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IN THE NAME OF ALLAH,
THE MOST GRACIOUS,
THE MOST MERCIFUL

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The Majmaah Journal of Health Sciences shall be an international peer reviewed journal, which intends to serve researchers through prompt publication of significant advances, and to provide a forum for the reporting and discussion of news and issues concerning health sciences.

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To lead the debate on health and to engage, inform, and stimulate the academicians, researchers, and other health professionals in ways that will improve outcomes for patients.

Objectives

To promote research & evidence based practice in health sciences, so that a firm scientific knowledge base is developed, from which more effective practice may be evolved.

To ensure that the results of the research are rapidly disseminated to the practicing clinicians and educators, in a fashion that conveys their significance for knowledge, culture and daily life.

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Majmaah Journal of
Health Sciences

Editorial

From Editor's Desk…..

It gives me immense satisfaction to reach you all through the 13th issue of MJHS. At the outset let me express my gratitude to our beloved Rector Dr.Khalid Bin Saad Al Meqrin and Vice Rector for Graduate Studies and Scientific Research Prof. Mohammad Bin Abdullah Al-Shaaya for the trust endowed upon editorial team and me.

Scientific publications are the most important ways for communicating scientific research work. Personally I feel the purpose of academic research should be to seek the truth and new knowledge for the benefit of humanity. Undoubtedly research complements and helps in improvisation of teaching and training, clinical care, and public health. Therefore research has become an integral responsibility of the faculty members.

Owing to the increase in the number of articles from Universities all over the Kingdom and outside, I am very happy to announce that from this year MJHS will bring out three issues per year. Thanks to the tireless efforts of editorial team and reviewers. It is also my privilege to introduce the editorial sub-committee formulated to increase the efficiency of working. On behalf of the editorial board I assure that we will continue to work hard for improving the quality of the journal and to bring pride to our University.

Dr.Khalid Mohammed Alabdulwahhab

Editor in Chief

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Original Article

Integration of Proteomics and Transcriptomics Data Sets Identifies Prognostic Markers in Chronic Lymphocytic Leukemia

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Abstract

Background and aim: Chronic lymphocytic leukemia (CLL) is a malignant disease of B-cells that is characterized by variable prognosis. This study aims to search for novel prognostic markers in CLL. **Methods:** Six publicly available data sets of omics (proteomics and/or transcriptomics) that were generated from CLL cells, normal B-cells and normal peripheral blood mononuclear cell (PBMCs) were integrated to perform a crude search for CLL-associated proteins. Next, two publicly available data sets of CLL transcriptomics based on two independent cohorts (130 and 107 CLL patients) with available clinical information were utilized to assess the relevance of the suggested CLL-associated proteins at the level of transcription (mRNA) to CLL prognosis. Finally, Pearson score (PS) was employed to conduct correlation analyses of gene expression. **Results:** Sixty candidates were suggested as CLL-associated proteins, from which 19 proteins (32%) were previously implicated in cancer, and over-represented CLL-related biological processes. Furthermore, amongst the 60 proteins, nine (15%) had transcripts that significantly predicted early therapy ($p = 0.0001$ to 0.05) and/or short survival in CLL patients ($p = 0.0002$ to 0.05). Four of these markers showed a prognostic significance in the two independent data sets of CLL transcriptomics, increasing their validity as predictors of CLL prognosis. Finally, genes of pathways known to contribute to the aggressiveness of CLL were significantly correlated with FCRLA ($PS \geq 0.50$; $p < 0.00001$), which is a currently reported marker of poor prognosis. **Conclusion:** This study shows the usefulness of integrating publicly available omics data sets to identify potential biomarkers.

Key words: Leukemia, CLL; Prognostic Markers, Overall Survival, Time of Therapy; Proteomics; Transcriptomics.

الملخص

الخلفية: سرطان الدم اللمفاوي المزمن (س.د.ل.م) مرض خبيث يصيب الخلايا اللمفاوية البائية ويتصف بنتائج سريرية مختلفة بشكل كبير بين المرضى المصابين. الهدف: تهدف هذه الدراسة للبحث عن علامات إنذار حيوية جديدة في المرض (س.د.ل.م). **طريقة البحث:** تم دمج ستة مجموعات بيانية مستقلة للبروتيومكس والترانسكربتومكس للخلايا السرطانية والخلايا الطبيعية للبحث عن بروتينات سرطانية. ثم بعد ذلك تم استخدام بيانات ترانسكربتومكس للخلايا السرطانية (س.د.ل.م) من مجموعتين من المرضى (١٣٠ مريض و١٠٧ مريض) وذلك لتقصي دور البروتينات السرطانية في إنذار السرطان (س.د.ل.م). وأخيرا تم توظيف مقياس بيرسون لدراسة الترافق في التعبير الجيني. **النتائج:** كشفت الدراسة النقاب عن ستين بروتين سرطاني منهم ١٩ سبق أن تم ربطهم بأمراض خبيثة مختلفة بدراسات سابقة. ايضا أظهرت تسعة من هذه بروتين السرطانية القدرة على التنبؤ بمسار المرض وبالتالي يمكن اقتراحها كعلامات حيوية يمكن أن تخدم في إنذار السرطان (س.د.ل.م). كما دلت تحاليل الترافق الجيني ترافق جينات في مسارات إشارية مهمة في شراسة السرطان (س.د.ل.م) مع أحد علامات الإنذار التي كشفتها الدراسة الحالية. **الخلاصة:** توضح هذه الدراسة فائدة دمج بيانات الأومكس السرطانية والطبيعية لإكتشاف علامات انذار سرطانية جديدة

Introduction

Chronic lymphocytic leukemia (CLL) is a malignant disease that affects B-cells and is characterized by lymphocytosis of mature-looking B-cells (>5000 cells/µl) that accumulate in peripheral blood, lymph nodes, bone marrow and the spleen [1]. The cause of CLL is still unknown, yet some hereditary factors have been associated with the risk of developing CLL [2]. While important advances in CLL therapy have been accomplished, the current treatment does not eradicate CLL but reduces the disease burden and improves the overall survival time of afflicted patients [3].

CLL is a heterogeneous disease with variable clinical outcomes. While some patients have an indolent form of CLL, others exhibit an aggressive form of the disease with an early need for therapy and short overall survival time [1]. Different prognostic markers have been widely implemented to predict the prognosis of CLL [4]. For instance, deletions in 11q and 17p; unmutated immunoglobulin heavy variable genes (IGHV; UM-CLL); and over-expression of CD38 and zeta-chain-associated protein kinase 70 (ZAP-70) are markers of poor prognosis [5-8]. In contrast, deletions in 13q and mutated IGHV (M-CLL); and low-expression of CD38 and ZAP70 are predictors of good prognosis [5-8]. Although the above prognostic markers have been well established and widely applied, providing an accurate prognosis of CLL is still challenging [9]. Therefore, the search for novel prognostic markers that may improve the prognostication of the disease is needed.

Cancer-associated genes and/or proteins can be a rich source to facilitate the search for prognostic markers. In the context of CLL, various molecules that are reported to possess prognostic value for the disease exhibit preferential expression in CLL cells as compared with normal B-cells [4]. A typical example is ZAP-70, which is not expressed in normal B-cells but highly expressed in CLL cells from a subset of patients who are characterized with inferior prognosis [8]. In addition, apoptosis regulator Bcl-2, which is an anti-apoptotic protein, is significantly over-expressed in CLL cells compared with normal B-cells and predicts poor prognosis of the disease [10]. In contrast to normal B-cells, CLL cells express elevated levels of C-X-C chemokine receptor type 4 (CXCR4), which is a poor prognostic marker in the disease [11]. Overall, these findings indicate that the search for cancer-associated genes and/or proteins can be an early step to facilitate the identification of prognostic markers.

The goal of the present study was to integrate proteomics and transcriptomics data sets to identify novel prognostic markers in CLL. As mentioned earlier, the search for disease-associated proteins may facilitate the discovery of prognostic markers. Consequently, this study integrated six publicly available data sets of proteomics and transcriptomics to conduct a crude search for CLL-associated proteins. Next, two publicly available data sets of CLL transcriptomics were used to evaluate the prognostic value of the cognate transcripts of the proposed CLL-associated

proteins in CLL patients. Collectively, nine transcripts were currently reported to significantly predict the prognosis of CLL.

