ISSN 2641-7154 (Print)

ISSN 2643-8151 (Online)

GCAT-R

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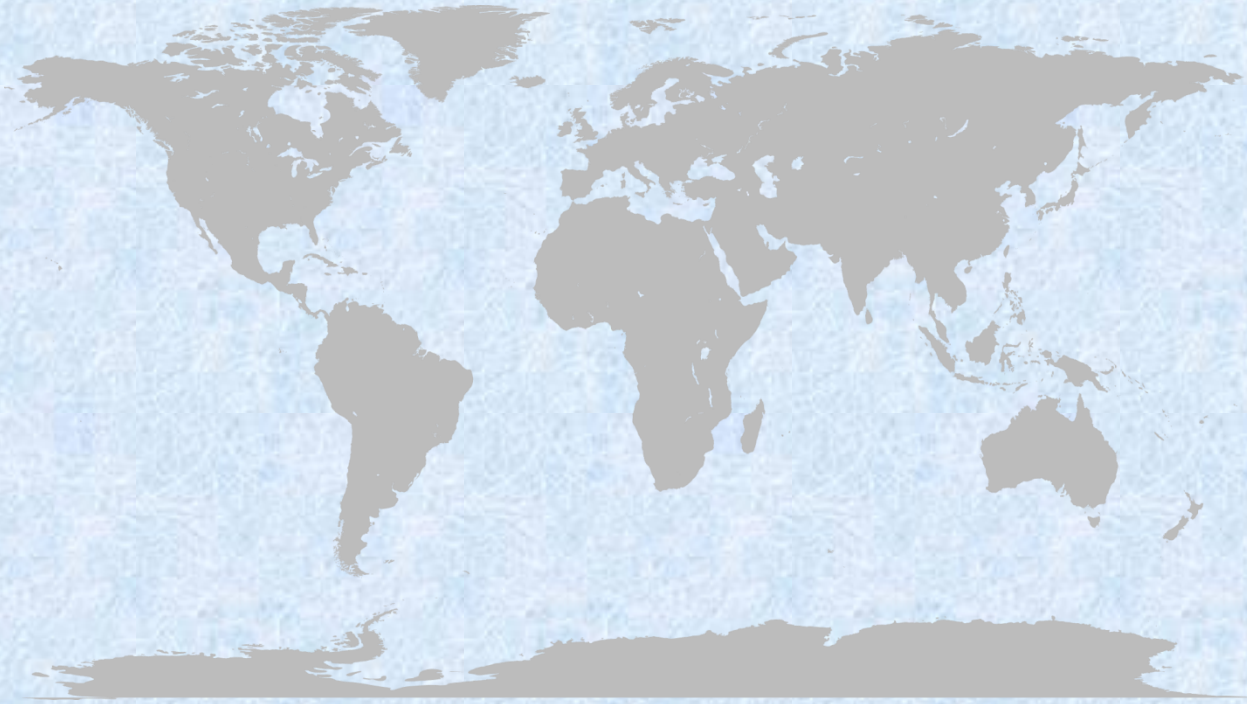

Vol. 1, No. 2 June 30, 2019

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Publisher

The journal of *Global Clinical and Translational Research* (GCAT-R) is published and printed quarterly by the Global Clinical and Translational Research Institute, Bethesda, MD, USA.

GUIDE FOR AUTHORS

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- Methods:
- Results:
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CONTENTS

Workshop report

Translating Fundamental Science of Acupuncture into Clinical Practice

Hsiao-hsien Yeh

Received March 10, 2019; Accepted March 26, 2019

The National Center for Complementary and Integrative Health (NCCIH) organized a 2-day workshop "Translating Fundamental Science of Acupuncture into Clinical Practice", at the National Library of Medicine, Bethesda, MD, from February 11-12, 2019. The workshop began with an overview by Dr. Helene Langevin, the director of NCCIH, focused on: 1) specific effect of the acupuncture intervention: neural mechanism and pathways, 2) non-specific effect of the acupuncture intervention, and 3) overcome the barriers of clinical research of acupuncture. Here we summarize the brief information on this workshop.

Specific effect of acupuncture: neural mechanism and pathways

The effect of acupuncture on reducing pain has a neural basis. Qiufu Ma, Dana Farber Cancer Institute at Harvard Medical School, gave a keynote speech on *mapping neural circuits and the neural basis of acupuncture*. Ma presented his recent work on the characterization of sensory pathways that drive the reflexive-defensive reactions to external threats and coping behaviors associated with ongoing pain, and the pathways may drive different autonomic reflexes in response to acupuncture.

Electroacupuncture (EA) may have effects on reducing pain caused by alcohol withdrawal. A study by Jiang-Hong Ye suggests that EA can alleviate hyperalgesia during alcohol withdrawal through a mechanism involving Mu Opioid Receptors (MORs) in the habenula; and EA could be of the potential treatment of hyperalgesia in alcohol dependence.

However, the effect of acupuncture may be varying with types of pain. Chronic pain biotypes predict differential analgesic response to verum and sham acupuncture. Because that not all patients with chronic pain and a given diagnosis have the same underlying pathophysiology, the existing pharmacologic and non-pharmacologic treatments are only effective for 30-40% of patients with fibromyalgia (FM), a widespread pain condition. Rick Harris from the University of Michigan presented data suggesting that the quantitative sensory testing and needling sensations at baseline can be used to identify different biotypes of patients with FM that respond differentially to sham and verum acupuncture. More sensitive patients with FM respond better to sham acupuncture; whereas less sensitive patients respond better to verum. This baseline information could be very useful for a personalized approach to the treatment of chronic pain with acupuncture. Following this talk, Jun Mao, from the Memorial Sloan Kettering Cancer Center, gave a presentation on "oncology acupuncture: precision medicine meets patient-centered care".

Lastly, in this session, Weidong Lu discussed his pilot study of randomized clinical trial with examining the molecular mechanism and pathways through which the acupuncture may act, in the treatment of taxane-related chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer. Their data suggests that increases of STATI and NF-kB expression levels in the pre-acupuncture are associated with degrees of neuropathic pain and sensory loss in breast cancer patients with CIPN. The percentage decrease in the levels of STAT1 expression was 56% in the acupuncture arm and 24% in the control arm, suggesting the involvement of transcription factors and inflammatory signaling pathways in the development of CIPN and the potential therapeutic role of acupuncture in the treatment of CIPN. He concluded that acupuncture may reduce CIPN related neuropathic pain by suppressing inflammatory signaling pathways and attenuating the over-expression of TRPV I receptors to alter the axon-degenerative process. Future research should continue to explore CIPN related molecular signaling pathways including TRPVI in humans and clinical conditions undergoing acupuncture stimulation.

Specific effect of the intervention: extra-neural mechanism and pathways

There might be some extra-neural mechanisms and pathways that explain the effect of acupuncture intervention on pain. These may include the glymphatic system, biophysical model and connective tissues, neuroinflammation, and endocrine and metabolic regulation. In session II, Maiken Nedergaard gave a keynote speech on the *glym-phatic system and pain*; and Helene Langevin discussed the biophysical model and connective tissues.

Rurong Ji, from Duke University, presented on the modulation of neuroinflammation and neuropathic pain by electroacupuncture. Increasing evidence suggests that neuroinflammation in the peripheral nervous system such as dorsal root ganglion (DRG) plays a more critical role in the pathogenesis of CIPN. Paclitaxel treatment induces not only neuropathic pain symptom but also cause sex-dependent neuroinflammation in DRGs, including infiltration and activation of macrophages and T cells and associated increases in the proinflammatory cytokines (e.g., IL-1β and IL-17). However, Electro-acupuncture (EA) at hindpaw acupoints in lightly anesthetized mice, before paclitaxel injecttion, effectively prevented the development of neuropathic pain (mechanical allodynia) and reduced the signs of neuroinflammation; and auricular EA stimulation was also effective in preventing the development of CIPN. In contrast, post-treatment of hEA after the development of CIPN did not reverse the established neuropathic pain. Ji presented a study showing that EA treatment during the early phase development of CIPN may be able to prevent or delay CIPN in cancer patients. Mechanistically, EA promotes the

resolution of neuroinflammation in part by increasing the production of specialized pro-solving mediators (SPMs).

Suzanna Zick discussed mechanistic clinical studies of chronic pain and cancer-related fatigue. In the presentation, Zick showed evidence from their studies examining inflammatory markers, spectroscopy, and connectivity in fatigued and non-fatigued, self-acupressure in breast cancer survivors and other acupuncture research to probe the usefulness and validity of this model. Future directions for which peripheral markers may prove useful in future human research. In addition, Elisabet Stener-Victorin from Karolinska Institutet gave a talk through video conference on acupuncture for Infertility in women with polycystic ovary syndrome.

Non-specific effects of the acupuncture interventions

Ted Kaptchuk, from Harvard Medical School, talked about "Placebo effects of acupuncture: clinical and genomic findings". Placebo effects are rarely mentioned in the classical East Asian or Chinese medicine. Acupuncture is believed to be effective based on the observation of individual patients report before and after treatment. He discussed the existing evidence of placebo acupuncture including the genetics of placebo acupuncture. Effective strategies to separate acupuncture from placebo effects are still an active concern in research.

Neuroimaging is used to examine the effect of acupuncture. One talk by Jian Kong focused on neuroimaging study of placebo effect of acupuncture; a talk by Vitaly Napadow was about "brain concordance supports patient/acupuncturist therapeutic alliance and modulates analgesia" based on a hyperscan functional magnetic resonance imaging (fMRI) approach.

Overcoming Barriers for Clinical Research of Acupuncture

This session began with a talk by Hugh MacPherson, from University of York in U.K, on the challenge of evaluating specific and non-specific effects in clinical trials of acupuncture.

Richard Niemtzow discussed how to overcome the barriers of acupuncture research for both clinician and researchers. The selected acupuncture procedure should be evidence-based, safe, and has the potential to demonstrate its value in achieving desired outcomes based on evaluating reviews, trials, and practical clinical experience.

Paul Crawford discussed how to the propagation of acupuncture research findings by creating teams of clinicians and scientists to achieve the next level. First, pain is the most common complaint/symptoms for which individuals seek outpatient care in the United States. It is surprising to know that medical care for the 50 million patients with chronic patients and secondary disability exceeds $ 100 billion annually. Despite significant demand for chronic pain management, pain care in the United States is highly variable. In addition, studies have demonstrated that acupuncture effective at treating chronic pain, and patients treated with acupuncture use less opioid. While this is encouraging, the mechanism of this reduction in opioid use is not clear. Understanding this mechanism could lead to some breakthrough in discovering novel pharmacological and non-pharmacological treatment of pain. To achieve this, it requires collaboration between clinicians and scientist. Finally he pointed out that a standardized protocol is needed to be developed for the purpose of a mechanistic study.

Songping Han, Peking University, presented "acupuncture and related techniques for pain relief and treatment of heroin addiction: mechanisms and clinical application." The vast amount of evidence suggests that primary afferent fibers, the descending inhibitory pathways and the central opioid peptides mediate the effect of acupuncture; and EA treatment has profound therapeutic effects on acute withdrawal syndrome in heroin addicts. Han pointed out the over-expression of cholecystokinin octapeptide in the CNS may be the mechanisms of acupuncture tolerance caused by frequent and prolonged EA treatments. It may also be responsible for the non-responders to EA treatment observed in clinical settings.

Rosa Schnyer presented that important insights can be derived from the clinical practice of acupuncture to inform the design of clinical trials. A bidirectional approach to a translational research strategy highlights critical gaps in building an acupuncture evidence framework. The gaps include the need for early phase research, standards to optimize the selection. Implementation and delivery of treatment protocols, more precise articulation of research questions and inclusion of hypothesis-driven secondary outcomes that better assess the impact of acupuncture in improving the patient's capacity to manage a specific condition.

Gary Deng, from the Memorial Sloan Kettering Cancer Center, presented a study of "reduction of opioid use by acupuncture during hematopoietic stem cell transplantation (HSCT): a randomized controlled trial." Adult patients with multiple myeloma undergoing high dose melphalan followed by autologous peripheral blood HSCT were randomized to receive either true (TA) or sham acupuncture (SA) once daily for five days starting on the gay luC'5 15 and 30 days after chemotherapy. Pain scores and use of pain medications were assessed at baseline, day 5, 15, and 30 days after transplantation. The HSCT team, patients and outcome evaluators were blinded to group assignment.

The study shows that among 60 evaluable participants, pain scores did not differ between the two groups at day 5, 15 and 30. Patients who received SA had more than fivefold odds of increasing pain medications from the baseline compared with those who received TA (OR=5.31, 95% CL: 1.35-20.93; p=0.017). Of patients who were opioid non-users at baseline, all 15 patients in the TA group remained free from opioids at the end of the study. In contrast, 20% (4 of the 20 patients) of those in the SA group started to use opioids after chemotherapy and stem cell infusion (Day 5)and 40%(8 of the 20)had become opioid users by Day30 after HSCT(Fisher exact test; p=0.006).

They conclude that true acupuncture was associated with reduced use of pain medications and prevented opioid non-users from using opioids after HSCT when compared to sham acupuncture. These findings need warrant a fur-

ther study.

Wenli Liu, from MD Anderson Cancer Center, discussed the gaps between acupuncture research and clinical practice. Liu discussed several potential issues that are very helpful in developing research protocols for conduct research on acupuncture. 1) there are gaps in translating evidence into specific and clear clinical practice; and methodological heterogeneity in acupuncture research is a significant contributor to the often inconsistent findings; 2) besides the biologic mechanism of acupuncture effect, the lack of understanding of the relationship between the defined syndromes within TCM might also contribute to differences in acupuncture approaches (i.e., point selection) in research design; 3)TCM diagnosis may be predictive of acupuncture response, and choosing appropriate comparison has been a significant barrier for acupuncture research. For example, sham acupuncture (SA) as a placebo control for real acupuncture (RA) has been considered less physiologically active than the real treatment but may not be inert; SA technique cannot be blinded to acupuncturists and may not be indistinguishable to participants who have received previous acupuncture; many others such as the number of needles to use, needle size, and level of insertion, intensity, and type of needle stimulation, retention time, and frequ-e-cy and duration of treatments, differ among research designs; all these can contribute to divergent research findings.

Liu also suggests to improve the understanding of the relationship of the physiological and pathophysiological foundation of TCM diagnostics with those of the modern conventional medicine, which help clearly define TCM diagnoses; and evaluating the efficacy in comparison with other medications, physical therapy, and mind and body modalities that are considered the standard of care or appropriate alternatives.

