3748/wjg.v16.i33.4221]
- Shen L**, Kong H, Hou X. Prevalence of irritable bowel syndrome and its relationship with psychological stress status in Chinese university students. *J Gastroenterol Hepatol* 2009; **24**: 1885-1890 [PMID: 19780881 DOI: 10.1111/j.1440-1746.2009.05943.x]
- Tan YM**, Goh KL, Muhidayah R, Ooi CL, Salem O. Prevalence of irritable bowel syndrome in young adult Malaysians: a survey among medical students. *J Gastroenterol Hepatol* 2003; **18**: 1412-1416 [PMID: 14675271]
- Ibrahim NK**, Battarjee WF, Almeahadi SA. Prevalence and predictors of irritable bowel syndrome among medical students and interns in King Abdulaziz University, Jeddah. *Libyan J Med* 2013; **8**: 21287 [PMID: 24054184]
- Song KH**, Jung HK, Min BH, Youn YH, Choi KD, Keum BR, Huh KC. Development and Validation of the Korean Rome III Questionnaire for Diagnosis of Functional Gastrointestinal Disorders. *J Neurogastroenterol Motil* 2013; **19**: 509-515 [PMID: 24199012 DOI: 10.5056/jnm.2013.19.4.509]
- Drossman DA**. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; **130**: 1377-1390 [PMID: 16678553 DOI: 10.1053/j.gastro.2006.03.008]
- Park JM**, Choi MG, Cho YK, Lee IS, Kim JI, Kim SW, Chung IS. Functional Gastrointestinal Disorders Diagnosed by Rome III Questionnaire in Korea. *J Neurogastroenterol Motil* 2011; **17**: 279-286 [PMID: 21860820 DOI: 10.5056/jnm.2011.17.3.279]
- Song HJ**, Jung HK. Reliability and validity of Korean bowel disease questionnaire for functional gastrointestinal disorders. *Ewha Med J* 2011; **34**: 39-46 [DOI: 10.12771/emj.2011.34.2.39]
- Sohn SI**, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. *Sleep Breath* 2012; **16**: 803-812 [PMID: 21901299 DOI: 10.1007/s11325-011-0579-9]
- Locke GR**, Weaver AL, Melton LJ, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004; **99**: 350-357 [PMID: 15046228]
- Zhou HQ**, Yao M, Chen GY, Ding XD, Chen YP, Li DG. Functional gastrointestinal disorders among adolescents with poor sleep: a school-based study in Shanghai, China. *Sleep Breath* 2012; **16**: 1211-1218 [PMID: 22203339 DOI: 10.1007/s11325-011-0635-5]
- Jarrett M**, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. *Dig Dis Sci* 2000; **45**: 952-959 [PMID: 10795760]
- Lee YY**, Waid A, Tan HJ, Chua AS, Whitehead WE. Rome III survey of irritable bowel syndrome among ethnic Malays. *World J Gastroenterol* 2012; **18**: 6475-6480; discussion p. 6479 [PMID: 23197894 DOI: 10.3748/wjg.v18.i44.6475]
- Markwell AL**, Wainer Z. The health and wellbeing of junior doctors: insights from a national survey. *Med J Aust* 2009; **191**: 441-444 [PMID: 19835538]
- McManus IC**, Winder BC, Gordon D. The causal links between stress and burnout in a longitudinal study of UK doctors. *Lancet* 2002; **359**: 2089-2090 [PMID: 12086767]
- Olson EJ**, Drage LA, Auger RR. Sleep deprivation, physician performance, and patient safety. *Chest* 2009; **136**: 1389-1396 [PMID: 19892678 DOI: 10.1378/chest.08-1952]

- 27 **Hayee B**, Forgacs I. Psychological approach to managing irritable bowel syndrome. *BMJ* 2007; **334**: 1105-1109 [PMID: 17525453 DOI: 10.1136/bmj.39199.679236.]
- 28 **Outlaw WM**, Koch KL. Dyspepsia and its overlap with irritable bowel syndrome. *Curr Gastroenterol Rep* 2006; **8**: 266-272 [PMID: 16888867]
- 29 **Miura S**, Sugano K, Kinoshita Y, Fock KM, Goh KL, Gibson P. Diagnosis and treatment of functional gastrointestinal disorders in the Asia-Pacific region: a survey of current practices. *J Gastroenterol Hepatol* 2011; **26** Suppl 3: 2-11 [PMID: 21443699 DOI: 10.1111/j1440-1746.2011.06635.x]
- 30 **Talley NJ**, Holtmann G, Walker MM. Therapeutic strategies for functional dyspepsia and irritable bowel syndrome based on pathophysiology. *J Gastroenterol* 2015; **50**: 601-613 [PMID: 25917563 DOI: 10.1007/s00535-015-1076-x]
- 31 **Wang A**, Liao X, Xiong L, Peng S, Xiao Y, Liu S, Hu P, Chen M. The clinical overlap between functional dyspepsia and irritable bowel syndrome based on Rome III criteria. *BMC Gastroenterol* 2008; **8**: 43 [PMID: 18808723 DOI: 10.1186/1471-230X-8-43]
- 32 **Vege SS**, Locke GR, Weaver AL, Farmer SA, Melton LJ, Talley NJ. Functional gastrointestinal disorders among people with sleep disturbances: a population-based study. *Mayo Clin Proc* 2004; **79**: 1501-1506 [PMID: 15595333 DOI: 10.4065/79.12.1501]
- 33 **Khanijow V**, Prakash P, Emsellem HA, Borum ML, Doman DB. Sleep Dysfunction and Gastrointestinal Diseases. *Gastroenterol Hepatol* (N Y) 2015; **11**: 817-825 [PMID: 27134599]

**P- Reviewer:** Day AS, Kim BJ, Macedo G **S- Editor:** Qi Y  
**L- Editor:** A **E- Editor:** Zhang FF





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