Methods

Proteomics data sets

Five proteomics data sets were used for the crude search for CLL-associated proteins. These data sets include three CLL proteomics data sets [12-14], one proteomics data set of normal B-cells [15] and one proteomics data set of normal PBMCs [16]. The proteomics data sets were selected because they were generated from primary cells (i.e. clinical CLL samples and normal cells from healthy donors) using the bottom-up proteomics approach and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) workflow. Further details about the five proteomics data sets are summarized in Supplementary Table 1. The proteomics data sets were obtained from the supporting information of the corresponding studies [12-16]. The data sets PXD001512-16 [14], PXD001657 [15] and PXD001415–23 [16] are also available at the ProteomeXchange Consortium http://proteomecentral.proteomexchange.org via the PRIDE partner repository https://www.ebi.ac.uk/pride/archive/. To insure a proper comparison between the proteomics data sets, the protein identifiers (protein-specific identifier) in the different data sets were cross-referenced with the UniProt entry identifiers (release: 2016_08) using the retrieve/ID mapping tool http://www.uniprot.org/uploadlists/ [17].

Transcriptomics data sets

For the analyses performed to crudely search for CLL-associated proteins, a transcriptomics data set of normal B-cells (Series GEO accession number: GSE10325; n= 6 samples) [18] was used. This data set was selected because it was generated from primary cells (normal B-cells of healthy donors) using Affymetrix Human Genome U133A Array. Additionally, two independent data sets of CLL transcriptomics [19, 20] were used for the analyses aimed to assess the impact of the suggested CLL-associated proteins (at the level of transcription; mRNA) on CLL prognosis. Three criteria led to the selection of these two data sets. First, they included prognostic information for the individual patients whose samples were studied; the data set GSE39671 [19] contained data regarding the time to first treatment (TTFT), which measures the time between diagnosis and initial therapy; and the data set GSE22762 [20] included information about the overall survival (OS), which indicates the time between diagnosis and death. Second, the two data sets were based on two independent patients cohort consisting of more than 100 patients each (GSE39671 = 130 patients, GSE22762 = 107 patients). Third, both data sets were generated using the same oligonucleotide microarray platform (Affymetrix Human Genome U133 Plus 2.0 Array).

All the transcriptomics data sets were obtained from Gene Expression Omnibus (GEO) http://www.ncbi.nlm.nih.gov/geo/

[21] The DataSet SOFT files of the transcriptomics data sets were downloaded from GEO. Then, the ID references (probe IDs) of the Affymetrix Human Genome U133A Array and Affymetrix Human Genome U133 Plus 2.0 Array were cross-referenced with the UniProt entry identifiers (release: 2016_08) using g:Profiler http://biit.cs.ut.ee/gprofiler/gconvert.cgi and the retrieve/ID mapping tool http://www.uniprot.org/uploadlists/ [17, 22].

Integration of the data sets and statistical analysis

The UniProt entry identifiers corresponding to the proteomics and transcriptomics data sets and Venn diagram tool http://bioinfogp.cnb.csic.es/tools/venny_old/venny.php [23] were used for the integration analysis that aimed to search for CLL-associated proteins. The correlation analysis using Pearson score was performed using Excel software. Kaplan-Meier curves of TTFT and OS were created using Prism Graphpad software;
p values and hazard ratios (HR) were calculated using the log rank test. The probability scores of the pathway enrichment analysis was calculated using Reactome pathway knowledgebase [24]. The heatmap visualization of the correlation analyses was conducted using the heatmapper web-based tool http://www1.heatmapper.ca/ [25].

Gene ontology annotations

To gain insight into the biological processes assigned to the proteins of interest, Quick Gene Ontology tool (Quick GO) https://www.ebi.ac.uk/QuickGO/annotations was employed [26]. The analysis was limited to gene ontology (GO) of Homo sapiens and only GO terms assigned to the aspect "Biological Process" was searched. Given that different proteins have different biological processes, the present study reported only biological processes that were over-represented by at least 4% of the proteins of interest.

Pathway enrichment analysis

Reactome, which is a curated pathway database https://reactome.org/, was used to perform pathway enrichment analysis of transcripts of interest [24]. The analysis was conducted using the "Analyze Data" tool and was limited to human-specific pathways. Reactome reports enriched pathways with p value, which indicates the probability of a pathway being identified by chance [24]. In the present study, only pathways that were significantly enriched ($p \leq 0.05$) were reported.

Results

Cancer-associated proteins can be a rich source for the search for cancer prognostic markers. Five proteomics data sets were used for the crude search for CLL-associated proteins; specifically, there were three CLL proteomics data sets (696 proteins [12], 728 proteins [13] and 3521 proteins [14]), one proteomics data set of normal B-cells (3029 proteins [15]) and one proteomics data set of normal PBMCs (6885 proteins [16]). The three proteomics data sets of CLL were combined to give a total CLL proteome consisting of 3615 distinct proteins. In addition, the pro-

teomics data sets of normal B-cells and normal PBMCs were combined to give a total proteome of the normal cells (control cells) containing 9086 distinct proteins. Next, the proteome of the CLL cells was compared with the proteome of the normal cells. From the CLL proteome, 3479 proteins (96%) were common to the proteome of the normal cells, while 136 proteins (4%) appeared only in the proteome of CLL cells (Fig 1A). To increase the stringency of the search for CLL-associated proteins, the proteins that were specific to CLL proteome (136 proteins) were further compared with a transcriptomics data set of normal B-cells (7976 distinct transcripts; GEO accession number: GSE10325 [18]) to eliminate proteins with a positive transcript expression in normal B-cells. Consequently, the current study reported 60 proteins (2% of CLL proteome) that were evident only in the proteome of CLL cells and had no detectable mRNA in the transcriptome of normal B-cells (Fig 1B). These proteins were suggested as CLL-associated proteins and were used for the search for CLL prognostic markers (Supplementary Table 2).

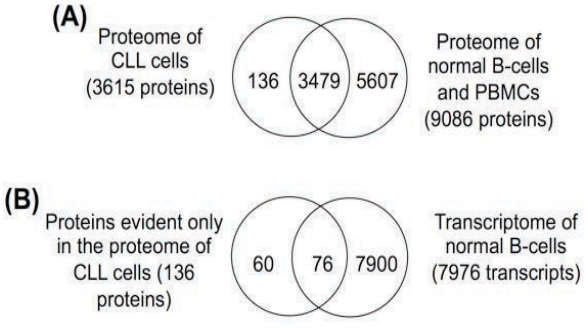

Fig.1 Integration of omics data sets. Proteomics and/or transcriptomics that were generated from CLL cells, normal B-cells and (PBMCs) were integrated for a crude identification of CLL-associated proteins

Existence of a relationship between the suggested CLL-associated proteins and cancer may indicate validity of the integration method applied in the present study. Thus, the literature was searched for the 60 proteins in the context of cancer. Interestingly, 19 proteins (32%) were previously shown to associate with cancer as opposed to normal tissues and/or implicated in the pathology and poor prognosis of different malignancies, including CLL (Supplementary Table 3). The Quick GO tool was also used to provide an insight into the biological processes of the proposed CLL-associated proteins (Table 1).

Table 1: Biological processes of the suggested CLL associated proteins

Biological process	Percentage of proteins
Signal transduction	12
Transcription, DNA-templated	12
Oxidation-reduction process	6
Protein ubiquitination	6
Phosphorylation	6
Kinase activity	6
Nucleosome assembly	6
Regulation of small GTPase mediated signal transduction	4
Positive regulation of MAPK cascade	4
Positive regulation of I-kappaB kinase/NF-kappaB (NF-κB) signaling	4
Positive regulation of B-cell proliferation	4
Inflammatory response	4
mRNA processing	4

Only biological processes reported for 4% or more of the proposed CLL-associated proteins are shown in the table. MAPK: mitogen-activated protein kinase.

The next goal was to use the proposed CLL-associated proteins for the search for CLL prognostic markers. To do that, two independent data sets of CLL transcriptomics were used (GEO accession numbers: GSE39671 [19] and GSE22762 [20]). The transcriptomics data set GSE39671 contained data regarding TTFT (number of patients = 130), while the transcriptomics data set GSE22762 included information concerning OS (number of patients = 107). Therefore, the two transcriptomics data sets were used independently to assess whether the transcripts corresponding to the suggested CLL-associated proteins predict TTFT and OS in CLL patients. The median level of transcripts corresponding to the proposed CLL-associated proteins was used to divide the patients into two groups: a low-expression group (patients with transcript expression smaller than the median) and a high-expression group (patients with transcript expression greater than the median). This was conducted for each one of the transcripts of interest in the two transcriptomics data sets. Next, Kaplan–Meier curves were constructed to compare TTFT and OS in the low expression and high expression groups of patients. Interestingly, the analyses showed that the cognate transcripts of 6 proteins and 7 proteins were significantly predictive of early therapy and short OS, respectively (Figs 2 and 3). Out of the six proteins whose transcripts indicated early therapy in the data set GSE39671 [19], four had transcripts that also predicted short OS in the data set GSE22762 [20], adding more validity to the reported findings.