Jiang-Ti Kong, Stanford University, presented preliminary results from two parallel, randomized, controlled clinical trials examining verum and sham electroacupuncture in the treatment of chronic low back pain. With 200 patients recruited from the San Francisco Bay Area, the study examined the clinical outcomes in both pain and function, and, more importantly, central pain regulatory mechanisms of electro-acupuncture approximated by quantitative sensory testing. Finally, taking advantage of 2 independent but similar clinical trials conducted around the same time, Kong developed and validated a prediction algorithm using data reduction techniques from machine learning on a large number of baseline for predicting the outcome.

Finally, a panel discussion was moderated by a group of panelists of Hugh MacPherson, Gary Deng, Wenli Liu, Jiang-Ti Kong, Baoyan Liu, Xianghong Jing, Bingmei Zhu, which focused on 1) Redefine the scope and recommendations; 2) Key barriers and building blocks for clinical trial studies of acupuncture; and key issues – blinding; specific vs. non-specific effects. In concluding the session, Dr. Helene Langevin introduced NIH Resources to support acupuncture research; Marge Good presented National Cancer Institute Clinical Trial Resources, and Linda Porter from National Institute of Neurological Disorder and Stroke (NINDS) introduced HEAL (help to end addition long-term) Initiatives Pain Basic Research Resources and Clinical Trial Networks.

How to cite this article:
Yeh H. Translating Fundamental Science of Acupuncture into Clinical Practice. Glob Clin Transl Res. 2019; 1 (2):59-61.

Article

Socioeconomic Status Impact Hypertensive Risk and Treatment among Older Adults in China

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Received January 26, 2019; Accepted: March 25, 2019

ABSTRACT

Background: Hypertension has become one of the significant health problems among the elderly. The disparities in the prevalence, awareness, and treatment of hypertension have been associated with socioeconomic status but lack of consistency especially in developing countries where is undergoing epidemiological transition.

Methods: Data used in this study was drawn from the 2013 wave of the China Health and Retirement Longitudinal Study (CHARLS), which was designed with a multi-stage clustering population-based sampling. The dependent variables were hypertension as well as self-awareness and treatment of hypertension, both of which were measured as binary outcomes. The independent variables included the community and individual socioeconomic conditions mainly measured by education, income and occupations. A hierarchical logistic regression model was used for statistical analysis to considering the clustering at community level.

Results: Individuals aged 45 years or older living in urban areas (Beta=0.144; p<0.1) and communities with higher mandarin fluency score (Beta=0.043; p<0.05) were positively associated with the risk of hypertension. Compared with agricultural workers, the retired (Beta=0.425; *p*<0.001), people working for government or institutions (Beta=0.519; p<0.001), working with a large company (Beta=0.362; p<0.05), farmer or working with a small private firm (Beta=0.302; p<0.05) were more likely to be hypertensive. We also found that urban living (Beta=0.194; p<0.1) and communities with a higher mandarin fluency score (Beta=0.061; p<0.05) were associated with a higher awareness of hypertension. There was a noted regional variation in both the awareness and treatment of hypertension; people living in the western China were less likely to be aware of (Beta=-0.186; p<0.1) and to manage their hypertension (Beta=-0.297; p<0.05) compared to those in the more developed eastern China. The inequality in treatment was also observed among occupations; the retired (Beta=0.785; p<0.001), individuals working for government or institutions (Beta=0.437; p<0.1) or for a private firm (Beta=0.395; p<0.1) were more likely to receive treatment for hypertension.

Conclusion: Occupation, urban dwelling, and living in the more developed eastern China were associated with more likelihood of developing hypertension and being aware of and treated for hypertension. However, income and levels of education, two classical measures of socioeconomic status, were not associated with either of the three outcomes-hypertensive risk, awareness and treatment in China.

KEYWORDS

Hypertension, blood pressure management, socioeconomic status

INTRODUCTION

Hypertension is defined as blood pressure elevated to an unhealthy level. It is a measure of the force exerted by the blood against the wall of the blood vessels and depends on the strength of heart pumping and the resistance of the blood vessels. Normally, the blood pressure is 120 (systolic) and 80 (diastolic) mm of mercury (mmHg) but can be acutely elevated by stress or physical activity; and blood pressure is increased as people aging. Hypertension is blood pressure higher than 130/80 (1) if unmanaged can lead to severe complications and increase the risk of heart disease, stroke, and mortality.

Hypertension has become one of the significant threats to health in the less developed country such as China where there has been a rapid social and economic, demographic and epidemiological transition. There are a large number of individuals with hypertension, as well as a high prevalence but low rate of treatment in China. Nationally, it was estimated that about 330 million people suffered from hypertension in 2012, accounting for one-third of global

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hypertension patients. Because of population aging and epidemiological transitions, hypertension became a major health problem that the elderly face. In 2002, 50% of the elderly aged at 60 years or above suffered from hypertension in China, but only 32.2% of individuals had medical treatment. In 2012, the prevalence of hyper-tension among the elderly in China increased to 60% and the treatment rate remained low as only 41% of patients received the treatment they needed; most of the patients did not get any effective treatment at all (2).

There is long-standing literature showing that generally people living in a relatively better community environment and with a higher individual socioeconomic status (SES) tend to be healthier. Socioeconomic status may determine the ability of an individual to acquire resources and live with a certain healthier lifestyle (3); whereas individuals with low socioeconomic status are more likely to smoke and drink excessively, have more stressful life events and high-calorie diet, which lead to a higher prevalence of diseases and less healthy conditions (4, 5). The community socioeconomic conditions also contribute to health and prevalence of illness. In the more developed regions, the standard of living and medical services are better and more accessible, which may result in a positive influence on health (6).

However, the relationship between individual socioeconomic status and prevalence of hypertension has been reported in multiple studies but lack of consistency (7). In the developing countries undergoing epidemiological transition, groups with a higher socioeconomic status may first experience the epidemiological transition that the pattern of dominant diseases is transited from communicable diseases to chronic diseases; therefore, they may first have increased the likelihood of being hypertensive. In contrast, in the more developed countries, there is a negative correlation between socioeconomic status and the risk of hyper-tension. A case-control study in Singapore indicates that the prevalence of hypertension was relatively low in the wealthy communities and the treatment rate was relatively high (8). A US-based study also shows that the prevalence of hypertension was low in communities with relatively higher average income per capita; and social and environ-mental exposure explained a substantial proportion of the racial disparity in hypertension (9). Data from Europe also indicates that low socioeconomic status was a significant risk factor for hypertension in adolescents (10).

Moreover, the relationship of socioeconomic status with hypertension is complicated in some other countries. In a study of women (15-65 years of age) in low-income regions of rural Mexico in 2003, groups with a higher level of house-hold income and assets were more likely to suffer from hypertension(11). This challenges the current popular hypothesis of socioeconomic status and health. In South Africa, the males with high levels of education and income had a higher prevalence of hypertension, but the result was opposite in the females (12). However, the socioeconomic conditions such as education, income and wealth had no significant effect on the risk of hypertension; and they also evidently influenced the treatment of hypertension (13). Recent research using panel data shows that the association between socioeconomic status and hypertension had started changing in China. In the males, people with a higher level of socioeconomic status were more likely to have hypertension from 1991 to 2006; whereas people with a lower level of socioeconomic status were more likely to have hypertension from 2006 to 2009. In both periods together from 1993 to 2009, a lower level of socioeconomic status was associated with the risk of hypertension in the females (13).

This inconsistency may reflect the dynamics and imbalanced change in social, economic transition, but may also be likely due to the lack of nationally representative sample. Identifying the groups that are most vulnerable to be hypertensive or less likely aware of and to control their blood pressure, may have an important implication for public health. Previous studies have mainly used the income and levels of educational attainment as the measures of socioeconomic status, but rarely considering the occupational influence and community socioeconomic conditions. With a large national representative sample, this study examined the relationship between hypertension and socioeconomic status, which was measured by not only the household income, personal education, and occupation, but also the community socioeconomic status and urban dwelling. We also examined how the socioeconomic status affects the self-awareness and treatment of hypertension, in which poor socioeconomic status has been associated with uncontrolled hypertension (14). Findings from this study will help to target vulnerable population for effective prevention.

METHODS

Dataset

Data used in our research was drawn from the 2013 national representative baseline survey of the China Health and Retirement Longitudinal Study (CHARLS). The original study design has been described elsewhere (15). In brief, the original survey was a national representative and samples were from 450 villages and communities in 150 counties across China, with a total of 18,604 samples aged 45 years old or above. The CHARLS survey comprised a community questionnaire that is used to collect an extensive set of information on the community income per capita and social development, and an individual questionnaire that was used to collect a detailed information on individual's education, occupation, household per capita income, behaviors and health conditions. Diastolic pressure and systolic pressure were measured by trained nurses and were recorded three times at the time when the survey was conducted. Respondents were also interviewed about their awareness and treatment conditions of hypertension.

Measurement of variables

Dependent Variables: Both self-reported and actual hypertension was collected as outcome variables of this study. The self-reported hypertension was defined as 1 if respondents in this survey answered "Yes" to the question "Have you been diagnosed with hypertension by a doctor?" which

means they had been diagnosed before, which may not reflect the current conditions of hypertension. The diagnosed hypertension was defined by the actual blood pressure of the respondents, which was the average of blood pressure recorded three times by trained nurses in this survey. A respondent was considered suffering diagnosed hypertension if any one of the following conditions met 1) the mean systolic pressure of three repeated measures was 140 mmHg or above, 2) the mean diastolic pressure was 90mmHg or above, and 3) the respondent was taking medicines to control blood pressure. In addition, the awareness of hypertension is defined as 1 if respondents actually suffered from hypertension and had been diagnosed with hypertension by a physician; and the treatment condition of hypertension is measured by whether the respondent is taking medicines or anti-hypertensive treatment to control blood pressure. The awareness of hypertension and the treatment condition of hypertension were only measured for the elderly who were diagnosed with hypertension in this paper.

Independent Variable: The main explanatory variables included community and individual socioeconomic status (SES) variables. Four indicators were used to measure community socioeconomic conditions: type of community (rural or urban), community income per capita, the level of mandarin fluency and the geographic regions (East, Central, and West) of the community. Three indicators were used to measure individual socioeconomic status: level of individual educational attainment, family income per capita, and occupations.

Control variables: We also included some variables such as age, gender, marital status, smoking history, social participation, diet control, body mass index (BMI), having medical insurance and taking a physical examination, to control for potential confounding.

Statistical analysis

Because the samples were from a cluster sampling, a random-effect (hierarchical) logistic regression model was used for statistical analysis. The individual variable was considered as level one, the community was considered as level two. The model is written briefly as follow:

$$\text{logit}(p) = \gamma_{00} + \gamma_{01} W_j + \gamma_{10} X_{ij} + \delta_{0j}$$

Where W_j is the community socioeconomic context and γ_{01} is its coefficient; X_{ij} represents the socioeconomic conditions at individual level and γ_{10} is its coefficient. In this model, a random effect varies with the communities but the slopes are the same; δ_{0j} is the random-effect at a community level. P represents the odds of being hypertensive. The data was analyzed using the software Stata Release 14.0.

RESULTS

Table 1 presents the coding and descriptive statistics of the variables. In the 2013 wave of CHARLS survey. The total number of samples were18, 604; however, the actual response rate was different for individual outcomes. Of the total sample, 14,298 (76.85%) participants of middle-aged and the elderly (age>= 45 years,) had complete information on clinical diagnosis; and 47.76% (6,829 of 14,298) were suffering from hyper-tension, which is confirmed by measuring the blood pressure in the survey. There was a high rate of response (94.81%, 17,639/18604) in self-reported hypertension; of which only 26.42% (4,660 of 17,639) respondents had self-reported hypertension, indicating that more than 30% (2,169/6,829) of hypertensive people failed to report that they had hypertension.

In addition, we noted that the rates of self-awareness and receiving treatment were low. Of the 6829 respondents who were actually suffering from hypertension, only 61.29% (4,022 /6,562; 267 missing) diagnosed with hypertension and responded to the survey were aware of their hypertension. About 60% (4,047/6,822, 7 missing) respondents who were diagnosed as hypertension were receiving treatment at the time when the survey was conducted.

Table 2 presents the association of socioeconomic status and other factors with the diagnosed and self-reported hypertension. Communities with a higher level of mandarin fluency score (Beta=0.043; p<0.05) are more likely to be hypertensive (Model 1). Compared with agricultural workers, the retired individuals (Beta=0.425, p<0.001), working for government or institutions (Beta=0.519; Odd Ratio, OR=1.68; p<0.001), working for a company (Beta =0.362; p<0.05), working for farmer or a private firm (Beta=0.302; p<0.05) were more likely to be diagnosed with hypertension. Individuals who living in the urban areas (Beta= 0.144; p<0.1) had a trend to be hypertensive. However, community income per capita, levels of educational attainment, and household income per capita were not significantly associated with hypertension. The estimates of socioeconomic status on the self-reported hypertension were similar to that was for the diagnosed hypertension (Model 3).

When controlling for factors such as drinking alcohol, diet behavior, and access to health care resource, urban living and high level of mandarin fluency score that was associated with diagnosed hypertension and self-reported hypertension became no longer significant (Model 2 and Model 4). We noted that BMI (Beta=0.144; p<0.001) and having alcohol-drinking history (Beta=0.161; p<0.01) were positively related to being hypertensive. When BMI, behavior, and access to health care were controlled in the analysis, the association between urban dwelling and mandarin language fluency with the diagnosed hypertension and self-reported hypertension were no longer significant, suggesting that those variables mediated the association with urban dwelling and mandarin language fluency. In addition, we noted that there were significant random-effects (RE) in model 1 (RE=0.239; P<0.001) and model 2 (RE=0.203; P<0.001) for the diagnosed hypertension; and significant random-effects were also noted in model 3 (RE= 0.251; P<0.001) and model 4(RE=0.124; P<0.001) for association with self-reported hypertension. These suggest that marked unobserved heterogeneity was at community level or some important factors that may be associated with hyper-tension were not observed and included in the analysis.