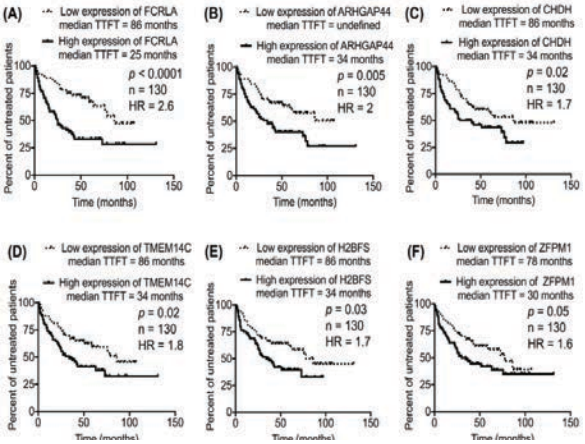

Fig. 2 Six of the CLL-associated proteins had transcripts significantly predictive of early therapy in CLL patients. Low expression: patients with a transcript expression smaller than the median; high expression: patients with a transcript expression higher than the median; TTFT: time to first treatment; HR: hazard ratio of high expression versus low expression.

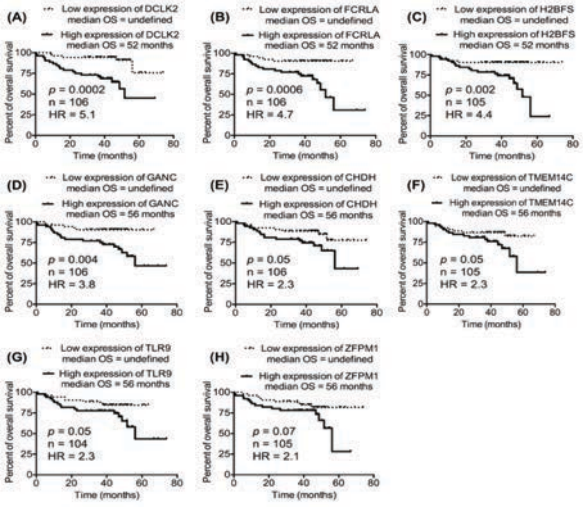

Fig. 3 Seven of the CLL-associated proteins had transcripts significantly indicative of short OS in CLL patients. Low expression: patients with a transcript expression below the median; high expression: patients with a transcript expression above the median; OS: overall survival time; HR: hazard ratio of high expression versus low expression.

Next, the present study attempted to explain the association of FCRLA with high-risk CLL. The Pearson score (PS; Pearson correlation coefficient) was applied using Excel software to the data set of CLL transcriptomics (GSE39671; 130 patients [19]) in order to identify genes that correlate with the expression of FCRLA. Next, genes that exhibited correlation with FCRLA (PS ≥ 0.50; $p < 0.00001$) were subjected to a pathway enrichment analysis using Reactome. Interestingly, the analysis showed a significant enrichment ($p < 0.05$) for CLL-related pathways (Table 2). Heatmap-based visualization of the significant correlation between genes assigned to CLL-related pathways and FCRLA in the 130 CLL patients is shown in Fig 4.

Table 2: Significant enrichment of CLL-related pathways by the genes that correlated with the expression of FCRLA

Name of enriched pathway	*p* value
S Phase (cell cycle)	0.0008
Extension of Telomeres	0.002
Downstream signaling events of BCR.	0.007
Telomere lagging strand synthesis	0.012
Activation of NF-κB in B cells	0.015
Cellular response to hypoxia	0.038

BCR: B-cell receptor; NF-κB: nuclear factor-κB

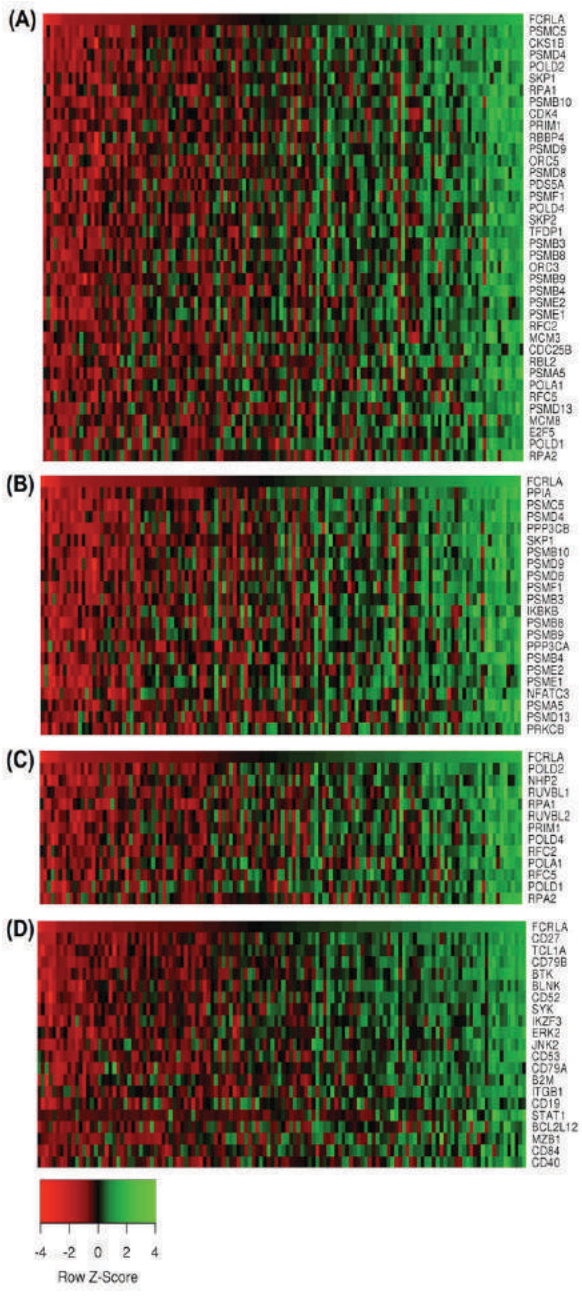

Fig. 4 Heatmap presentation of the correlation between genes assigned to CLL-related pathways and FCRLA. Excel software was used to sort the 130 CLL patients (from the data set GSE39671) horizontally based on the ascending expression FCRLA (from lowest expression to highest expression). Then, the genes that significantly enriched S phase (A), downstream signaling events of B-cell receptor (BCR) (B) and extension of telomeres (C); and other CLL-related genes (D) in the 130 CLL patients were sorted vertically according to their Pearson scores, with FCRLA being at the top of each list. Next, heatmapper web-based tool was used to construct a heatmap graphic based on the expression of the genes of interest and FCRLA in the 130 patients.

Discussion

The integration method of the omics data sets that was applied in the present study aimed for a rough identification of CLL-associated proteins from the massive CLL proteomics data [12-14]. This method targets proteins that were detected (present) in the CLL proteome but were not detected (absent) in the proteome of the normal cells (control cells). However, this method is not sensitive for the identification of differentially expressed proteins in CLL cells compared with the normal cells. Therefore, such proteins might have been missed because they were marked as "present proteins" in the proteomes of the malignant and the control cells. Although the proteome of the malignant cells was mainly derived from CLL cells, approximately 10% of the cellular population was PBMCs [12-14]. Therefore, the proteome of normal PBMCs [16] was included in the proteome of the control cells.

Direct comparison between independent proteomics data sets could misidentify disease-irrelevant proteins as proteins of interest. Therefore, the present study applied three actions in an attempt to avoid false identification. First, only proteomics data sets generated using the bottom-up approach and LC-MS/MS workflow were included to minimize technical variations. Second, the proteome coverage of the normal cells was larger than that of the CLL cells (9086 proteins compared with 3615 proteins, respectively). Therefore, this reduced the false identification of random proteins as CLL-specific proteins due to limited proteome coverage in the normal cells. Finally, for a candidate to be suggested as a CLL-associated protein, it had to be evident only in the CLL proteome and undetectable in the transcriptome of normal B-cells. Consequently, only 2% (60 proteins) of the CLL proteome was suggested as CLL-associated proteins, of which 32% (19 proteins) were previously linked to different neoplasms, including CLL (summarized in Supplementary Table 3), and 15% (9 proteins) had transcript expression that was currently shown to significantly predict the prognosis of CLL. In addition, the proposed CLL-associated proteins over-represented biological processes that were implicated in the progression of CLL, such as positive regulation of MAPK cascade, signaling of NF-κB and B-cell proliferation [4].