Table 1. Coding and descriptive statistics of variables (n=18,604)

Variable	Coding	Mea	Medi	SD	N	%
Dependent variables						
Diagnosed hypertension	1=Yes				6,829	47.76
	0=No				7,469	52.24
Self-reported hypertension	1=Yes				4,660	26.42
	0=No				12.979	73.58
Awareness of hypertension	1=Yes				4,022	61.29
	0=No				2,540	38.71
	NA				267	
Treating hypertension	1=Yes				4,047	59.32
	0=No				2.775	40.68
	Missing				7	
Individual socioeconomic conditions						
Education	0=Illiterate				8,099	43.57
	1=Elementary school				4,148	22.32
	2=Middle school and above				6,340	34.11
Occupation	0=Agricultural worker				9.431	51.48
	1=Retired				5,885	32.13
	2=Self-employed				833	4.55
	3=Government or Institution worker				405	2.21
	4=Company employee				555	3.03
	5=Farmer or private firm				682	3.72
	6=Others				530	2.89
Household income per capita (ln)		8.71	8.95	1.52	17,543	
Community socioeconomic conditions						
Community type	1=Urban				4,577	24.64
	0= Rural				14,002	75.36
Community income per capita(ln)		8.00	8.07	1.21	17,603	
Degree of mandarin fluency		3.86	4.00	1.83	18,555	
Region	0=Eastern				7.796	41.88
	1=Central				6,085	32.69
	2=Western				4,733	25.43
Controlled variables						
Age		60.2	59.00	10.0	18,205	
Gender	1=Female				8,861	47.66
	0=Male				9.733	52.34
Marital status	1=Currently married				3.500	18.83
	0=Otherwise				15,085	81.17
Ever drinking alcohol	1=Yes				6,411	34.93
	0=No				11.945	65.07
Participating in social activities	1=Yes				11,405	61.80
	0=No				7,050	38.20
Controlling diet	1=Yes				14,149	84.08
	0=No				2,680	15.92
Body Mass Index		23.8	23.59	3.86	12,959	
Taking physical examination	1=Yes				7,543	42.12
	0=No				10,364	57.88
Having medical insurance	1=Yes				17,672	95.87
	0=No				761	4.13

Note: actual sample size for each item could be varied due to the missing value.

Table 3 shows the associated factors for the awareness and treatment of hypertension. Communities with higher mandarin fluency score (Beta=0.061; p<0.05) and urban living (Beta=0.194; p<0.1) were with a relative higher awareness (Model 1). Inequality in the proportion of awareness was found different between occupations, with retired people (Beta=0.785; p<0.001), government employee (Beta= 0.437; p<0.1), working for a firm (Beta=0.395; p<0.1) were more likely to be aware of hypertension compared with agricultural workers. People living in the less developed Western China (Beta=-0.186; p<0.1) were less likely aware of their hypertension. When the access to health care resource such as having medical insurance and taking a physical examination were controlled (Model 2), the association of urban living with the awareness of hypertension was no longer significant (Beta=0.177; t=1.51). This may indicate that the inequalities in the access to health services between rural and urban residents were responsible for the disparity of the awareness. Community income per capita, levels of educational attainment and household income per capita had no significant association with the awareness of hypertension.

The treatment varied significantly with the region and occupation among the middle-aged and the elderly who were diagnosed with hypertension. People living in the western China were less likely to treat their hypertension (Beta =-0.297; p<0.05). The retired (Beta=0.592; p<0.001) and people working for the business company (Beta=1.112; p<0.05) were more likely to treat their hypertension than agricultural workers were (Model 3). Community income

per capita, level of educational attainment and household income per capita had little effect. We noted that there were significant random-effects in model 1 (RE=0.361; p<0.05) and in model 2 (RE=0.37; p<0.001) for the awareness of hypertension, and in model 3 (RE=0.248; p<0.05) and in model 4 (RE=0.239; p<0.05) of hypertension treatment, suggesting that there were unobserved heterogeneity at community or factors that may be associated with aware-ness and treatment of hypertension.

Table 2 Multiple logistic regression estimates of socioeconomic conditions on the incidence of hypertension (n=12,131)

	Diagnosed hypertension						Self-reported hypertension					
	Model 1			Model 2			Model 3			Model 4		
	Beta	SE	Sig	Beta	SE	Sig	Beta	SE	sig	Beta	SE	Sig
Intercept	-2.78	0.194	***	-7.011	0.375	***	-3.132	0.307	***	-7.971	0.402	***
Community												
Urban living	0.144	0.087	+	-0.034	0.087		0.184	0.086	*	-0.043	0.084	
Community income per capita (ln)	-0.04	0.027		-0.027	0.027		-0.044	0.028		-0.027	0.026	
Mandarin fluency score	0.043	0.019	*	0.016	0.019		0.058	0.020	**	0.036	0.018	+
Education												
Illiterate												
Elementary school	0.001	0.052		-0.026	0.057		0.033	0.056		-0.001	0.063	
Middle school and above	0.008	0.055		-0.022	0.06		-0.043	0.059		-0.119	0.067	+
Occupation												
Agricultural worker												
Retired	0.425	0.089	***	0.230	0.057	***	0.587	0.054	***	0.29	0.062	***
Self-employed	0.166	0.102		-0.086	0.114		0.282	0.113	*	0.02	0.13	
Government worker	0.519	0.155	***	0.236	0.174		0.551	0.167	***	0.151	0.196	
Company employee	0.362	0.142	*	0.095	0.167		0.442	0.156	*	0.226	0.191	
Farmer or individual firm	0.302	0.122	*	0.098	0.142		0.286	0.137	*	0.066	0.168	
Others	0.452	0.122	***	0.282	0.138	*	0.563	0.125	***	0.423	0.144	**
Household income per capita (ln)	-0.02	0.014		-0.020	0.017		0.019	0.015		-0.01	0.019	
Controlling variables												
Ever drinking alcohol				0.161	0.053	**				0.112	0.059	+
Participating in social activities				-0.030	0.031					-0.042	0.057	
Controlling diet				-0.073	0.091					0.016	0.071	
Body Mass Index				0.144	0.006	***				0.155	0.007	***
Having medical insurance				-0.083	0.117					0.286	0.144	*
Physical examination				0.095	0.046	*				0.441	0.050	*
Random intercept	0.239	0.029	***	0.203	0.03	***	0.251	0.033	***	0.124	0.026	***

Note: 1. ***P < 0.001, **P < 0.01, *P < 0.05, +P < 0.1;

2. Coefficients are adjusted by age; gender and marital status in all models.

DISCUSSION

Through the analysis of a large national representative sample, we found that socioeconomic conditions were associated with the risk of hypertension. In China, the middle-aged and elderly living in urban, mandarin language fluency, and working in non-agricultural sectors were more likely to be hypertensive. These associations were to a certain degree mediated by BMI, drinking history and access to health services; and controlling for BMI and drinking history, the associations were no longer significant. We did not find a significant association of personal education and household income with the risk of hypertension.

Our findings confirmed that socioeconomic status with the risk of hypertension, but showed some different from previous literature or studies conducted in other countries. We noted that household income per capita, individual's education, and community income per capita, two of which are well known for measuring individual's SES, are not significantly associated with risk of hypertension. However, these factors have been associated with the risk of hypertension in other countries including both developing and less developed countries (7, 14, 16). Instead, occupation is strongly associated with the risk of hyper-tension in China, which has been reported in the previous study(17). It is interesting to note that government and institutional workers, which are mostly state-own, have the highest risk of hypertension compared to the agricultural workers and other occupations in China. These probably suggest that lack of activity may play a role in the risk of hypertension because they are mostly engaged with work in the office but fewer outside activities. In the meantime, people who live in urban areas may have first experienced the epidemiological transition that is mostly induced by socioeconomic development and they may be likely hypertensive. In addition, a study in Japan did not find a clear association of SES with hypertension (18). Moreover, the association between individual socioeconomic status and the risk of hypertension may be affected by some unobserved hetero-

geneity of the elderly who were from different birth cohorts and suffered varied impacts from socioeconomic factors, which can be further explored by using multi-waves data.

Table 3 Multiple logistic regression estimates of socioeconomic conditions on awareness and treatment of hypertension

	Hypertension awareness						Hypertension treatment					
	Model 1			Model 2			Model 3			Model 4		
	Beta	SE	Sig	Beta	SE	Sig	Beta	SE	Sig	Beta	SE	Sig
Intercept	-0.272	0.429		-0.369	0.462		1.612	0.711	*	1.533	0.782	*
Community												
Urban	0.194	0.115	+	0.177	0.117		0.150	0.174		0.089	0.175	
Community income per capita (ln)	-0.039	0.037		-0.048	0.038		0.018	0.052		0.023	0.052	
Mandarin fluency	0.061	0.026	*	0.065	0.026	*	0.028	0.036		0.026	0.037	
Region												
Eastern (ref)												
Central	0.039	0.102		0.076	0.104		-0.001	0.148		0.017	0.15	
Western	-0.186	0.109	+	-0.223	0.112	**	-0.297	0.151	*	-0.312	0.155	*
Education												
Illiterate (ref)												
Elementary school	0.044	0.079		0.034	0.08		0.039	0.145		0.064	0.148	
Mid school above	-0.056	0.083		-0.115	0.085		-0.047	0.151		-0.08	0.153	
Occupation												
Agricultural worker												
Retired	0.785	0.074	***	0.555	0.076	**	0.592	0.141	***	0.643	0.143	**
Self-employed	0.173	0.163		0.22	0.166		0.358	0.302		0.428	0.311	
Government employee	0.437	0.239	+	0.317	0.246		0.131	0.382		0.068	0.384	
Company worker	0.395	0.235	+	0.423	0.245	+	1.112	0.541	*	1.158	0.544	*
Farmer or firm	0.286	0.194		0.135	0.2		0.175	0.34		0.106	0.344	
Others	0.654	0.178	***	0.673	0.181	***	0.321	0.308		0.353	0.31	
Household income per capita (ln)	0.037	0.022		0.028	0.023		-0.069	0.045		-0.078	0.046	+
Having medical insurance				0.299	0.159	+				-0.071	0.336	
Physical examination				0.609	0.063	***				0.39	0.116	**
Random effect	0.361	0.054	*	0.37	0.057	***	0.248	0.105	*	0.239	0.105	*

Note: 1. ***P < 0.001; **P < 0.01; *P < 0.05; +P < 0.1;
2. Coefficients are adjusted by age, gender and marital status in all models.

Our study also finds that socioeconomic conditions were strongly and positively associated with the awareness and treatment rates of hypertension. This evidence was based on a large national representative samples with more than 6,800 people with hypertension. The middle-aged and elderly living in the urban area, people who live in the more developed eastern China and working in government or institutions or retired had higher rates of awareness and treatment of hypertension. Advantages of awareness and treatment of hypertension in elderly with higher socioeconomic status will help reduce their disadvantages on the prevalence of hypertension. This may suggest that China is in transition and as the economic conditions continue developing, the hypertension will be reduced in those with a higher level of SES.

In addition, having medical insurance and taking physical examination regularly may contribute to the positive association of SES with the awareness and treatment rates. As the proportion of awareness and treatment of hypertension are quite low in China, more medical resources and policies are needed to prevent from and control for hypertension, especially in the groups with lower socioeconomic status. We also found a significant random-effect, suggesting that factors at the community may help to reduce the disparity of awareness and treatment of hypertension. However, a study in Japan did not find a clear association of SES with unaware, untreated and uncontrolled hypertension (18), although a multi-nation study in urban clinics of 12 countries in Sub-Saharan Africa also indicated that people in the lowest individual wealth groups are more likely to have uncontrolled hypertension (14).

CONFLICTS OF INTEREST

We declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENTS

This study is supported by National Natural Science Foundations of China (Grant No. 71490732).

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How to cite this article:
Xia C and Li J. Socioeconomic Status Impact Hypertensive Risk and Treatment among Older Adults in China. Glob Clin Transl Res. 2019; 1 (2): 62-68.

Editorial

Reporting Standards for Clinical and Translational Research

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Transparency in reporting the results of clinical and preclinical research is critical for unbiased publications. Funding agencies, publishers, and regulators have the responsibility to advocate and implement reporting standards for rigorous design. While individual study protocols may have included these standards, the items reported in the respective publications have often been inconsistent or lack transparency. This editorial intends to provide some specific guidelines for reporting results of clinical research with standards required for a rigorous study design. We recommend that reporting clinical research should include sufficient information on study design and analysis plan that contains data processing, quality assurance, and appropriate methods used for rigorous statistical analysis or modeling. Any discrepancy between publications and original study design should be disclosed and discussed. Additionally, recent advances in the analysis of outcome with repeated measurements and statistical modeling should be employed to obtain an unbiased estimates. Finally, we briefly discuss some issues reporting real-world evidence in clinical research.

Keywords

Reporting standards, clinical research, reporting transparency

Research publications on clinical research are the primary essential vehicle to disseminate knowledge that drives further research and have real-world impacts on patients, clinicians, regulators, and policymakers. Selective reporting of the results of clinical research has been noted (1, 2) within academia, funding and regulatory agencies, and biopharmaceutical institutions and organizations. Examples include that outcomes have been measured and collected but not reported and that investigators have analyzed the data but only reported positive results (3, 4). Discrepancies between publications and other study documents such as study protocol and statistical analysis plan are not trivial (1) and may distort the results and lead to bias in subsequent meta-analyses. In addition, inconsistent findings in both clinical and pre-clinical research have been noted. While the problems of selective reporting might be reduced by broad encouragement to publish negative results or by data sharing, as a general principle, reporting of consistent results may depend upon the rigor of study design.

A group of leading scientists from the US National Institutes of Health (NIH) and stakeholders have made a call for transparent reporting of preclinical studies and proposed a set of standards for reporting of rigorous design (5). The NIH held a joint workshop with the then Nature Publishing Group and *Science* in Bethesda, MD, and discussed the issues of reproducibility and rigor in research, with editors from more than 30 journals in basic or translational sciences (6, 7). They came to a consensus on a set of principles and guidelines for reporting preclinical research and a considerable number of journal editors have endorsed the principles and guidelines. Soon afterward, these principles and guidelines were adopted and extended by other societies such as the Biophysical Society and the Center for Open Science. Some journals have started to implement the guidelines and require authors to report some specific items when a manuscript is considered for a potential publication. This helps editors assess the study design and transparency in reporting.

In this editorial, we advocate for transparency in reporting clinical research and suggest some specific recommendations for publications. Our primary recommendations focus on rigorous statistical analysis that should reflect the recent advances in statistical methods, then the reporting standards for a rigorous study design in clinical research, and finally, additional measures to assure transparent reporting for publications in clinical research. Some of these recommendations can be adapted for observational studies including population-based health research.

Rigorous statistical analysis

Study design determines what outcomes to collect and what statistical analysis to perform. In most clinical research, biostatisticians are involved and may have a protocol and analysis plan in place before beginning a study. Once data is collected, the data processing and statistical analysis may have to be carried out by or under the supervision of biostatisticians. In recent years, there has been discussions regarding inconsistent replication of research findings in terms of p-value (8). Statistical analysis involves a series of steps, in which mishandling occurring at any step will lead to an incorrect p-value (Box 1**)**. Any

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discrepancy between report and protocol should be noted and discussed as to how the discrepancy affect the study results, and what measures taken to ensure unbiased results including controls for potential confounding.

Box 1. The process of design, measurement, and analysis

1. Design: Study population and sample, clinical diagnosis, inclusion and exclusion criteria, sample size calculation, randomization, blinding;
2. Measurement: Clinical evaluation of primary and secondary outcomes, measurement, quality control, biospecimen collection and testing, and covariates that may require adjustments;
3. Data process: Data entry and management software, variable types (numeric, string, etc.), coding book, data cleaning, detection of outliers or data errors, data recording, summary statistics, cross-tabulation;
4. Analysis: Single variable analysis and statistical modeling: data science to evidence-based analysis;
5. Replication: independent replications are required for a cross-sectional study

Statistical methods selected for data analysis should fit the type of outcome measure. An outcome could be measured in a form of continuous, binary, categorical (or nominal), time or duration to an event. The general linear model including analysis of variance (ANOVA) and analysis of covariance (ANCOVA) or multivariate linear model is the first choice of methods for analyzing continuous variables. Duration data such as time to failure or death, or time to stop using medication is the most common primary outcome in clinical trials of cancer and is often analyzed using the Cox proportional hazard regression. In addition, a binary outcome (e.g., remission or not, hypertension or not) can be analyzed using logistic or Logit regression, or Probit regression if a latent variable (i.e., intermediate endpoint) underlying a dichotomous outcome follows a normal distribution (9). Categorical variables, meaning an outcome measured in more than two categories such as a choice of methods, can be analyzed using multinomial logistic regression (Table 1).

The number of adverse events or episode of relapses throughout a trial may be considered as an outcome in clinical research. This type of data can be treated as ordinal outcomes and analyzed using ordinal Probit or Logit regression model, which usually requires an assumption of proportional hazard between individual categories. While they can be treated as continuous and analyzed using a general linear regression model, a negative predicted value likely occurs; and especially when the count is fewer (e.g., <10), least square regression may produce a bias in the results. Poisson regression and negative binomial regression may provide optimal analysis(10).

So far, most clinical trials have still been using classical statistical methods. However, recent advances in statistical methods have not been well reflected in data analysis. For example, multicenter clinical trials have often been used (11). Patients recruited from multiple centers may be more heterogeneous than those from a single-center study and thus a larger sample size may be required; but in turn, results from a multi-center study may be generalized to a broader "real world" population. Patients within the same center may have some dependence due to sharing diagnosis or treatment under the same physician or subject to a local standard-of-care within the same hospital; and as such, they may share some common unobserved or even unobservable heterogeneity at a level of physician or hospital (12). This dependence violates the underlying assumption of independence among observations for a parametric statistical model; and if not corrected through analysis, it will lead to a underestimating of the standard errors for parameter estimates. However, very few multicenter clinical trials have employed a particular approach to consider the unobserved heterogeneity at higher levels, which consequently, cause false positive findings.

Table 1. Type of outcome measure and methods for analysis

Type of measure	Example	Methods
Continuous	Blood pressure, cognitive score	Linear regression, ANOVA, ANCOVA
Binary	Case vs. control	Logistic or Logit, Probit regression
Categorical	Choice of methods (A, B, C)	Multinomial Logit regression
Ordinal	Number of adverse outcomes	Ordinal Logit or Probit regression
Count data	Number of adverse events, episode of relapse	Poisson or negative binomial regression
Duration data	Time to failure, death, or stop the medication	Cox proportion regression model

In recent years, people have expressed concerns about possible biased results in publications (13), which has provoked a series of debates across multiple disciplines on the reliability of the statistical error, p-value (14). In response to this, the American Statistical Association issued a statement on the interpretation of p-value in 2016. Later, a group of methodologists proposed to lower the routine p-value threshold from 0.05 to 0.005 for designating statistical significance for a discovery(15). The occurrence of false positives likely arises from data quality and inappropriate data analysis rather than the p-value threshold, which has served as a gold standard for nearly a century. Shrinking the p-value threshold may not help reduce false positive findings. Instead, such a change will

increase not only false negatives but also the number of patients required for clinical studies. Therefore, there is an urgent need to call for rigorous statistical analysis and analysts should have a better understanding of the nature and quality of the data, the assumptions for a specific statistical method, and model diagnosis.

Hierarchical statistical modeling (also known as multilevel modeling) has been an active field of statistical and methodological research (16) and population-based research over the past decades (17, 18). This concept can be applied to analyzing all types of outcomes that are collected in multi-center clinical trials. With the development of computing power and computational programming, hierarchical statistical modeling has been implemented in major standard statistical packages such as SAS and R package (12). Nevertheless, performing such model-based analyses and interpretations of results may require a sophisticated statistician.

Standards for reporting transparency

Publishers or funding agencies can play a critical role in reinforcing transparency in reporting of rigorous study designs. A core set of standards for reporting have been proposed for preclinical studies (5). We suggest implementing specific guidelines adapted for clinical research (see Table 2 and below).

Subjects and design. The investigators/authors need to define the study population clearly from which the subjects are sampled or recruited for a clinical study. This will determine the population that results of a sample study can be generalized *ex post facto***.** In general, the study population for a single-center study may be different from that for a multi-center study. Investigators/authors are required to state 1) the criteria for inclusion and exclusion of individual subjects, 2) reliability of criteria for the diagnosis of patients, and for clinical evaluations of the primary and secondary outcomes, and 3) the measurements of primary and secondary outcomes. Any significant discrepancy between the report and the original study protocol should be discussed in term of its influence on potential biases of results. For a secondary analysis or retrospective clinical studies based on medical records, investigators /authors are required to state how subjects are selected for analysis if the study sample is not all possible subjects within the institution(s) during a specified period. Purposive selection of subjects into the analysis will result in biased results.

Randomization and blinding. Randomization, blinding, and placebo-control are vital components to minimize bias in results. The investigators/authors are required to state how the recruited subjects are randomized and with what methods (e.g., simple randomization, block randomization, stratified randomization, covariate adaptive randomization), and if blinding is used and what type, such as single or double blinding, triple blinding if data analysts are also unaware of treatment the patient received.

Table 2. List of the items for reporting in publications

Category	Items
Subjects and design	Criteria for inclusion and exclusion;
	Diagnosis and clinical evaluation to collect the data
	Primary and secondary outcomes or measurement
	Ethics approval and trial registration
	Treatment group
Sample size and power	Methods for determining the sample size
	Post-hoc power analysis if not meeting the required sample size
Randomization and blinding	Randomization and methods;
	State if blinding is used or open-label
	Use of a placebo
Descriptive statistics	The effective sample size for outcomes and covariate
	Central tendency (mean and median)
	Dispersion (standard deviation, min, max, and inter-quartile range)

Sample size estimation and power analysis. A well-designed study should meet the sample size estimated at the design stage. The investigators/authors should state how the sample size was determined and what methods and parameters are used. In most cases, a range of sample sizes need to be provided under variable number of parameters, such as different effect sizes, thresholds for significance level, and levels of statistical power. When a study is completed, the actual sample size may have deviated from the original design (e.g., fewer samples). In such a case, a post hoc power analysis should be performed according to the actual sample size and effect size.

Statistics. Descriptive statistics should first be reported with sufficient details. The needed details usually include actual sample size, effective sample size for each outcome or covariates by treatment group, central tendency and dispersion. A frequency distribution should be reported for a binary or categorical variable. This is usually reported along with the definition and coding for possible values of each individual variable. Reporting more than one meas-

ure of central tendency or dispersion is generally recommended. This will help provide a quick assessment for a reader that the collected data do or do not meet the assumptions for a specific statistical method. For example, in a metabolic syndrome study where multiple measures are collected and analyzed (19), one can tell if an assumption such as normality for a continuous variable are severely violated by merely comparing the mean and median.

Estimation of effect size should be reported with enough details to accord with the type of outcome and statistical methods used. Besides p-value, estimates of coefficients or least square mean, with their standard errors or 95% confidence limits, should be reported for a continuous variable; whereas odds ratio (OR) or hazard ratio (HR), or relative risk (RR) should be reported, with their 95% confidence limits. In addition, it is important to note that if authors choose to report statistics in graph or plot, the related statistics should also be included. This will be helpful for any future use in meta-analyses. The plot is more intuitive for presentation but does not wholly replace the role of statistical details in scientific publications.

Analysis of outcome with repeated measurement

With regard to the analysis of an outcome with repeated measurements, some care is needed in reporting of results. In clinical trials, time to the occurrence of certain events such as time to relapse (20), treatment failure (21), or discontinuation of medication(11,18), are often considered as a primary outcome, particularly in cancer research. However, continuous outcomes are collected at multiple time points during a period of clinical trials, for example, psychopathological symptoms and cognition in psychiatric research (22, 23). Repeated measures by design allow investigators to examine the timing and trajectory of a treatment effect. It is a powerful approach, but also creates some concerns about consistency, such as when and where data are collected and performed the clinical evaluation to collect study data.

Missing values due to dropout is a common problem in an analysis of outcome with repeated measurement. In a study with scheduled follow-up at multiple time points, subjects may have missing values due to skipping one of the scheduled follow-up visits or subjects may be lost to follow-up before the end of a study. A standard method to deal with missing values due to dropout is the Last-Observation-Carried-Forward (LOCF). LOCF assumes that the measurement of an outcome variable at one follow-up time can be replicated as the presumed observed value at later missing time points. This causes a biased estimate of treatment effect and reduced estimates of standard errors due to the increase in the number of constant observations within an individual (24). The US National Academy of Science has made a recommendation to the Food Drug Administration (FDA) against the use of LOCF in clinical trials and recommends an alternative approach such as generalized estimating equation (GEE) to deal with the missing value for repeated measurement (25). In addition, the random-effect model has recently gained support to be used as a primary methodology for analysis of outcome with repeated measurement. However, this type of modeling may require additional care in order to produce appropriate estimates.

Statistical modeling

Randomization is used to reduce potential confounding that is caused by the unequal distribution of an independent variable across treatment groups. In theory, a randomized trial should not have a significant difference in independent variables at baseline. However, due to the occurrence of an adverse event, a tolerability problem, ineffectiveness of treatment in some individuals, or compliance issues, treatment groups may consist of subgroups of patients who are unequally distributed and have divergence in some of their key characteristics. Multiple regression models are recommended for validating final estimates of parameters. If a treatment effect and a covariate are both significant, then the potential interaction between the treatment and covariates should be assessed. Finally, a model diagnosis should be carried out to make sure that a model is well fitted. With regression modeling, one can also perform stratification or sensitivity analysis to examine the internal validity of estimates across centers.

Real-world evidence in clinical research

While efficacy and safety from clinical trials have been acepted as standard evidence for approval of a drug for marketing, post-approval studies are commonly required. The core concern is usually that the drug approval was based on a few studies in well-characterized samples of recruited patients and that such study samples are often subject to some degree of recruiting bias, and thus may not represent the broader populations where the drug will be marketed or used. Real-world evidence (RWE) refers to "the output of real-world data (RWD) analysis that is used to generate insights, using appropriate study design and scientific methods, to inform decision-making by health care stakeholders."(26). Due to the wide-spread use of mobile devices and electronic medical or health records, collecting all kinds of data about patients from the real world is feasible, and analysis of RWD is anticipated to help satisfy post-approval study needs in many instances.

RWD may help generate evidence for a new indication for a previously approved drug. In the original clinical trials that generated the evidence for drug approval, potential interaction of the drug with other factors may not have been assessed due to the lack of prior evidence to collect those data, or data such as adverse events have been collected but lacked the power to generate statistically meaningful evidence. One of the most promising aspects of RWD is in its large sample sizes and rich variables, which could allow detection of high-order interactions and generate new hypotheses for further studies or approval of a drug for a new indication. For example, specific drug-food interactions that may have been known at the time of conduct of pivotal clinical trials(27) but might have been excluded in the primary study protocols. Note that the FDA

currently allows the use of RWE for monitoring drug safety and for drug approval for rare diseases (28). Analysis of RWD may require additional techniques such as machining learning and advanced data analyses for high dimensional data. For example, variables in RWD are not equally important; some of them may be more informative than the others. In addition, with highly diverse data, application of machine-learning techniques could lead to the selection of an extreme min or max case, which might, in turn, be difficult to replicate consistently or be fundamentally misleading. Therefore, findings generated from RWD may have to be subsequently validated by conducting additional rigorously designed prospective studies.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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How to cite this article:
Zhang F and Hughes C. Reporting Standards for Clinical and Translational Research. Glob Clin Transl Res. 2019; 1(2): 69-73

Case report

Acupuncture might Increase Efficacy of Neoadjuvant Chemotherapy for Ultralow Rectal Cancer: A Case Report and Review of Related Literature

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Received March 28, 2019; Accepted April 10, 2019

ABSTRACT

Background: We report a case of a patient with ultra-low rectal cancer who had a successful anus-preserving operation with fire needling to increase the efficacy of neoadjuvant chemotherapy and an overview of the related literature.

Case presentation: A 38-year-old male with a diagnosis of rectal cancer (cT4N0-2M0 Stage III), the lower edge of the tumor was 2 cm away from the anal margin. He had a strong desire for anal preservation and received six cycles of neoadjuvant chemotherapy by FOLFOX6 regimen at the China-Japan Friendship Hospital. The tumor shrinkage was not significant, and then fire-needling acupuncture was added to the original plan at *baliao acupoints* during the period of chemotherapy. After another six cycles of acupuncture, the tumor disappeared in the imaging examination. He underwent general anesthesia for laparoscopic rectal cancer (ISR) radical surgery.

Results: The specimen showed no tumor, and no metastatic carcinoma was found in the peri-intestinal lymph nodes.

Conclusion: Acupuncture combined with chemotherapy may increase the anti-tumor effect, which could be of great significance for ultra-low rectal cancer patients if evidence can be replicated in additional study. Further case series research is needed.

KEYWORDS

Fire needling acupuncture; ultralow rectal cancer; neoadjuvant chemotherapy; case report

Colorectal cancer is one of the most common malignant tumors around the world, and low, ultra-low rectal cancer accounts for 70-80% of all rectal cancers in China(1). The treatment of low rectal cancer emphasizes surgery-based multidisciplinary treatment including radiotherapy and chemotherapy(2). According to Miles who first described the operation of abdominoperineal resection (APR)(3), there was no possibility of preserving anal sphincter in low and ultra-low rectal cancer (4). However, more and more studies have found that the tumor infiltrates into the distal intestinal wall rarely exceeds 2 cm, and good oncological prognosis can be guaranteed when the distal resection distance is more than 2 cm (5). The emergence of the 2 cm rule dramatically expands the anus sphincter-preserving scope of low and ultra-low rectal cancer. In this article, we reported a case that ultra-low rectal cancer 2 cm away from the anal margin was resected, and the anus was preserved by fire needling acupuncture combined with chemotherapy.