Nine prognostic markers were currently reported, of which five were previously linked to CLL. For example, an increased expression of TLR9 significantly predicted short OS in the present study supporting a previous report that showed an elevated expression of TLR9 in CLL cells compared with normal B-cells and a higher expression of TLR9 in patients with progressive CLL compared with those having a stable form of the disease [27]. In addition, an up-regulated expression of DCLK2 was described in the present work as a marker of short OS. Consistently, an independent transcriptomics study found an increased expression of DCLK2 in CLL samples from high-risk patients (UM-CLL and ZAP-70 positive) compared with low risk group (M-

CLL and ZAP-70 negative) [28]. The present study also reported a significant prediction of early therapy and/or short OS by an elevated expression of FCRLA, ARHGAP44 and CHDH. Interestingly, another independent transcriptomics study reported high expression of these three markers as risk factors of developing CLL, suggesting an involvement of these markers in the initiation of the disease [29]. Furthermore, the protein products of DCLK2, FCRLA and CHDH were also shown in the CLL proteomics data set [14], which was used in the present study, to be overexpressed in patients with high-risk CLL (UM-CLL) compared with patients having low-risk CLL (M-CLL).

Among the reported prognostic markers, increased expression of FCRLA was the strongest predictor of early therapy and second most accurate indicator of short OS in CLL patients using the two independent CLL transcriptomics data sets. These findings seem to fit with the role of FCRLA in B-cells. FCRLA was implicated in the activation and proliferation of B-cells; elevated expression of FCRLA was shown to mark activated B-cells and the highest level of FCRLA expression was reported in B-cells that reside in the proliferation centers of lymphoid tissues [30, 31]. Furthermore, FCRLA interacts with intracellular Ig and is required for the proper assembly of IgG and IgM [32, 33]. In consistence with the role of FCRLA in B-cells, the correlation analysis reported in the current study demonstrated a significant enrichment of CLL-related pathways; such as S phase (cell cycle), downstream signaling events of B-cell receptor (BCR), extension of telomeres and activation of NF-ϰB, by the genes that significantly correlated with the expression of FCRLA in the 130 CLL patients [34-37]. In addition, genes that are known to derive the proliferation and/or survival of CLL cells, in particular those that participate in the signal transduction of BCR like CD79A, CD79B, BLNK, BTK and SYK; and other genes, such as TCL1A, CD40, IKZF3 and CD27, exhibited a significant correlation with the expression of FCRLA [38-44]. This may provide an insight into the significant prediction of the aggressive form of CLL by the elevated expression of FCRLA.

A number of points should be considered while viewing the results of the current report. First, the integration of the omics data sets aimed for a rough identification of candidates that could be proposed as CLL-associated proteins. However, to draw a definitive conclusion of the association of those proteins with CLL, either overexpression or specific expression of those proteins in CLL cells compared with normal B-cells has to be confirmed by a specific protein detection technique like western blotting. Second, the significant identification of the 9 prognostic markers was based on TTFT data of 130 patients (GSE39671) and OS information of 107 patients (GSE22762) whose transcriptomics data sets were published before the era of novel treatment of CLL. Therefore, the clinical usefulness of these markers in the context of the new modalities of CLL therapy merits investigation. Third, a comparison between

the present markers and those commonly applied in CLL, such as IGHV, ZAP-70, CD38 and the chromosomal aberrations, was not possible to conduct due to the unavailability of the common makers of the 237 patients. Consequently, studying the present markers in parallel with those frequently applied is necessary to assess whether the present markers add prognostic information to what can be known by the commonly used markers. Fourth, conventionally, real-time PCR is used to confirm findings generated using DNA microarray-based transcriptomics. Therefore, measuring the expression of the 9 markers using real-time PCR is worthwhile to validate the expression patterns of the 9 transcripts in CLL samples.

Conclusion

The integration method applied on the omics data sets suggested 60 candidates as CLL-associated proteins, of which 32% (19 proteins) were previously implicated in neoplasms, including CLL. Moreover, the increased transcript expression of 9 of the suggested CLL-associated proteins significantly predicted early therapy and/or short OS in CLL patients. Interestingly, 4 of the 9 transcripts retained prognostic significance in the two independent transcriptomics data sets (237 CLL patients). Therefore, they may have the potential to serve as prognostic markers in the disease. Importantly, further assessment of the reported prognostic markers (using real-time PCR) in parallel with those frequently applied in a cohort of patients who have been treated with the new modality of CLL therapy is worthwhile to validate the utility of the present markers in the prognosis of CLL.

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Supplementary Tables (1, 2 and 3)

Supplementary Table 1: Technical information about the proteomics data sets used in the present study

Source of sample	Number of samples	Type of protein extract	Mass label	Protein database	Mass spectrometry	Ref.
PBMCs isolated from CLL patient	1 sample from an untreated patient	Crude-membrane extract	N/A	Human SwissProt database	Q-TOF API US (Waters)	[1]
PBMCs isolated from CLL patients	12 samples from 12 patients with different prognoses, some of whom were treated.	Cytosolic and nuclear extracts	iTRAQ	Human SwissProt database	4800 MALDI-TOF/TOF (Applied Biosystems)	[2]
PBMCs isolated from CLL patients	18 samples from 18 patients with different prognoses, some of whom were treated.	Whole cell lysate	iTRAQ	Human SwissProt database	TripleTOF 5600 system (AB SCIEX)	[3]
Normal B-cells isolated from PBMCs of healthy donor	2 sample from 2 healthy donors	Whole cell lysate	iTRAQ	Human Ensembl protein database	LTQ-OrbitrapXL (Thermo Fisher Scientific)	[4]
Normal PBMCs isolated from healthy donors	3 samples from 3 healthy donors	Supernatant, cytosolic and nuclear extracts	N/A	Human SwissProt database	QExactive Orbitrap (Thermo Fisher Scientific)	[5]

Protein database indicates the database that was used in each study for the identification of proteins based on the MS and MS/MS spectra. Q-TOF: Quadrupole-time of flight mass spectrometry; MALDI-TOF/TOF: matrix assisted laser desorption/ionization-time of flight tandem mass spectrometry; TripleTOF: triple time of flight mass spectrometry; LTQ-OrbitrapXL: linear trap quadrupole-orbitrap XL mass spectrometry; iTRAQ: isobaric tags for relative and absolute quantitation; N/A indicates that mass label was not used in the corresponding study; PBMCs: peripheral blood mononuclear cell. PBMCs isolated from CLL patients were ≥90% CD5+ and CD19+ (CLL cells).

Supplementary Table 2: The proposed CLL-associated proteins.

UniProt identifier	Protein name
Q8NHW5	60S acidic ribosomal protein P0-like
Q9UKP5	A disintegrin and metalloproteinase with thrombospondin motifs 6 (ADAM-TS 6) (ADAM-TS6) (ADAMTS-6) (EC 3.4.24)
P49753	Acyl-coenzyme A thioesterase 2, mitochondrial (Acyl-CoA thioesterase 2) (EC 3.1.2.2) (Acyl-coenzyme A thioester hydrolase 2a) (CTE-Ia) (Long-chain acyl-CoA thioesterase 2) (ZAP128)
Q9HCE9	Anoctamin-8 (Transmembrane protein 16H)
P03928	ATP synthase protein 8 (A6L) (F-ATPase subunit 8)
Q7Z6A9	B- and T-lymphocyte attenuator (B- and T-lymphocyte-associated protein) (CD antigen CD272)
Q9BX70	BTB/POZ domain-containing protein 2
Q9Y4F5	Centrosomal protein of 170 kDa protein B (Centrosomal protein 170B) (Cep170B)
Q8NE62	Choline dehydrogenase, mitochondrial (CDH) (CHD) (EC 1.1.99.1)
Q9Y5K3	Choline-phosphate cytidylyltransferase B (EC 2.7.7.15) (CCT-beta) (CTP:phosphocholine cytidylyltransferase B) (CCT B) (CT B) (Phosphorylcholine transferase B)
Q8IWD4	Coiled-coil domain-containing protein 117
Q7LFL8	CXXC-type zinc finger protein 5 (CF5) (Putative MAPK-activating protein PM08) (Putative NF-kappa-B-activating protein 102) (Retinoid-inducible nuclear factor) (RINF)
P00414	Cytochrome c oxidase subunit 3 (Cytochrome c oxidase polypeptide III)
Q8NCM8	Cytoplasmic dynein 2 heavy chain 1 (Cytoplasmic dynein 2 heavy chain) (Dynein cytoplasmic heavy chain 2) (Dynein heavy chain 11) (hDHC11) (Dynein heavy chain isotype 1B)
P49619	Diacylglycerol kinase gamma (DAG kinase gamma) (EC 2.7.1.107) (Diglyceride kinase gamma) (DGK-gamma)
P0C6T2	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 4
Q7L513	Fc receptor-like A
Q96LA6	Fc receptor-like protein 1 (FcR-like protein 1) (FcRL1) (Fc receptor homolog 1) (FcRH1) (IFGP family protein 1) (hIFGP1) (Immune receptor translocation-associated (protein 5) (CD antigen CD307a
Q96P31	Fc receptor-like protein 3 (FcR-like protein 3) (FcRL3) (Fc receptor homolog 3) (FcRH3) (IFGP family protein 3) (hIFGP3) (Immune receptor translocation-associated protein 3) (SH2 domain-containing phosphatase anchor protein 2) (CD antigen (CD307c