CASE PRESENTATION

A 38-year-old man with recurrent bloody stool, paroxysmal abdominal pain, and difficulty in defecation was referred to the China-Japan Friendship Hospital for urgent preservation of anal function. On October 17, 2016, enteroscopy showed circumferential protuberant lesions 2-4 cm away from the anus with a rough surface and bleeding upon touch. The lower rectal wall was irregularly thickened. The lower margin of the lesion was about 2 cm away from the anal margin. Pelvic contrast-enhanced magnetic resonance imaging (MRI) showed the length of the lesion was about 5-6 cm, the intrinsic muscle layer of the lesion was rough, and the boundary between the lesion and the right levator ani muscle was not clear. Several swollen lymph nodes were seen in the peripheral space between the bilateral pelvic wall and the straight intestine; the larger was about 0.7 cm (Figure 1). High-grade intraepithelial neoplasia (rectum) was considered in puncture pathology, malignancy is not excluded. After a multidisciplinary team consultation, the diagnosis was rectal malignancy (cT4N0-2M0 Stage III), considering that the tumor was large, invading the surrounding tissues and swollen lymph nodes exceeded 0.5cm.

# Xin Jiang and Li-na Wang contributed equally to this work.
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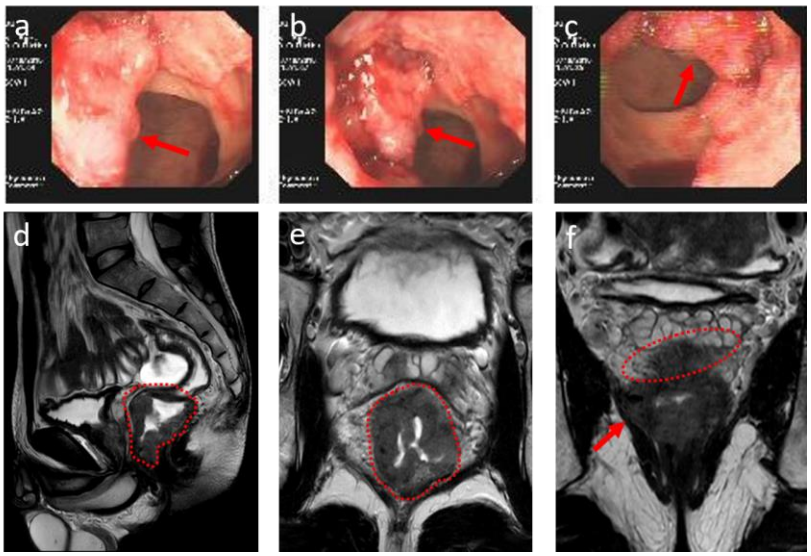

Figure 1. Colonoscopy and MRI examination before chemotherapy**.** a, b and c were tumor uplift under the colonoscopy field of view, with a rough surface and bleeding; d and e were MRI findings in coronal and transverse positions; f. The boundary between the tumor and the levator ani muscle on the right was unclear, and the lesion edge was rough at the intrinsic muscle level.

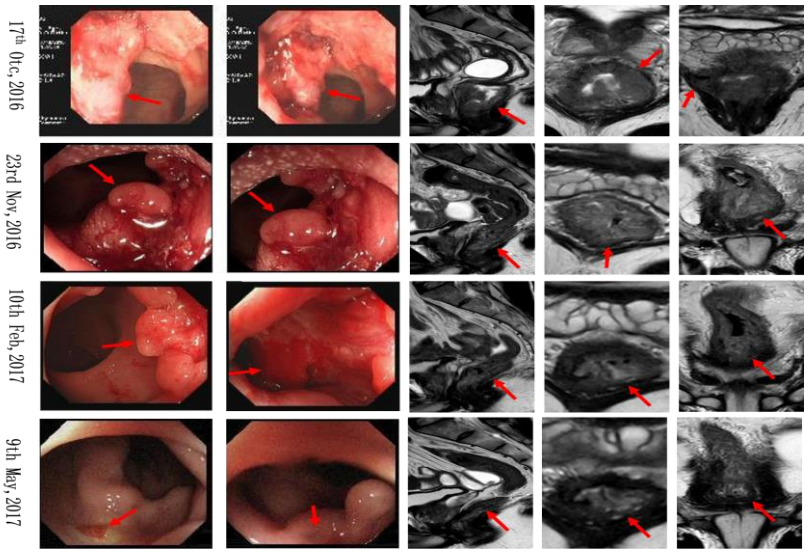

Figure 2. Tumor changes during treatment by colonoscopy and MRI examination

According to the National Comprehensive Cancer Network (NCCN) guidelines (2015 edition), preoperative concurrent chemoradiotherapy is recommended. Considering there are defecation disorders, urinary incontinence, and intestinal dysfunction after preoperative radiotherapy, and there is a risk of anastomotic fistula (6, 7), FOLOX6 regimen was used for 6 cycles (October 2016 to January 2017). The tumor shrinkage was not evident, but watery stools, fever, nausea, vomiting, and hand-foot syndrome occurred. Subsequently, after a multidisciplinary consultation decision, the fire needling acupuncture on *Baliao, Yaoyangguan,* and *Changqiang* was given on the first, third, and fifth days of the original chemotherapy regimen for another six cycles (February-May 2017). Imaging examination showed that the tumor disappeared after acupuncture was completed (Figure 2).

The patient underwent laparoscopic intersphincteric resection (ISR) and ileostomy under general anesthesia on June 21, 2017, and the tumor was removed entirely. Postoperative pathology: No tumor tissue was found in the samples of the specimen, with fibrous tissue hyperplasia

and scattered calcification. The upper and lower ends and the circumferential margin were clean, and no cancer metastasis was found in the peri-intestinal lymph nodes (0/19) (Figure 3). The patient received ostomy return surgery on July 31, 2018, and the patient retains some of the anal function, although most of the anal sphincter was resected.

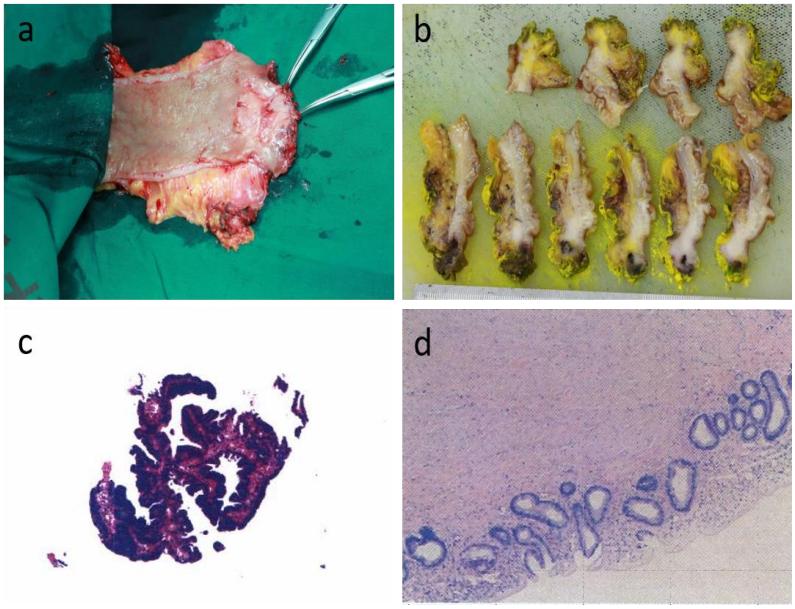

Figure 3. Gross specimen and staining. a. intraoperative gross specimen; b. Fixed section of specimens; c. HE staining of preoperative specimens; d postoperative specimen HE staining

DISCUSSION

Surgery is still the most important radical treatment for rectal cancer, and the most important reference factor for performing anal sphincter preservation surgery for lower rectal cancer is the distance from the lower edge of the tumor to the anal margin. Anatomical studies have shown that the anal margin is 2.5 cm from the dentate line, and 0.5 cm above the dentate line is the upper edge of the levator ani muscle. Therefore, to ensure the integrity of levator ani muscle, at least 3 cm of anorectum should be preserved after resection of tumors, and 2-3 cm of the normal intestinal tube should be resected at the lower edge of the tumors. The distance between the lower edge of the tumors and the anal edge should be at least 5-6 cm before anus-preserving surgery can be performed. Recent literature indicates that distal resection distances <2 cm and>2 cm did not affect oncologic prognosis with intraoperative frozen sections, and even a 5 mm distal margin was safe (8).

Anal function preservation is an urgent desire for patients with low rectal cancer. How to improve the anus presservation rate of middle and low rectal cancer and to reduce the local recurrence and the incidence of anastomotic leakage after an operation is still a major clinical problem. This goal leads to the use of preoperative neo-adjuvant chemotherapy(9). Neoadjuvant chemotherapy can reduce the size of the tumors, increase the distance between the lower edge of the tumors and the anus, and create favorable conditions for radical operation of rectal cancer. However, chemotherapy resistance may not only weaken the efficacy of chemotherapy but also lead to the failure of chemotherapy. The patient reported was with a more massive rectal tumor, a lower tumor edge which was only 2 cm away from the anal margin, a unclear tumor boundary near the levator ani muscle on the right side, accompanied by lymph node metastasis, and a strong desire for anus preservation, the efficacy of neoadjuvant chemotherapy directly determines the success of anus preservation.

Improving the efficacy of chemotherapy has always been the main aim in oncology. Increasing the local drug concentration of intravenous chemotherapy is of great significance to improve the efficacy of chemotherapy. Investigators continue to explore targeted delivery systems such as intratumoral injection (10), interventional chemotherapy (11), and drug-loaded particles(12). In the ancient literature of Chinese medicine, there are records of fire needling therapy for tumors, but fire-needling therapy for tumors has rarely been used in modern times. In this report, we administered the fire needling acupuncture therapy concurrently with chemotherapy in one patient, and the tumor disappeared completely. Acupoints such as *Baqiao*, *Yaoyangguan,* and *Changqiang* are close to the location of low rectal cancer; and acupuncture at these points can exert specific stimulation in the local area, appeared to significantly increase the efficacy of chemotherapy.

In our mouse model research of acupuncture enhancement of anticancer effect of chemotherapy drugs (13), we found that the inhibition rate, defined by the percentage of tumor shrinkage, in peritumoral acupuncture combined with cyclophosphamide (53.68%) was significantly ($p<0.05$) better than that of cyclophosphamide (31.62%) or acupuncture alone (34.56%). This suggests that acupuncture and chemotherapy interactively inhibit the growth of 4T1 breast cancer in mice. One possible explanation is that the process of angiogenesis in local tumors may be modified. Another intriguing possibility is that peritumoral acupuncture may increase the drug concentration of tumors by promoting the normalization of blood vessels and thus increasing the efficacy of chemotherapy. These observa-tions warrant a further investigation in a larger patient sample and the potential mechanisms by which acupuncture, chemotherapy, and their interaction may enhance the anticancer effect on solid tumors.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

ETHICAL APROVAL

The study was examined and approved by the institutional review board of the third hospital affiliated to Beijing University of Chinese Medicine (Approval No. BZYSY-YJKT-3.1). Written informed consent was obtained from the patients for the information to be included in our manuscript. His information has been de-identified to the best of our ability to protect his privacy.

FUNIDNG

Supported by the National Natural Science Foundation for Young Scientists of China (No. 81804177) and Beijing Municipal Natural Science Foundation (No.7172128).

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How to cite this article:
Jiang X, Wang L, Zhang Q, Tian Y, Yang M, Wan Y, Qi X, Yao L, Huang J. Acupuncture might increase efficacy of neoadjuvant chemo-therapy for ultralow rectal cancer: a case report and review of related literature. Glob Clin Transl Res. 2019; 1 (2):74-77.

Article

Retirement and Management of Diabetes in Medically Underserved Patients with Type 2 Diabetes: Preliminary Findings and Literature Review.

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Received April 7, 2019; Accepted May 20, 2019

ABSTRACT

Background: Studies have found that diagnosis of Type 2 diabetes increases the risk of early retirement in the high-income countries. In this study, we examined the levels of glycated hemoglobin (HbA1c) by employment status to determine if early retirement confers a benefit to managing diabetes.

Methods: The data was from a primary care center serving the uninsured and medically underserved in the greater Williamsburg area in the State of Virginia. Plasma concentration of HbA1c (%) from the last visit was used to measure the average level of blood glucose and as an assessment test for glycemic control in people with diabetes. Data analyses were carried out using general linear regression with HbA1c as the dependent variable and employment status, gender and age as the independent variables; and the interaction of gender and employment status and interaction of age and employment status were assessed to control for potential confounding factors.

Results: The results showed that males tended to have a higher level of HbA1c; overall age was negatively associated with the levels of HbA1c; there was a significant difference in the mean levels of HbA1c between the retired people and people working part-time (p=0.032). After controlling for age and gender in the multiple linear regression analysis, employment status became non-significantly associated with HbA1c levels. *Post hoc* analysis showed a difference in HbA1c between individuals working part-time (the highest HbA1c group) and the full-time employed at a marginal significance (p=0.0823). While almost 20 years older, the retired people had the lowest level of HbA1c. However, the mean level of HbA1c was no longer significantly different from that in other groups, probably because age explained much of this variation in the levels of HbA1c among employment status. Multiple regression analysis showed that age was negatively associated with the levels of HbA1c (The retired people mainly derived Beta=-0.046, p<0.0001).

Conclusion: In this underserved population, the HbA1c level is the lowest in people after retirement, even though they are older. Our study indicates that retirement may be a beneficial factor to the management of diabetes, which warrants further investigation.

KEYWORDS

Retirement, type 2 diabetes, underserved populations, HbA1c

INTRODUCTION

Diabetes is a group of metabolic diseases with excessive level of blood glucose over a prolonged period (1). Type 2 diabetes is the most common form of the disease and is caused by the body not making enough or appropriately using insulin, a hormone that helps glucose get into cells to be processed into energy (2). Having too much glucose in the blood may cause severe problems, including damaging eyes, kidneys, and nerves; and untreated diabetes can also cause heart disease and stroke. Women who are pregnant are may develop diabetes, which is called gestational diabetes. The prevalence of diabetes is increasing in the US and globally, and the increasing rates of overweight and obesity in people and the aging of populations drive this trend.

Diabetic conditions may require long-term management of blood glucose, which is defined as to keep levels of blood glucose as close to normal as possible by balancing food intake with medication and activity. Low income and low educational attainment have been associated with the increased risk of hypoglycemia in diabetes (3), which may be caused by taking too much insulin or other diabetes

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medications, reduced eating foods, or doing more exercise. Both diabetes and hypoglycemia in diabetes harm employment such as early labor-force exit and income (4-8). In this study, we examined the level of HbA1c as the measure of diabetes management, by employment status. There are reports that people diagnosed with diabetes start an exercise regimen but that this often tapers off over time with aging (9, 10). Retired people with diabetics could either have more time to do physical exercise, which improves the levels of their hemoglobin A1c or taper off over time due to aging. Many patients with diabetes also have co-morbidities and are on several medications. The number of co-morbidities and medications would be expected to increase with age, which could inhibit their ability to manage their diabetes through exercise. With the aging global population, more people than ever before will have diabetes when they retire, and therefore, understanding management of diabetes after retirement is essential for healthy aging.

METHODS

Using medical records from a clinic that serves a medically under-served population, we examined the effect of employment status and retirement on the management of diabetes. The data was from the Olde Towne Medical and Dental Center in Williamsburg, Virginia, which is a primary care center providing health services to the uninsured and underinsured in the Greater Williamsburg area. The Institutional Review Board approval was obtained from the Institutional Review Board of the College of William and Mary. The plasma level of HbA1c was based on the measurement in the last visit to the clinic. Blinded data for all patients with diabetes in the clinic database was downloaded into an Excel spreadsheet.

Data collected included age, the number of co-morbidities, number of medications, plasma levels of hemoglobin A1c (%), gender, and residence address, which was mapped to the distance from the clinic. Hemoglobin is the part of red blood cells that carries oxygen from the lungs to the rest of the body. Because the lifespan of a red blood cell is about 100 to120 days, an HbA1c test can measure the average amount of glucose attached to hemoglobin over the past three months. HbA1c is used for making a diagnosis of diabetes. Typically, a diagnosis of diabetes is made when HbA1c about 6.5% or higher, and pre-diabetes when the plasma HbA1c levels were between 5.7 and 6.4%.

Linear regression analysis was performed with the outcome variable levels of HbA1c measured as a percentage, and the independent variables were employment status, gender, and age. The model was defined as HbA1c = α + β_1*age + β_2*gender + β_3*employment status; possible interactions between age and employment status and between gender and employment status were also assessed. Statistical analyses were carried out using XLSTAT in Excel and SAS.

RESULTS

Table 1 gives the characteristics of subjects by employment status. Of the total 413 participants, there were 40 retired people (9.69%), 194 unemployed (46.97%), 95 working full time (23%), 71 working part-time (17.19%) and 13 no available information on employment (3.15%), who were likely self-employed. The mean age of the retired people was 74.52 years, which was 20 years older than people with another employment status. The median numb-er of co-morbidities and medications in the retired people were 4 and 10, respectively, which were not significantly higher, given that their age was 20 years older, compared with other groups. People who worked full-time had a rela-tively low proportion of females (46.32%) compared with the people retired (67.5%) and unemployed (63.93%); women were more predominant in working part-time (78.87%).

Table 1. Characteristics of subjects in five employment groups (N=413)

						Females, %	
Employment status	N	%	Mean age	Co-morbidities*	Medications*	n	%
Retired	40	9.69	74.52	4	10	27	67.50
Unemployment	194	46.97	54.50	4	7	124	63.92
Full-time employed	95	23.00	52.06	2	8	44	46.32
Part-time employed	71	17.19	50.73	3	5	56	78.87
Undefined (mainly self-employed)	13	3.15	52.00	3	7	5	38.46

Note: * median number of co-morbidities and medications

We noted that the levels of HbA1c were different by employment status (**Table 2**). The overall crude mean level of HbA1c was 7.9% (min-max: 4.6-15; SD=2.3), mean age was 55.2 years (min-max: 22-98; SD=12.8 years). The retired people tended to have a lower level of HbA1c (Mean= 7.23%; SD=2.06) and even with smaller min-max range (4.9-12.9%); whereas the part-time employed had the highest level of HbA1c (Mean=8.21%; SD=2.46). There was a significant difference in the mean level of plasma HbA1c between the retired and the part-time employed (p= 0.032); no significant difference in the mean levels of HbA1c was observed between other employment status based on the Analyses of Variance (ANOVA). We also noted that males had a higher level of HbA1c (Mean=8.1%; SD=2.3) than females (Mean=7.12%; SD=2.31).

Because the sample was highly heterogeneous, we examined the relationship between HbA1c and age by employment status **(Figure 1**). We noted a consistent trend across a different group of employment status that the levels of HbA1c tended to be negatively associated with age in all groups, and the most influential association seemed in the unemployed people and people working full time. However, the correlations between age and HbA1c was flatter in people who worked part-time and had the highest mean level of H1A1c, as well as the retired people who had the lowest mean level of HbA1c.

Table 2. Summary of plasma HbA1c %) in patients with Type II diabetes by employment status and gender

Variable	Code	n	Mean	Median	SD	Min	Max
Overall		413	7.87	7.0	2.31	4.6	15
Gender							
	Male	157	8.10	7.5	2.30	4.8	15
	Female	256	7.12	6.8	2.31	4.6	15
Employment							
	Retired	40	7.23	7.5	2.06	4.9	12.9
	Unemployed	194	7.92	7.0	2.19	4.6	15
	Fulltime	95	7.78	6.8	2.46	5.0	15
	Part-time	71	8.21	6.9	2.46	5.2	15
	Undefined (mainly self-employed)	13	8.08	9.9	2.15	5.3	12.4

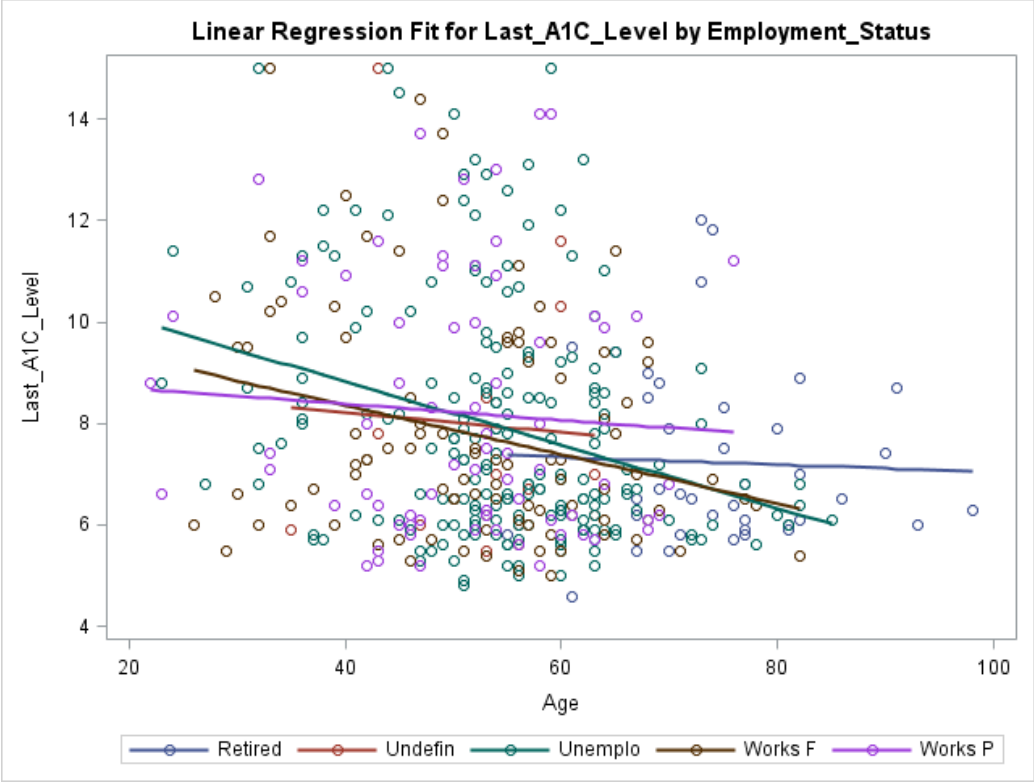

Figure 1. Linear regression fitted line of levels of HbA1c and age by employment status. Retired, retired people; Undefin, undefined category; Unemplo, unemployment; Works F, worked full-time; Works P, worked part-time.

We further performed multiple linear regression analysis while controlling for age, gender, employment status, and an inter-action term of gender by employment because the type 2 diabetes is more prevalent in males (11) and females pre-dominated in part-time work with the highest level of HbA1c (mean=8.21%; SD=2.46) in our data (**Table 3**). We found that the overall model was significant and that age was negatively associated with levels of HbA1c significantly (Beta=-0.46, $p<0.0001$); and females tended to have a lower level of HbA1c (Beta=-0.51, $p=0.0291$) compared with males. However, there was no significant difference in the mean level of HbA1c between employment statuses ($p=0.5504$); and no significance was found for the inter-action between employment status and age ($p=0.450$) and the interaction between employment status and gender ($p=0.735$).

Based on the model with an interaction term of age and employment status, we performed a post hoc test for the least-square mean of HbA1c by employment status (**Figure 2**). Except that there was a difference in the least-square mean of HbA1c between work full-time and part-time at a marginally significant level ($p=0.0823$), we found no significant difference in the mean level of HbA1c among other groups ($p=0.3049$), although the retired people still had the lowest while people working part-time had the highest level of mean HbA1c. This is

probably because that age had accounted for the retirement effect on HbA1c.

Table 3. Multiple linear regression analysis of levels of HbA1c with age, gender and employment status.

Variable	Code	Beta	SE	t Value	*P*	*P**
	Intercept	11.0261	0.6119	18	<.0001	
Age	Years	-0.0475	0.0101	-4.72	<.0001	
Gender						
	Female	-0.5103	0.2329	-2.19	0.0291	
Employment Status						0.5504
	Retired	0.0934	0.5040	0.19	0.8531	
	Undefined	-0.3498	0.6833	-0.51	0.6090	
	Unemployment	-0.1899	0.3152	-0.6	0.5471	
	Work full time	-0.5348	0.3596	-1.49	0.1378	
	Work partime	0.0000	.	.	.	

Note, p*, the overall p-value for association with HbA1c

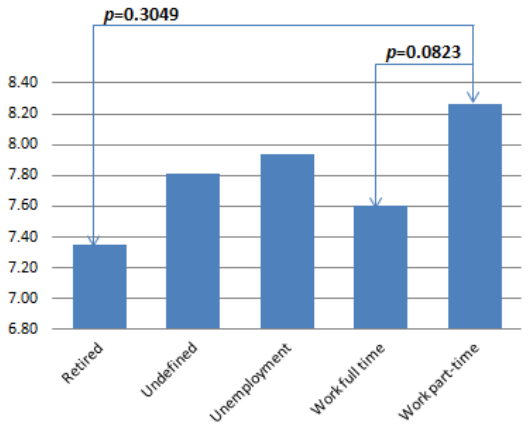

Figure 2. Least square means of HbA1c by employment status based on multiple linear regression with an interaction term of age and employment.

DISCUSSION

Several papers have investigated the effect of work on the management of Type 2 diabetes, and its impact seems to be that people with diabetes tend to leave employment and retire early. Whether retirement results in better control of diabetes for patients that are retired have not been examined. In our limited data from one medical facility serving the uninsured and underinsured, we found that people of older age, who were mainly retired people have better management of their HbA1c levels.

Walzer theoretically evaluated the influence of early retirement on healthcare budget and insurance premiums and found that it might not be desirable for insurance companies and countries to have patients with diabetes retire early(12). Studies using two independent datasets show that levels of HbA1c are increased with age in healthy populations without known diabetes (13). In addition, diabetes is a progressive disease, but retirement could be an effective intervention to delay progress.

While studies have generally found that patients with diabetes retire earlier, Miah and Wilcox-Gok (14), found that patients with diabetes and other chronic illnesses accumulate fewer assets over time and so tend to retire later. Their study did not show a reduction in activities of daily living for people with diabetes and given the effective medications available and if combined with diet and exercise should lead to the effective long-term management of diabetes. Their result is supported by a study in Finland (15), showing that patients with diabetes work about two years longer than people not diagnosed with diabetes do. This finding may be related to the superior health system in Finland, which provides effective management of diabetes to every citizen and to having flexible jobs situations that allow people the opportunity to stay employed and manage their disease. It would be interesting for high-income countries with aging populations to evaluate the effect of job change on the control of diabetes to allow such patients to stay in the workforce. An Australian study also found that diabetes reduced income and that people with diabetes tend to retire early (16).

However, an individual's decision to retire is based on many factors, including the type of job, retirement savings, family support, or other types of retirement funding as well as age. Patients with diabetes as older adults tend to have clinical complexity or cognitive impairment that may have reduced their ability to do exercise or manage their diabetes (17, 18). Using Finnish data, Kivimaki et al found that retirement was associated with an increased likelyhood of poor adherence to antidiabetic drugs in men and associated with poor adherence to antihypertensive medications in both men and women (19).

The theoretical argument can be made that since people with chronic diseases are likely to die earlier, there is a benefit to having them retire earlier; however, if retirement then allows them to manage their chronic conditions better, their lives might not be shortened. Rodriguez has

posited that since people with chronic diseases at low social and economic status die at younger ages, their contribution to economic participation is lost (20). As the burden of chronic non-infectious diseases grows with aging populations, countries will have to find a way to encourage active aging. It is worth examining in future studies what types of jobs lead to better management of diabetes and advising a change of employment rather than early retirement for low-income people with diabetes. It may also be a policy intervention for governments to provide people with chronic diseases such as diabetes with training to change jobs to less stressful ones or posts that are more conducive to the management of their condition. As the population ages, the prevalence of diabetes will continue to rise, and having diabetic patients stay in the working population will be critical for society.

People over 50 years with diabetes have higher levels of physical disability and faster rates of deterioration of the physical ability compared with people of the same age without diabetes; and the difference is more pronounced in women, racial minorities and people with lower levels of education with diabetes compared to the same group without diabetes (21). The deterioration in physical ability explains why studies have found higher rates of not working and retirement in diabetes patients. Vijan et al. (22) found that people with diabetes are more likely to be disabled, retired, or taken sick days off work compared to people of the same age not diagnosed with diabetes. They estimated approximately an annual economic loss of one billion dollars a year due to the decline in economic productivity among people with diabetes. The rate of diabetes has increased significantly since their analyses in 2004, and the loss will be higher today. It is, therefore, important to find ways of having people with diabetes stay employed and manage their diabetes while at work.

Certain types of jobs where workers have low control are associated with increased risk of diabetes (23). A way forward could be that after diagnosis with diabetes, people could move to other types of jobs that offer more control such as jobs where they can work from home or schedule on their own time rather than retire. Kouwenhoven-Pasmooij et al. (24) found that while workers with diabetes had increased probability of early retirement and getting disability benefits, this probability increased mostly for people with low control jobs. Whether jobs can be generated for people with diabetes that allows them to stay in the workforce depends on how co-workers accept such programs and if co-workers were willing to have changes in the workplace to assist diabetes patients to remain at work in Denmark (25). This may not be the case globally as things like taking blood sugar measurements at work and thriving to eat differently from peers has been associated with stigmatization (26). Mutambudzi et al. (27) also found that jobs with more effort than reward were associated with a diagnosis of diabetes. How to change work environments for an aging population with more prevalence of chronic diseases such as diabetes especially in low paying jobs where people have less control will be a challenge for the high-income countries in the coming years.

Social support has been found to improve diabetes management in the middle-aged and elderly patients with Type 2 diabetes (28) and people in retirement should be able to do more exercises and eat healthier but also find time to associate with family and friends in situations that leads to less stress and more communal circumstances. In our study with small limited data, there is an indication that retirement could confer some benefit for older people with diabetes.