Q6DKI2	(Galectin-9C (Gal-9C) (Galectin-9-like protein B
Q9UK08	(Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-8 (Gamma-9
P23527	(Histone H2B type 1-O (Histone H2B.2) (Histone H2B.n) (H2B/n
P57053	(Histone H2B type F-S (Histone H2B.s) (H2B/s
Q6PFW1	Inositol hexakisphosphate and diphosphoinositol-pentakisphosphate kinase 1 (EC 2.7.4.21) (EC 2.7.4.24) (Diphosphoinositol pentakisphosphate kinase 1) (Histidine acid phosphatase domain-containing protein 2A) (IP6 kinase) (Inositol pyrophosphate syn- (thase 1) (InsP6 and PP-IP5 kinase 1) (VIP1 homolog) (hsVIP1
Q9H293	(Interleukin-25 (IL-25) (Interleukin-17E) (IL-17E
Q9P2G3	Kelch-like protein 14 (Protein interactor of Torsin-1A) (Printor) (Protein interactor of (torsinA
O75525	KH domain-containing, RNA-binding, signal transduction-associated protein 3 (RNA- binding protein T-Star) (Sam68-like mammalian protein 2) (SLM-2) (Sam68-like phos- (photyrosine protein
Q6IPR1	LYR motif-containing protein 5
O15481	(Melanoma-associated antigen B4 (MAGE-B4 antigen
Q9UPN3	Microtubule-actin cross-linking factor 1, isoforms 1/2/3/5 (620 kDa actin-binding pro- (tein) (ABP620) (Actin cross-linking family protein 7) (Macrophin-1) (Trabeculin-alpha
Q08AG7	Mitotic-spindle organizing protein 1 (Mitotic-spindle organizing protein associated with a (ring of gamma-tubulin 1
Q7Z5P9	(Mucin-19 (MUC-19
Q8TET4	(Neutral alpha-glucosidase C (EC 3.2.1.20
Q86XR2	(Niban-like protein 2 (B-cell novel protein 1) (Protein FAM129C
Q9H0G5	Nuclear speckle splicing regulatory protein 1 (Coiled-coil domain-containing protein 55) ((Nuclear speckle-related protein 70) (NSrp70
Q13515	Phakinin (49 kDa cytoskeletal protein) (Beaded filament structural protein 2) (Lens fiber cell beaded filament protein CP 47) (CP47) (Lens fiber cell beaded filament protein CP (49) (CP49) (Lens intermediate filament-like light) (LIFL-L
A4D1U4	Protein LCHN
Q9NQ39	Putative 40S ribosomal protein S10-like
Q5VTE0	Putative elongation factor 1-alpha-like 3 (EF-1-alpha-like 3) (Eukaryotic elongation fac- tor 1 A-like 3) (eEF1A-like 3) (Eukaryotic translation elongation factor 1 alpha-1 pseu- (dogene 5
Q6DN03	(Putative histone H2B type 2-C (Histone H2B.t) (H2B/t
A8MVU1	Putative neutrophil cytosol factor 1C (NCF-1C) (Putative SH3 and PX domain-contain- (ing protein 1C

Q8NHM4	(Putative trypsin-6 (EC 3.4.21.4) (Serine protease 3 pseudogene 2) (Trypsinogen C
Q17R89	Rho GTPase-activating protein 44 (NPC-A-10) (Rho-type GTPase-activating protein (RICH2) (RhoGAP interacting with CIP4 homologs protein 2) (RICH-2
Q8N568	Serine/threonine-protein kinase DCLK2 (EC 2.7.11.1) (CaMK-like CREB regulatory kinase 2) (CL2) (CLICK-II) (CLICK2) (Doublecortin domain-containing protein 3B) ((Doublecortin-like and CAM kinase-like 2) (Doublecortin-like kinase 2
Q9P246	Stromal interaction molecule 2
Q6ZRP7	Sulfhydryl oxidase 2 (EC 1.8.3.2) (Neuroblastoma-derived sulfhydryl oxidase) (Qui-(escin Q6-like protein 1
Q86XK3	Swi5-dependent recombination DNA repair protein 1 homolog (Meiosis protein 5 homo-(log
Q8N103	T-cell activation Rho GTPase-activating protein (T-cell activation GTPase-activating (protein
Q8N4P2	(Tetratricopeptide repeat protein 30B (TPR repeat protein 30B
Q9NR96	(Toll-like receptor 9 (CD antigen CD289
Q9P0S9	Transmembrane protein 14C
Q6P9G4	Transmembrane protein 154
Q6ZMU5	(Tripartite motif-containing protein 72 (Mitsugumin-53) (Mg53
P09936	Ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1) (Neuron cytoplasmic pro-(tein 9.5) (PGP 9.5) (PGP9.5) (Ubiquitin thioesterase L1
Q5SQH8	Uncharacterized protein C6orf136
Q9ULV0	Unconventional myosin-Vb
Q6VEQ5	WAS protein family homolog 2 (CXYorf1-like protein on chromosome 2) (Protein (FAM39B
Q6ZNA1	Zinc finger protein 836
Q96IR2	Zinc finger protein 845
Q8IX07	Zinc finger protein ZFPM1 (Friend of GATA protein 1) (FOG-1) (Friend of GATA 1) (Zinc (finger protein 89A) (Zinc finger protein multitype 1

The integration of the proteomics data sets of CLL cells, normal B-cells and normal PBMCs; as well as the transcriptomics data set of normal B-cells suggested 60 candidates as CLL-associated proteins. This table shows these proteins.

Supplementary Table 3: Reported role of the suggested CLL-associated proteins in cancer

UniProt identifier	Protein name (*gene name*)	Reported role in cancer
Q8N4P2	Tetratricopeptide repeat protein 30B (*TTC30B*)	• Promotes survival of acute myeloid leukemia (AML) [6].
Q9HCE9	Anoctamin-8 (*ANO8*)	• Enhances the growth and metastasis of gastrointestinal tumor and head/neck squamous cell carcinoma [7].
Q7LFL8	CXXC-type zinc finger protein 5 (*CXXC5*), also known as RINF	• Promotes survival of AML cells and associates with poor prognosis of the disease [8]. • In comparison with normal tissues, breast cancer and melanoma cells exhibit significantly increased expression of CF5 [9]. • Associates with poor prognosis of breast cancer [9].
P49619	Diacylglycerol kinase gamma (*DGKG*)	• Promotes survival, migration and invasion of breast cancer cells and colon cancer cells [10, 11].
Q6DKI2	Galectin-9C (*LGALS9C*)	• Associates with lymphoma, leukemia and colon cancer cells as compared with normal tissue [12, 13].
Q9H0G5	Nuclear speckle splicing regulatory protein 1 (*NSRP1*), also known as NSRP70	• Associates with acute lymphoblastic leukemia (ALL) and considered a good diagnostic marker of the disease [14]. • Associates with poor prognosis of ALL and AML [14].
Q7L513	Fc receptor-like A (*FCRLA*)	• Associates with the risk of developing CLL [15].
Q17R89	Rho GTPase activating protein 44 (*ARHGAP44*)	• Associates with the risk of developing CLL [15].
Q8NE62	Choline dehydrogenase (*CHDH*)	• Associates with the risk of developing CLL [15].
Q9P0S9	Transmembrane protein 14C (*TMEM14C*)	• Over-expressed in ovarian cancer compared with normal tissue and required for tumor growth and invasion of the malignant cells [16]. • Suppresses the pro-apoptotic protein BAX and protects glioblastoma tumor cells from apoptosis [17].

Q9NR96	Toll-like receptor 9 (*TLR9*)	• Highly expressed on CLL compared with normal B-cells and associates with high-risk CLL [18, 19].
P09936	Ubiquitin carboxyl-terminal hydrolase isozyme L1 (*UCHL1*)	• Promotes proliferation, migration and metastasis of colorectal cancer cells [20]. • Induces metastasis of prostate cancer cells [21]. • Promotes the development of B cell lymphoma [22].
Q7Z6A9	B- and T-lymphocyte attenuator (*BTLA*)	• Preferentially expressed in gastric carcinoma compared with the normal tissue and associates with high-risk of the disease [23]. • Strongly associates with CLL cells compared with normal B-cells [24].
Q8NCM8	Cytoplasmic dynein 2 heavy chain 1 (*DYNC2H1*)	• Associates with glioblastoma as compared with the normal tissue [25].
Q96LA6	Fc receptor-like 1 (*FCRL1*)	• Contributes to the progression of melanoma [26].
Q96P31	Fc receptor-like 3 (*FCRL3*)	• Associates with poor prognosis of T cell lymphoma [27].
O75525	RNA-binding protein T-Star (*KHDRBS3*), also known as SLM-2	• Contributes to the development of medulloblastoma [28].
Q86XK3	Swi5-dependent recombination DNA repair protein 1 homolog (*SFR1*)	• Promotes the progression of breast cancer [29].
Q8N568	Serine/threonine-protein kinase (*DCLK2*)	• Associates with poor prognosis of CLL [30].

The integration of the omics data sets of CLL cells, normal B-cells and normal PBMCs suggested 60 candidates as associated proteins. This table shows what is known in the literature about the relativeness of these proteins to malignant diseases.

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Original Article

Prevalence and Causes of Delay in Seeking Medical Care Among Al-Madina Population, Saudi Arabia

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Abstract

Background: Delay in seeking medical care has many negative effects on the patient's condition and medical cost, and it reduces the potential benefits of early interventions. Delay in seeking medical care, which is affected by many factors, is a common global problem. This study aimed to study the prevalence and causes of delay in seeking medical care in Al-Madina, Saudi Arabia. **Method:** This research was a cross-sectional study conducted among Al-Madina population using a self-administrated questionnaire which was only administered when the inclusion and exclusion criteria for the study have been met by the participants. The questionnaire collected the demographic characteristics and information about the prevalence and the reasons of delaying in seeking medical care in Al-Madina, Saudi Arabia.

Results: The study included 441 subjects out of which 61.9% were females while 38.1% were males. Seventy-eight and point two percent had university education level. Only 27.4% of participants always seek medical care as soon as they feel they need it. Delayed seeking medical care due to a financial impediment was stated by 26.1% of the subjects. Merely 25.2% had health insurance. The language was the most important criteria when choosing health service providers for 42% of patients. Severe pain forces 40.1% of participants to seek medical care, while moderate pain drives only 4.3% to seek medical care while 58.9% seek medical care when the pain or discomfort increases with time.

Conclusion: There was a high prevalence of delay in seeking medical care among Al-Medina population, Saudi Arabia. Economic factors and lack of health insurance are among the main obstacles in seeking medical care. Acute pain serves as the principal reason in seeking medical care among Al-Madina population.

Key words: Delay, Seeking, Medical, Madina, Saudi Arabia

الملخص

مقدمة: التأخر في طلب الرعاية الصحية له العديد من الآثار السلبية على حالة المريض وتكاليف العلاج وهو ايضاً يقلل من الفوائد المحتملة من التدخل العلاجي المبكر. لاتزال هذه المشكلة شائعة عالميا وهي مشكلة تتأثر بالعديد من العوامل. هذه الدراسة تهدف الى معرفة الأسباب التي تؤدي الى التأخر في طلب الرعاية الصحية ومدى انتشارها في المدينة المنورة، المملكة العربية السعودية.

الطريقة: هذه الدراسة هي دراسة مقطعية تم اجرائها على سكان المدينة المنورة. تم جمع البيانات عن طريق استبيانات ذاتية التعبئة تم ارسالها للمشاركين في الدراسة ممن تنطبق عليهم معايير التضمين والإقصاء. يحتوي الاستبيان على عدة أسئلة تشمل البيانات الديموغرافية بالإضافة الى أسئلة تهدف لمعرفة مدى انتشار هذه المشكلة والأسباب المؤدية اليها.

النتائج: شملت الدراسة ٤٤١ مشارك منهم ٦١,٩٪ أناث و ٣٨,١٪ ذكور. ٢٧,٤٪ من المشاركين يطلبون الرعاية الصحية فور احتياجهم، ٢٦,١٪ من المشاركين لديهم تأخير في طلب الرعاية الصحية لأسباب مادية، ٢٥,٢٪ لديهم تأمين طبي، تمثل اللغة اهم العوامل المؤثرة في اختيار مقدم الرعاية الصحية بنسبة ٤٢٪. الألم الشديد هو من أكثر الأسباب المؤدية لطلب الرعاية الصحية بنسبة ٤٠,١٪ بينما الألم المتوسط هو السبب لدى ٤.٣٪ فقط. ٥٨,٩٪ من المشاركين يطلبون الرعاية الصحية في حال ازدياد شدة الألم مع الوقت.

الخلاصة: تعد نسبة انتشار التأخر في طلب الرعاية الصحية بالمدينة المنورة عالية، الحالة المادية وعدم توفر التأمين الصحي هما السببان الرئيسيان في تأخر طلب الرعاية بينما يعد الألم الحاد والشديد هما السببان الرئيسيان في طلب الرعاية الصحية.

الكلمات المفتاحية: التأخر، طلب الرعاية الصحية، المدينة المنورة، المملكة العربية السعودية

Introduction

The outcome of medical care is based solely on the degree of promtness in seeking for medical care services and a delay in doing this aggravates the state of disease and even less beneficial in achieving a low cost of management. Various research studies have proved that so many reasons are involved as to why patients do not seek medical care early and majority of results showed that a high percentage of people within the entire population delay seeking medical care. A research conducted in Nigeria[1] noticed that the delay in seeking medical care among the educated population was due to several reasons, 175 (49.29%) of participants involved in the study claimed that their first response to illness is to see the doctor immediately, 128 (36.06%) admitted that they will go to a pharmacy to buy drugs while 46 (12.96%) will go to a patent medicine dealer for treatment. Among the participants in the study, very few 6 (1.69%) admitted that they will consult a priest or go to a prayer house while none of them admitted that they would see a native doctor/medicine man. 173(48.73%) opted for self-medication as first line of treatment while 132 (37.18%) preferred to follow treatment for a similar previous complaint. of all those surveyed 45.35% admitted that they always seeking medical care. Among 175 respondents who claimed seeing the doctor immediately they fell sick, almost half of them 45.71% indicated that it took hours to see a doctor in the hospital. These people claimed that it is a contributing factor in delay in seeking medical care. Majority (45.71%) of those who indicated that the delay they experience in seeing the doctor was a contributing factor for delay in seeking medical attention, 42.25% complained of delayed attention in the hospital, 22.82% would rather wait to see how the illness goes while 16.34% reason was cost of treatment and inaccessibility or distance to the nearest doctor (2.25%) respectively. However, 88.45% of all the respondents overwhelmingly admitted that medical facilities in Nigeria were inadequate for medical and health care. In another study aimed to detect the cause of delay in seeking emergency medical care (2), of the surveyed patients who completed the questionnaire, 32.2% reported they delayed seeking medical care and of those who delayed seeking care, the majority (71%) delayed because they thought the problem would go away. Other reasons included not having the time to be seen (7.2%), high cost (5.4%), and inability to get an appointment (4.6%).

Furthermore, a systematic review of the factors associated with delays in medical and psychological help-seeking among men [3] in Japan, Ghana, Australia found four themes: Embarrassment, anxiety, distress, and/or fear related to using health services: This stemmed from unfamiliarity with health services and 'medical culture,' and adherence to ideas about masculinity that imply men are 'weak' for seeking help. Three themes, appearing in multiple papers using various methodologies and samples, were worthy of special attention:

Need for emotional control: Some men

felt that by worrying about their symptoms they were 'losing control' of their emotions and therefore their masculinity; this was particularly relevant to seeking mental health care.

Viewing symptoms as minor and insignificant: This often resulted from men's lack of knowledge about symptoms and low interest in their body and health.

Poor communication/rapport with health professionals: Men were uncomfortable with health professionals who were not polite, rushed without explaining important information, used medical jargon, and lacked sensitivity to their needs.

The objectives of our study were to determine the prevalence and causes of delay in seeking medical care, health insurance state and behaviors related to seeking medical care in Madina, Saudi Arabia.