Limitations

Our data from medical records were not collected for the sole purpose of research. One major limitation of this study is that we did not obtain longitudinal data and only used the last HbA1c for patients to determine if patients had their diabetes under control and therefore effects over time could not be determined.

CONCLUSION

Our study showed that older diabetics who are mainly retired people have better management of their diabetes. Earlier studies have shown that people with diabetes retire early, and we show that retirement helps with the management of diabetes, indicating that retirement may be an effective intervention for diabetes, especially in the low-income patients. As populations age, there may be a need for investigating alternatives to retirement such as job change to keep people employed and contributing economically.

CONFLICT OF INTEREST

We declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLEDGMENTS

We acknowledge Nandini Singh and Emma Freiling for the blinded data download, Moussa Dia for mapping the distance to residential addresses from clinic address and Kendra Robinson, the Diabetes Clinic Director at Olde Towne Medical and Dental Center who manages the diabetes patients at the clinic.

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How to cite this article:
Obasanjo I and Mann W. Retirement and management of diabetes in medically underserved patients with type 2 diabetes: preliminary findings and literature review. Glob Clin Transl Res. 2019; 1 (2):74-77.

Article

Serum levels of oxidants and protein S100B were associated in the first-episode drug naïve patients with schizophrenia

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Received January 29, 2019; Accepted May 20, 2019

ABSTRACT

Background: Patients with schizophrenia have been noted with an elevation of serum S100B protein concentration, but the pathological process is not known. This study was to investigate the relationship between levels of S100B protein and oxidative stress.

Methods: General information and blood sample were collected from the first-episode drug naïve or drug-free acute stage of patients who met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for schizophrenia and healthy controls. The serum levels of S100B, total oxidants (TOS) and malonaldehyde (MDA) were used to measure the level of oxidative stress in both patients and healthy controls. General linear regression analysis was performed to examine the association of S100B protein with the levels of oxidative stress.

Results: The levels of serum protein S100B were associated with the concentration of both TOS (Beta=15.77; p=0.0038) and MDA (Beta=7.90; p=0.0068) in the first-episode drug-naive patients (n=29).While both associations were no longer significant in the drug-free acute phase patients (n=29) (p>0.05), the levels of serum S100B was still consistently associated with TOS (Beta=12.42;p=0.0026) and MDA(Beta=4.11;p=0.0480) in the combined group of patients group(n=58). Simultaneous analysis of both oxidative markers, we still found that both TOS (Beta=12.88; p=0.0103) and MDA (Beta=6.46; p=0.0167) were associated with the serum level of protein S100B in the first-episode drug-naive patients, but not drug-free acute phase patients.

Conclusion: Our results suggest that astrocyte activity, serum levels of oxidants, and their cross-talking might be involved in the pathogenesis of schizophrenia. This warrants a further study for understanding the underlying mechanism.

KEYWORDS

Oxidative stress, S100B protein, schizophrenia, MDA, total oxidants

INTRODUCTION

Extensive evidence suggests that astrocytes play a crucial role in the central nervous system functions, which have been implicated in the dynamic regulation of neuron energy metabolism and production, synaptic network formation, neuron electrical activity, neurotransmitter release, and immune responses. S100B is a protein of the calcium-binding protein family that is localized in the cytoplasm and nucleus of cells and involved in the regulation of multiple cellular processes including cell cycle progression and differentiation. The protein S100B is glial-specific and secreted by astrocytes; it may function in neurite extension, the proliferation of melanoma cells, stimulation of Ca^{2+} fluxes, inhibition of protein kinase C (PKC)-mediated phosphorylation, astrocytosis, and axonal proliferation, and inhibition of microtubule assembly. S100B acts as a neurotrophic factor and neuronal survival protein in the developing central nervous system(CNS)(1); whereas it can spill from the injured cells and enter the extracellular space or bloodstream, and then cause an increase in the serum levels of protein S100B during the acute phase of brain damage.

While the protein S100B is considered a potential clinical marker for blood-brain barrier (BBB) permeability, CNS injury or presence of neurological conditions (2), evidence has also supported that protein S100B may play a role of immune pathology in the etiopathogenesis of schizophrenia(3), which has been believed involving brain-derived neurotrophic factor (BDNF) (4, 5), the immune and inflammatory changes (6, 7), the oxidative stress (8-11). The protein S100B has gained attention as a potential peripheral biomarker of schizophrenia (3, 12-17) and displays neuroprotective or neurodegenerative abilities that depend on its concentrations. At pico- and nanomolar concentrations, S100B promotes cell promotion and differentiation, but induces cellular death at micromolar concentrations (18-20). Elevated levels of S100B in blood have been linked to brain damage (21-24) and a group of psychi-

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atric disorders including schizophrenia, major depressive disorder, bipolar and mood disorder (25-27). Most of these studies were based on the sample of serum, plasma, or cerebrospinal fluid in comparison with healthy controls (16, 28-30). Studies have indicated that dysfunction of glial cells, a decreased brain density of glial cells, and alterations in genes associated with astrocytes and oligodendrocytes might present a pathogenic factor in schizophrenia (15, 31). However, there is still a lack of consistent association of the levels of S100B with schizophrenia(32) or no association(33). Our recent study has shown that levels of S100B were elevated in the patients of first-episode drug-naive or acute-stage drug-free with schizophrenia in comparison with healthy controls (34).

The elevation of S100B may involve the inflammatory hypothesis of schizophrenia pathogenesis (13, 35, 36). Activated glial cells release a variety of pro-inflammatory mediators (e.g., cytokines) which can potentially contribute to neuronal dysfunction and result in the progression of the CNS pathology (37). In addition, S100B, expressed by subsets of $CD3^+$ $CD8^+$ T cells and natural killer (NK) cells, is suspected associated with the immune hypothesis of schizophrenia(13). Evidence has indicated that the level of S100B secretion is increased by pro-inflammatory cytokines in C6 glioma of cells and hippocampal slices of rats through the mitogen-activated protein kinase (MAPK) pathways; and the antipsychotic drugs such as haloperidol and risperidone can inhibit the secretion of S100B that is induced by interleukin (IL)-6 stimulation, in which oxidative stress is believed as a component (38).

Free radicals leading to elevated oxidative stress have similar property compared with S100B. Free radicals are species usually produced during cellular metabolism in aerobic cells. In the conditions of increase in production or decrease in scavenging of free radicals, an excessive free radical production can injure neurons in schizophrenia and affect their functions such as membrane transport, impairment of energy production in mitochondria, changes in membrane phospholipid composition, alteration of receptors and transporters as well as neurotransmission (39), which may be involved in the pathophysiology of patients with schizophrenia.

A few studies have investigated the correlation between the protein S100B and oxidative stress. Protein S100B is shown to suppress oxidative cell damage; whereas oxidative stress impairs the ability of S100 proteins to bind and activate protein phosphatase 5 (PP5), a serine/threonine phosphatase involved in oxidative stress responses (40). Studies have shown that a long-term exposure to high blood glucose concentrations leads to an increase in the TOS in the patients with diabetic ketoacidosis and that the neurotransmitter changes in response to this exposure lead to an increase in the levels of S100B (41). It is also found that copy number variations on chromosome 21 disrupted gene human serum albumin (HSA) 21 associated S100B contributes to oxidative stress and apoptosis in Down syndrome human neural progenitors (42) and the role of S100B in the development of cerebral vasospasm and brain damage may result from the induction of oxidative stress and neuroinflammation after subarachnoid hemorrhage (43). In investigating the serum levels of multiple oxidative stress biomarkers and S100B in patients with major depressive disorder (MDD) in an acute phase, only serum superoxide dismutase (SOD) and catalase (CAT) activities were found significantly higher compared with healthy subjects; the Hamilton Depression Scale (HAMD) scores have been positively associated with the levels of S100B (44).

In this study, we aimed to investigate the relationship between the level of protein S100B and oxidative stress status in first-episode naive drug patients with schizophrenia, which allows us to minimize the potential impact of confounding factors such as illness duration, medication effects, and the psychiatric and medical co-morbidities. We used malondialdehyde (MDA) and total oxidant status (TOS) in serum to measure the levels of oxidants. MDA is one of the end products of this self-perpetuating lipid peroxidation reaction, which is considered a specific and sensitive measure of lipid auto-oxidation(45); the level of TOS reflects the total effect of all oxidants existing in plasma or serum and body fluids(46).

METHHODS

Participants

Participants were recruited from Beijing Huilongguan Hospital, a Beijing-city owned and one of the largest psychiatric hospitals in China. Inpatients, who met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for schizophrenia (American Psychiatric Association, 1994) with an agreement of two senior psychiatrists using the Structured Clinical Interview for DSM-IV (SCID), were recruited. It has also been suggested that some antipsychotics, primarily typical antipsychotics may have pro-oxidant effects and increase the oxidative stress and oxidative cell injury(47). Kropp et al. reported that three weeks of treatment with typical antipsychotics might increase the plasma MDA levels compared with the atypical antipsychotics (48). To avoid potential confounding, two groups of patients were recruited. One group of patients were first-episode and had never taken antipsychotics (first-episode drug-naive); the other group of patients were acute stage and had not taken antipsychotics for at least three weeks prior to the study (drug-free acute stage). Healthy subjects without current or past psychiatric disorders and matched on age and gender were selected from the local community, and Axis I psychiatric disorders was ruled out through psychiatric review evaluation by a psychiatrist.

A complete medical history and physical examination, laboratory tests including a urine and blood screen, and electrocardiogram were obtained from all participants, in order to rule out any neurological or other medical diseases. Neither the patients nor the control subjects had a diagnosis of alcohol or illicit drug abuse/dependence. Excluded criteria: 1) subjects who had another psychiatric disorder or drug and alcohol abuse or dependence, 2) subjects who was incapable of completing the investigation for any reason such as non-cooperation, and mental

retardation, and 3) subjects who have a family history of diabetes or eating disorders either.

The ethics committee of Beijing Huilongguan Hospital approved the study (Number: 2015-012). After a complete description to all participants, the written informed consent was obtained.

Clinical evaluation

Information on general socio-demographics and clinical and psychological conditions were collected for each patient or subject with structured forms. Additional information was collected from available medical records or with assistance from a family member or relative and treating clinician. The patient's psychopathological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) on the day of the blood draw, which was conducted independently by two psychiatrists. To ensure consistency and reliability of ratings across the study, two psychiatrists had simultaneously attended a training session in the use of the PANSS before this study started. After necessary training, an intra-rater correlation coefficient higher than 0.8 was required for the evaluation of PANSS total score. Brief psychiatric rating scale (BPRS) and the measurement and treatment research to improve cognition in schizophrenia (MATRICS) and Matrics Consensus Cognitive Battery (MCCB) were also assessed and collected for each patient at baseline as part of other studies. The concentration of MDA was measured in terms of nmol/gmHb. The levels of TOS was determined using a colorimetric method developed by Erel(46). The assay is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidant species in acidic medium and the measurement of the ferric ion by xylenol orange. The assay is calibrated with hydrogen peroxide, and the results are measured in term of μmol H2O2 Equiv. /L.

Blood samples and Assays

Serum samples from all subjects were collected at 7 AM following overnight fasting for laboratory tests. 5 ml of the venous blood sample was taken from the antecubital vein of each participant. The blood sample in lithium heparin tube was centrifuged (4^0C, 3500rpm, 10min), aliquoted, and then stored at -70^0C until assayed. The same technician, who was blind to the clinical data, assayed all samples. The identity of all subjects was coded and maintained by the investigator until when all biochemical analyses were completed. Inter- and intra-assay variation coefficients were 7% and 5%, respectively.

Serum levels of S100B were measured within one week by the sandwich enzyme-linked immune sorbent assay (ELISA) using a commercially available kit (Ad Litteram Diagnostic Laboratories, Inc., San Diego, CA, USA). The detailed information has been described elsewhere (34). The levels of MDA were measured using monitoring thiobarbituric acid-reactive substances (TBARs) assay kit (Cayman Chemical Company, Ann Arbor, MI, USA). The principle of the assay, based on the procedure of Dawn-linsley (49).

Statistical analysis

SPSS, Statistical Package for Social Sciences, for Windows 17.0 and R 3.2.0 Package (https://www.r-project.org/) were used for the statistical analysis. General linear regression analysis was performed to examine the association of S100B with the levels of oxidative stress as measured by TOS and MDA. The analysis was first performed using all participants together, with schizophrenia patients with the first episode drug-naive and acute phase drug-free patients with schizophrenia, and healthy controls, by fitting a group by levels of S100B interaction term while adjusting for age and sex, followed by a stratification analysis by the group. We then performed an analysis of patients only to maximize the statistical power and adjusting for age of onset (years), duration of illness, smoker status, and years of education. A threshold level of 0.05 was used for declaring statistically significant.

RESULTS

Table 1 presents the demographics and descriptive statistics of all measurement and patient characteristics including psychopathological symptom and cognitive measures. In total, the study included 29 schizophrenia patients with the first-episode drug-naive (Mean age=27.62; SD=7.18 years), 29 patients with the drug-free acute stage (Mean age=27.03, SD=7.68 years), and 50 healthy controls (Mean age=25.92, SD=6.69 years). There was no significant difference in mean age and distribution of sex among three groups (p>0.05). We noted significant differences in the levels of S100B, TOS, and cognitive functions as measured by MCCB composite score (p<0.01), but no significant difference in the levels of MDA (p>0.05) were found among the three study groups.

While no significant difference in the levels of protein S100B, TOS and MCCB composite score between the two groups of patients (i.e., drug-naive and drug-free patients), there were significant differences in these measures between patients and healthy control (Table 1). We noted a difference in psycho-pathological symptoms of PANSS Positive score and general psychopathology (p<0.05) between two patient groups. The first-episode drug-naive patients appear more severe in symptoms. Specifically, the schizophrenia patients of first-episode drug-naive had a higher PANSS positive score (Mean, 25.10; SD, 5.07) than the drug-free acute stage patients (Mean, 22.12; SD, 6.79), and a higher PANSS total score (Mean, 89.36; SD, 15.11) than drug-free group (Mean, 82.35; SD, 14.97).

In analysis of all groups together adjusting for age and sex, we found that levels of protein S100B were associated with the concentration of both TOS (Beta= 15.45; p=0.0050) and MDA (Beta=7.33; p=0.0066) in the first episode drug-naive patients with schizophrenia (Table 2). However, there was no association of TOS (Beta=11.256; p=0.0789) nor MDA (Beta=-2.819; p=0.3578) with protein S100B in the drug-free acute phase patients with schizophrenia; no significant association of either TOS (p=0.7458) or MDA (p=0.651) with S100B in the healthy controls. We noted a significant interaction between the participant group and TOS (p=0.0014) and between participant group and MDA (p=0.0159) on the levels of S100B in serum, suggesting that the association of serum oxidants and S100B was different between patients and healthy controls.