Material and Method

Data Collection Tool and Method: This was a cross-sectional study which was conducted in Madina between May and August 2018. The study surveyed 441 randomly selected participants over the age of 18 years. All the participants were living in Madina. An electronic and printed questionnaire was used to collect data, in Arabic language. The questionnaire contained questions about patient's socio-demographic characteristics, including race, age, ethnicity, marital status, education, nationality, household income, work status, and insurance status. Patients also were asked about their use of primary care, emergency department services, and hospitals in the previous year. Patients were asked about causes that prevent them from seeking a medical care and they were asked about standards and factors affecting the service provided by the doctor or health center from their perspective. The study included all Madina residents aged more than 18 years without mental disorder. Those excluded are individuals who were not residents in Madina, under the age of 18 years and subjects with mental disorders. The questionnaires were assessed for completeness and accuracy. Only completed questionnaires were analyzed using Statistical Package for Social Sciences (IBM SPSS for Windows, version 24.0). Statistics was used to see the extent and the degrees of delay and to examine the relationship between delay and the related variables included in the questionnaire at a level of significance 5% ($P < 0.05$). Descriptive statistics were calculated and reported as the mean and standard deviation, as well as frequencies, absolute values and percentage.

Ethical considerations: Ethics approval was obtained from the Research Ethics Committee of Taibah University at Madina. All who met the inclusion criteria were invited to participate in the study by the researchers. Informed verbal consent was obtained from all participants and only those who agreed to participate were included. Administered Confidentiality was realized during this study.

Results

Table (1): The Participants Socio-Demographic Data

Age	mean ± SD	28.59.853±	
		Freq. N= 441	Per. 100%
Gender	Male	168	38.1
	Female	273	61.9
Nationality	Saudi	405	91.8
	Non-Saudi	36	8.2
Marital status	Single	247	56.0
	Married	183	41.5
	Divorced	9	2.0
	Widow	2	.5
Education Level	Primary level	5	1.1
	Preparatory level	19	4.3
	Post-secondary diploma	72	16.3
	University level	345	78.2

The Socio-demographic characteristics of the study participants are shown below in Table (1). The mean age of participants is 28.5 years with a standard deviation 9.853 and majority (61.9%) of participants are female with majority (91.8%) been from Saudi Arabia. Majority (56%) of participants were single, and for 78.2% of them, highest level of education was university.

Table (2) Seeking health care as soon as they feel the need

Item	Frequency	%
Never	25	5.7
Sometimes	295	66.9
Always	121	27.4
Total	441	100.0

In Table (2), it is noticed that only 27.4% always seek medical advice when needed while the majority 66.9% sometimes seek medical advice when needed.

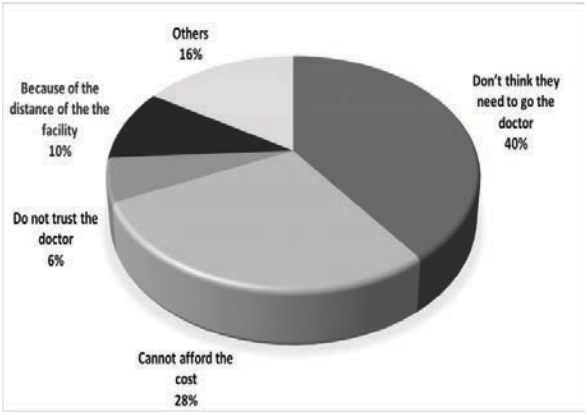

Figure (1): Reasons behind delay in seeking medical care

This Figure (1) shows various reasons behind delay in seeking medical care with the most common reason being that they don't think they needed to seek help first (40%), followed by the inability to afford the cost of medical care (28%). Far distance from the health facility is the cause mentioned by 10% of the sample and lack of trust in doctors was the reason for 6% of participants.

Table (3): Health insurance state and behaviors related to seeking medical care

behaviors related to seeking medical care	Frequency	Percentage
During the last 12 months, Financial impediment prevented participants from visiting the doctor		
Yes	115	26.1
No	295	66.9
Don't know/I'm not sure	32	7.0
Currently have a health insurance		
Yes	111	25.2
No	330	74.8
Type of health insurance		
Government	24	21.6
Private	77	69.4
I don't Know	10	9.0
Visiting a health facility first when having health insurance:		
Yes	91	81.9
No	20	27.3
Seeking medical care while don' have health insurance:		
Yes	240	72.7
No	90	27.3

As shown in table (3), Only 26.1% of the participants needed to visit the doctor during the past year but could not because of a financial impediment. Only 25.2% of the participants have health insurance from which 81.9% visit the doctor or medical center first when needed, on the other hand 72.7% of participants who don't have insurance go to the doctor or medical center first when needed.

Table (4): Health seeking behavior for medical care

behaviors related to seeking medical care	Frequency	Percentage
What participants do first when don't visit a doctor:		
Advice from friends and family	35	38.9
Alternative medicine	17	18.9
Spiritual or religious therapy	6	6.7
Nothing from the previous	21	23.3
Others	11	12.2
Where participants seek help beside medical care		
Advice from friends and family	105	43.8
Alternative medicine	51	21.3
Spiritual or religious therapy	14	5.8
Nothing from the previous	52	21.7
Others	18	0.08
Where participants seek medical advice:		
Pharmacy	75	17.0
Clinic (Private Hospital)	122	27.7
The Hospital	226	52.2
Others	18	0.04
Criteria when choosing health service providers.		
Sex		
I don't Care	301	68.3
Different	35	7.9
Similar	105	23.8
Nationality		
I don't Care	335	76.0
Different	39	8.8
Similar	67	15.2
The Language		
I don't Care	236	53.5
Different	20	4.5
Similar	185	42.0
Religion		
I don't Care	265	60.1
Different	15	3.4
Similar	161	36.5
When participants seek medical care:		
When feeling pain or discomfort immediately.	85	19.3
When pain or discomfort increases with time	260	58.9
Loss of pain or discomfort with time	12	2.7
When new symptoms appear	84	19.0

Table (4) shows the participants' health care seeking behavior. Concerning participants who don't go to the doctor or medical center first when needed, majority (38.9%) first seek advice from friends and family. Majority (51.2%) used to go to the hospital, 23.8% of respondents choose health providers of the same sex and 15.2% of respondents choose health providers of the same nationality. (58.9%) of participants seek medical care when the pain or discomfort increases with time.

Discussion

The present study aimed to examine the delay in seeking medical care, causes and prevalence in Al-Madina, Saudi Arabia. Our study included 441 participants with mean age of 28.5 years. The majority (61.9%) of them were females. The education level of the most of our participants were university level but despite this high level of education our results showed a high prevalence of delay in seeking medical care among participants, as only 27.4 % of them always seek medical care as soon as they feel they need it. This act isn't good for patients' health and patients underestimate their illness severity until it gets worse which is similar to the findings in the study done in Nigeria where it was reported that only half of the educated participants see the doctor immediately when they fall sick. [1]

Also, our study is online with other studies; in one study it was noted that one third of adults only seek medical care when they had deemed necessary. [5] Another study among women with infectious cervical cancer in western Kenya showed that 55% had delayed in seeking medical care [6]. Additionally, one study also found close results among acute coronary syndrome patients where it was recorded that only half of the respondents seek medical care immediately when they fall sick. [4]

Financial barrier at the time participants need to visit the doctor is a reason why a quarter of the participants were prevented from visiting the doctor and closely related when compared to a study done in USA [7] which found that 24.1% avoid medical care due to high cost. Also, another study conducted among breast cancer patients from southern part of Iran [8] found that 16% of the participants reported the high cost of diagnosis and medical care as the main reason for the delaying in seeking healthcare and diagnosis of their disease.

Lack of health insurance is one of the main reasons for delayed treatment. Almost 27% of participants who don't have health insurance don't go to the doctor or the medical center first when needed. This is a significant indicator of the role of health insurance in contributing to medical care. This is consistent with several previous studies which found that lack of health insurance is a major barrier to receiving medical care [7,9-10]. In this study we found that in participants who do not have health insurance, advice from friends and family was the most important source of medical advice. Unsuitable advice may delay individuals seeking medical advice

from competent professionals, which lead to adverse clinical outcomes.

Given this point, it is important that all family members give only accurate information and encourage the patient to seek health advice from a medical professional. Regarding the criteria followed by the participants when choosing health service providers. Language was the most important of these standards and this is expected because the common language is important for the possibility of communication between the doctor and the patient and the description of the situation and treatment plan. Sex also was among the common criteria for choosing health service providers, this may be due to the culture and community constraints of this society. Some tests may also seem embarrassing to some patients and this play a role in delaying seeking medical care. One study confirmed this where it was found that fear of embarrassment during examination play a role in delaying seeking medical care. [11]

It was observed that, most participants in this study would not seek medical care if their pain was acceptable, but if the pain increased, they would go to seek medical care. This is a big mistake because, as we noted previously, many health problems begin with simple or moderate pain, if addressed from the beginning, it will be easy to treat and will not take long treatment time with the patient. But, if the pain increases or other symptoms develop, this indicates that the condition will be worse and the consequences will be greater, harder and treatment will be more expensive. A previous study reported that misunderstanding of the seriousness of the symptoms and signs of diseases could lead to delaying the seeking of medical care after the onset of symptoms has been attributed. [4]

This study showed that among Al Madina population there was a high prevalence of delaying in seeking medical care. Economic factors and lack of health insurance are among the main obstacles in seeking medical care. Therefore, the study recommends conducting awareness campaigns about the importance of seeking medical care when needed without delaying and showing the risks of delaying in seeking medical care and addressing fears of medical care. People are advised that, embarrassment in seeking medical care and subjecting to medical examinations is not related to grace and integrity but can be potentially life-threatening.