Table 1. Demographics and descriptive statistics of serum biological markers and characteristics of the participants

	First episode drug-naive				Drug-free acute stage					Healthy control				
	N	Mean	Median	SD	N	Mean	Median	SD	Sig*	N	Mean	Median	SD	Sig**
Age (year)	39	27.62	27.00	7.18	34	27.03	26.00	7.68	n.s.	50	25.92	24.00	6.69	n.s.
Sex	39	0.59			34	0.59			n.s.	50	0.48	0.00	0.50	n.s.
S100B1(μg/L)	29	234.91	239.06	79.33	29	210.15	202.97	72.53	n.s.	50	117.72	108.50	46.91	**
Total oxidant capacity(μmol/L)	29	8.83	7.69	2.89	29	10.08	9.94	2.02	n.s.	50	15.66	15.36	4.26	**
Malondialdehyde (nmol/gmHb)	29	8.35	5.74	5.69	29	8.06	7.04	4.48	n.s.	50	6.41	4.34	4.11	n.s.
PANSS score														
Positive	39	25.10	24.00	5.07	34	22.12	21.50	6.79	*					
Negative	39	21.95	22.00	6.39	34	23.38	21.50	6.54	n.s.					
General	39	42.31	40.00	8.02	34	36.85	35.50	7.41	*					
PANSS total score	39	89.36	87.00	15.11	34	82.35	81.50	14.97	n.s					
Brief psychiatric rating score	29	47.69	46.00	7.12	29	42.76	43.00	7.64	*					
Smoker (%)	29	6.90			29	37.93			*					
Education (year)	29	12.65	12.00	2.92	29	12.48	12.00	2.31	n.s.					
Age at onset (year)	39	24.94	24.00	6.54	34	23.42	23.12	5.89	n.s.					
Total duration of illness(month)	39	31.15	20.00	33.83	34	46.29	34.00	47.14	n.s.					
MCCB composite score	35	44.74	45.00	11.19	27	45.07	44.00	11.08	n.s.	50	54.90	56.50	8.35	**

*, $p<0.05$, a significant difference between first episode drug-naive and drug-free acute stage of patients with schizophrenia;
**, $p<0.01$, a significant difference among three groups; n.s., non-significance ($p>0.05$);
Sig*, significance between first-episode drug naive and Drug-free acute stage;
Sig**, significance between all cases and healthy controls

Table 2. Regression analysis of oxidative stress with levels of S100B in the serum of patients with Schizophrenia

	Group	N	Beta	SE	t Value	*P*	R^2 (%)	P_{int}
TOS	Control	50	-0.524	1.606	-0.33	0.7458	0.22	0.0014
	Drug-naive	29	15.445	5.015	3.08	0.0050	25.28	
	Drug-free	29	11.256	6.143	1.83	0.0789	9.75	
MDA	Control	50	0.766	1.682	0.46	0.6510	0.43	0.0159
	Drug-naive	29	7.330	2.476	2.96	0.0066	23.86	
	Drug-free	29	-2.819	3.009	-0.94	0.3578	2.79	

P_{int}, the p value for the interaction between the group and oxidative stress; Analysis was performed by stratifying group while adjusting for age, sex and participant group.

In the patient specific-analysis, we found that the levels of S100B were associated with TOS (R^2=25.28%; Figure 1, A1) and MDA (R^2=23.86%; Figure 1, A2) in the first-episode drug-naive patients. While the TOS was not associated with the levels of serum protein S100B in the drug-free acute phase patients with schizophrenia (p=0.0789; R^2= 0.0975; Figure 1, B1), we noted a clear linear trend in the small size of sample (n=29). However, we find no trend of association of S100B with MDA (Figure 1, B2).

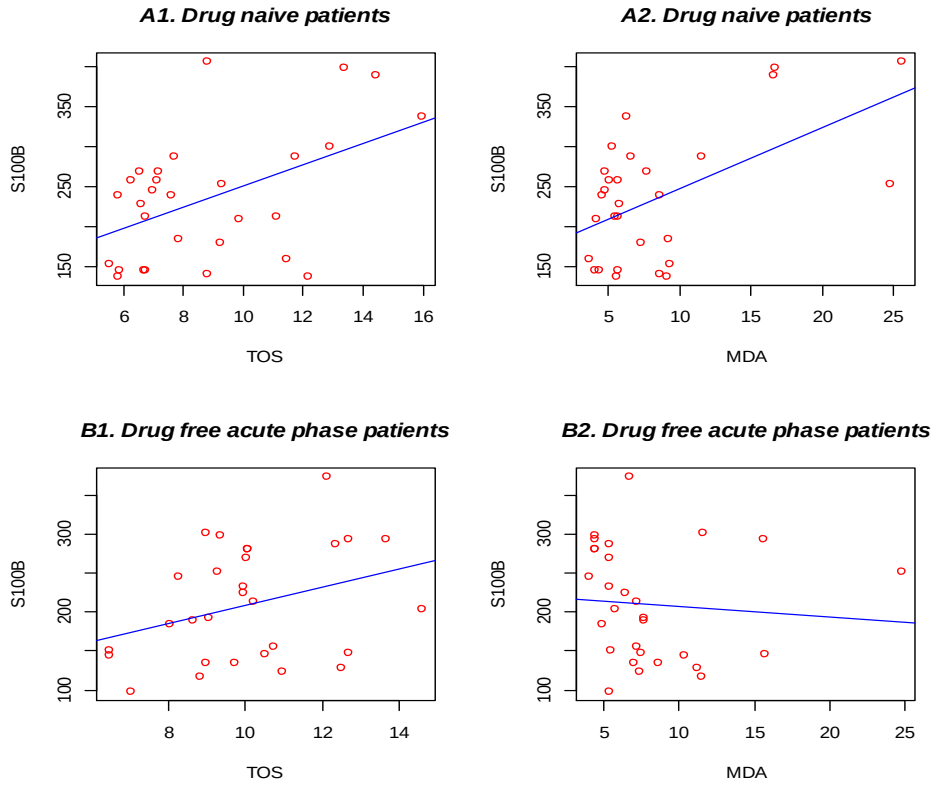

Figure 1. The best-fitted lines from the simple linear regression analysis of oxidants and levels of S100B in patients with schizophrenia (**A1**. TOS in the first-episode drug-naive; A**2**. MDA in the drug-free acute stage; B**1.** TOS in the first-episode drug-naive; **B2**. MDA in the drug-free acute stage).

To control for potential confounding factors in patients characteristics such as smoke status, duration of illness and educations, we further confirmed the association of oxidants and levels of S100B in the patient-only analysis (Table 3). The associations of TOS with S100B became slightly more significant in both groups of the first-episode drug-naive (p= 0.0038) and drug-free acute phase (p=0.0670). In the combined patient groups, TOS was more significantly associated with S100B (p=0.0026), and there was no interaction between TOS and patient group

(p=0.4390). However, we did not find any change in the association of MDA in either of patient groups. It is interesting to note that in the patient combined, MDA was still associated with S100B (p=0.0480), but we noted a significant interaction between the patient group and MDA on the levels of S100B, which had been noted in the scatter plot (**Figure 1, A2 vs. B2**)

To further determine which oxidant measures were associated with S100B, we performed multiple regression analysis of two markers in the same regression model (**Table 3**). In the first episode drug-naive patients, both TOS (Beta=12.88; p=0.0103) and MDA (Beta =6.46; p=0.0167) were significantly associated with S100B. However, two markers were no longer significantly associated with S100B in the drug-free acute phase patients, although TOS showed a strong effect size (Beta=10.95; p=0.1116) on the levels of S100B. Combined together two groups of patients, only TOS was associated with S100B (Beta=12.83; p=0.0015), but not MDA (Beta= 2.52; p=0.1827).

Table 3. Multiple regression analysis of oxidants (TOS and MDA) and levels of serum S100B in patients with schizophrenia after further adjusting for potential confounding such as smoke status, duration of illness and years of educations.

	Group	Parameter	**Beta**	**SE**	**t-Value**	**p**
Simple regression						
	First-episode	TOS	15.77	4.87	3.24	0.0038
	Drug-free	TOS	12.71	6.59	1.93	0.0670
	Combined	TOS	12.42	3.91	3.17	0.0026
	Interaction	TOS*Patient group	6.33	8.11	0.78	0.4390
Simple regression						
	First-episode	MDA	7.90	2.65	2.99	0.0068
	Drug-free	MDA	-2.98	3.37	-0.89	0.3857
	Combined	MDA	4.11	2.03	2.03	0.0480
	Interaction	MDA*Patient group	8.86	4.20	2.11	0.0400
Multiple regression						
	First-episode	MDA	6.46	2.47	2.61	0.0167
		TOS	12.88	4.55	2.83	0.0103
	Drug-free	MDA	-2.29	3.16	-0.72	0.4778
		TOS	10.95	6.58	1.66	0.1116
	Combined	MDA	2.52	1.86	1.35	0.1827
		TOS	12.83	3.82	3.36	0.0015

DISCUSSION

In the present study, we found that the levels of oxidants measured by TOS and MDA in serum were associated with the elevated levels of serum protein S100B in patients with schizophrenia. The associations of S100B with both TOS and MDA were consistent in the first-episode drug-naive patients with schizophrenia, but no significant association in drug-free acute stage patients. We did not find that any significant association of oxidants with protein S100B in healthy controls.

Our findings that association of oxidants with the levels of protein S100B is consistent with the previous study (50). One speculation is that a higher level of oxidants causes an increase in the levels of serum protein S100B. The reactive oxygen species (ROS) overproduction in myoblasts has been shown to cause an upregulation of protein S100B via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) activation (51). In the high concentrations of oxidants, excessive reactive oxygen species (ROS) cause the damage on the components of the cells, including the proteins (enzymes, receptors), the lipids and deoxyribonucleic acid (DNA), which may consequently affect the apoptosis and the cell death(52-55). Oxidative stress is not only responsible for the neuron apoptosis but also can provoke the astroglial cell death. In the meantime, pituitary adenylate cyclase-activating poly-peptide (PACAP), a substance that can promote neuron survival, exerts a potent protective effect against the oxidative stress-induced astrocyte death. The anti-apoptotic activity of PACAP on the astrocytes is mediated through the protein kinase A, PKC and MAPK transduction pathways, by the inhibition of the ROS-induced mitochondrial dysfunctions and caspase 3 activations. Therefore, the oxidative stress has toxic effects on the astroglial cells and then affects the synthesis and the secretion of S100B (56).

Conversely, the elevated level of protein S100B leads to an increase in oxidant levels. In the Down syndrome neural progenitor cells, constitutively over-expression of S100B leads to an increase in reactive oxygen species (ROS) formation and activation of stress response kinases(57). S100B stimulates inducible nitric oxide synthase in rat primary cortical astrocytes through a signal transduction pathway that involves activation of the transcription factor NF-kappaB (58). Furthermore, S100B-induced inducible

nitric oxide synthase promoter activation was inhibited upon the mutation of the NF-kappaB response element in the promoter, whereas transfection of cells with an NF-kappaB inhibitor blocked the S100B-induced inducible nitric oxide synthase promoter activation and nitric oxide production. These studies define a signal transduction pathway by which S100B activation of glia could participate in the generation of oxidative stress in the brain. The astroglial cells are, the most important source of the free radicals in the CNS (59) and S100B was primarily expressed in astrocytes. High glucose environments enhanced the pentose phosphate pathway (PPP) in the astroglia, reducing the ROS production and thereby play a neuroprotective role (60). Activated astroglial cells produce large amounts of nitric oxide (NO) which, through the binding to the soluble guanylyl cyclase, rapidly increases the cyclic guanosinc monophosphate (GMP) concentrations. The stimulation of these glucose-metabolizing pathways by NO would represent a transient attempt by the glial cells to compensate for the energy impairment and the oxidative stress, and thus to emerge from an otherwise pathological outcome (61). These point out that the increased S100B may be a source of the oxidative stress or a compensatory response to the oxidative stress.

It is also likely that there is no direct interaction between the oxidative stress and the S100B and both may be associated with the neurodegenerative process (62). Studies have indicated a neurodegenerative component in schizophrenia (63, 64); and the accelerated aging in schizophrenia was supported by the structural and the functional brain abnormalities, the higher incidence of the aging-associated metabolic profiles and disease(65), the early cognitive decline, and the altered telomere dynamics(66). In addition, the oxidative stress and the mitochondrial dysfunction play essential roles in the pathogenesis of the neurodegenerative disorders(67) may also support the "accelerated aging" in schizophrenia. On the other hand, in an S100B over-expressing mouse model of pathological aging, the antioxidant vitamin E is shown to increase S100B-mediated microglial activation (68). There is inconsistent evidence that dietary compounds (such as trans-resveratrol) can inhibit or reverse oxidative stress, and the reduction of S100B secretion induced by H_2O_2 was not changed by resveratrol (69). In cirrhosis repre-sents, a negative correlation between S100B and oxidative stress measured by the thiobarbituric acid method in the case group was found (70). The inconsistent results were interpreted by the difference in the assay methods on oxidative stress.

In summary, we observed that the levels of the serum protein S100B was associated with the concentration of both TOS and MDA in the first episode drug-naive group and the association of protein S100B with TOS was weaker and no association with MDA in the drug-free group.

Limitations

Our results should be read with care. This was only based on the baseline measures of S100B and TOS or MDA. We only analyzed two measures of oxidant levels: TOS and MDA but did not measure the antioxidant levels, the imbalance of antioxidants and oxidants determine the level of oxidative stress. In addition, our sample size is still limited in both inpatient groups and healthy controls, and we did not collect detailed information on smoking history except for the current smoke status, other medications, etc. To gain statistical power and test the possible causal relationship, a therapeutic study would help validate these findings.

CONCLUSION

Our study indicates that the high level of oxidants is associated with an elevated level of protein S100B. This warrants a further study for validation of this association and examines the potential causal relationship.

CONFILICT OF INTERESTS

We declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLWDGEMENTS

This work was supported by the National Natural Science Foundation of China (81761128201), and by Dengfeng plan of Beijing Municipal Administration of Hospitals (DFL20151901). The authors are grateful to Jia Li and Yue-Chan Wang for their technical assistance. Appreciation is also owned to the patients, clinical psychiatrists and nursing staff of the Wards 1, 2, 3 and 5 in Beijing Huilongguan Hospital for their participation and collaboration.

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How to cite this article:
Liu L, Li Y, Bian Y, Yang F, Li X, Han X, Tian L, Chen S, Wang Z, Tan Y. Serum levels of oxidants and protein S100B were associated in the first-episode drug naïve patients with schizophrenia. Glob Clin Transl Res. 2019; 1 (2):84-92.

Introduction to the editors