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Original Article

Tobacco Brand Names and Logos Recognition by 1st Grade Schoolchildren

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Abstract

Background & Aims: Prosmoking messages, delivered through smoking parents, media and other exposure factors, can reach very young children and influence attitudes and behaviors toward smoking. This study aimed to assess the ability of 1st grade of primary schoolchildren to recognize tobacco products and logos of widely advertised tobacco products compared with other common commercial products.

Methods: Cross-sectional survey in class room settings using a questionnaire designed to measure 3 popular tobacco products and logos for 3 common commercial products (1 food, 1 beverage and 1 restaurant brand) were conducted in primary schools at different regions nationwide The students were instructed individually under supervision of researcher and their teachers about each logo with one of 6 products pictured on an A4 colored paper and the answers were recorded.

Results: The sample consisted of 1,369 students, of whom 47.5% were girls. In general, overall tobacco recognition rate was much lower than other products reaching 53%, which was statistically significant (p=0.0001). Boys showed a higher recognition rate to cigarette brands than girls that was statistically significant (p=0.002).

Conclusions: The majority of first grade school children are familiar with tobacco brands. This study's findings suggest that children are widely exposed to tobacco products and promotion. More effective regulations are needed to combat a generation of nicotine addicts.

Keywords: Tobacco; Children; Cigarette; Brand recognition; Saudi Arabia

الملخص

الرسائل المزيفة للتدخين والتي يمكن ان تنتقل من خلال الآباء والامهات او وسائل الاعلام او أي وسيلة أخرى قادرة على الوصول للأطفال والتأثير على سلوكياتهم واخلاقياتهم تجاه التدخين. الهدف من هذه الدراسة هو تقييم مقدرة طلاب وطالبات الصف الأول الابتدائي على التعرف على منتجات التبغ المعلن عنها على نطاق واسع مقارنة بالمنتجات الشائعة الأخرى.

المنهج: تم إجراء مسح مقطعي باستخدام استبيان مصمم لقياس ثلاثة من منتجات التبغ المعروفة وثلاثة منتجات أخرى منتشرة بين الأطفال (١غذاء، ١ مشروب، ١ مطعم).الدراسة أجريت في المدارس الابتدائية لطلاب وطالبات الصف الأول الابتدائي في مناطق مختلفة على مستوى المملكة. وكان الاطفال يقومون بالإجابة على الاستبيان تحت اشراف وتعليمات الباحث والمدرسين والمدرسات. كان الاستبيان يحمل ستة صور ملونة لثلاثة علامات تجارية من منتجات التبغ وثلاثة علامات تجارية لمنتجات أخرى شائعة وتم تسجيل الإجابات.

النتائج: كان عدد الاطفال١٣٩٦ طالباً، منهم ٤٧.٥٪ من الفتيات. وبصفة عامة، كان المعدل العام لمعرفة منتجات التبغ للفتيات اقل من الفتيان الي اظهروا نسبة تعرف وصلت إلى ٥٣٪ وكانت هذه النسبة مثبتة احصائياً. أيضا الفتيان اظهروا نسبة تعرف عالية لمنتجات التدخين وكانت النتيجة مثبتة احصائياً ايضاً.

الاستنتاجات: غالبية أطفال الصف الأول ابتدائي على دراية ومعرفة بمنتجات التبغ. وتشير نتائج هذه الدراسة إلى أن الأطفال معرضون على نطاق واسع لمنتجات التبغ والترويج له. وهناك حاجة إلى لوائح أكثر فعالية لمكافحة جيل من مدمني النيكوتين.

Introduction

Smoking is a noteworthy general well-being issue. It is considered the biggest preventable reason for death in the industrialized world [1]. In spite of the fact that there is a wellbeing cautioning on every bundle of cigarettes demonstrating that smoking is the fundamental driver of lung disease, lung cancer and heart diseases, and disregarding the opposition to smoking centers circulated everywhere throughout the Kingdom, and smoking in Saudi Arabia is expanding quickly, especially among the adolescent, somewhat because of forceful advertising methods by tobacco organizations [2].

In the last two decades, adolescents have become more exposed to tobacco advertising at early ages [3]. Many risk factors have been embroiled in the prediction of adolescent to be smokers. These factors include smoking of parents [4], friends smoking [5], family social problem [6], and tobacco advertising [7]. In Saudi Arabia, smoking is prevalent at different age groups, and the prevalence of current smoking is much higher in males than in females [8].

The advertising of smoking can increase the prevalence of smoking, especially with young children. In the past, twenty-three years ago, a small study had a massive effect on the way tobacco is marketed in the United States [9]. Fischer et al., found that 6-year-old young boys and girls perceived with likewise high rates logos of the Disney Channel's Mickey Mouse and Camel Cigarettes' Old Joe Camel [10]. Camel is one of the three most well-known cigarette brands among youth smokers, with 15.1 percent inclining toward Camel, as indicated by the 2011 National Survey on Drug Use and Health. This and similar studies uncovered complex and powerful advertising practices that were unmistakably arriving at youngest children. The level of recognition in children is high, and when they believe in something even if it's useful or harmful it will represent in their behavior at the future.

Prosmoking messages, delivered through smoking parents, media which has become more influential element currently and other exposure factors, can reach very young children and influence their attitudes and behaviors toward smoking [9, 10, 11]. Given, the association between exposure to tobacco marketing and usage of tobacco products, this study aimed to assess the ability of 1st grade primary schoolchildren to recognize tobacco products and logos of widely advertised tobacco products compared with other common commercial products.

Methods

Study Population

Multi stage sampling method was conducted between January 2016 and April of 2017, we surveyed 1,369 first grade schoolchildren among whom 718 (52.5%) were boys and 651 (47.5%) were girls. All the students were in first grade. We randomly collected the responses from governmental primary schools in different regions nationwide. The surveyed population consisted of all students

whom attended the class at the time of the survey. The study was approved by the Research Ethics Committee at Prince Sultan Military College of Health Sciences (study reference IRB-2017-02-02).

Study design and setting

An anonymous survey was distributed in a class room setting using a questionnaire designed to measure 3 popular tobacco products and logos for 3 common commercial products (1 food, 1 beverage, and 1 restaurant brand) were conducted in primary schools at different regions nationwide. The questionnaire incorporated different questions related to knowledge of different kinds and logos of the smoking brands and food. The students were instructed individually under supervision of researcher and their teachers about each logo with one of 6 products pictured on an A4 colored paper and the answers were recorded, Fig.1.

Figure 1. Brands and logos were shown to schoolchildren.

Statistical analysis

Data were analyzed using GraphPad Prism 7 software (GraphPad Software Inc., La Jolla, CA, USA). Descriptive statistics (absolute values and proportions) were used to analyze responses to the survey. Chi-square tests were conducted as appropriate.

A P value <0.05 was considered statistically significant.

Results

The sample consisted of 1,369 students, of whom 47.5% were girls. The mean age of the surveyed students was 6.8 ±0.56years. In general, overall tobacco recognition rate was much lower than other products reaching 53%, which was statistically significant (p=0.0001). Boys showed a higher recognition rate to cigarette brands than girls that was statistically significant (p=0.002), Table 1.

Table 1. Gender wise recognition rate for brand and logo

	Boys			Girls	
	n	%		N	%
Tobacco Products					
Cigarettes (Marlboro; L&M)	485	*67.2%		270	*41.4%
Hookah	302	*42%		221	*33.9%
Foods					
McDonald's	561	78.1%		458	70.3%
Lay's chips	681	94.8%		632	97.1%
Pepsi	688	95.8%		643	98.7%

* p<0.05. Chi-square test overall recognition rate was higher for tobacco products vs. foods (p=0.0001); Chi-square test showed a higher recognition rate between boys than girls (p=0.002).

Both boys and girls showed similar rate of recognition of logos for other commercial products. For example, 96% boys reported recognition of Pepsi logo while 99% of girls identified it. Similarly, 78% of boys identified McDonald's logo in comparison to 70% of girls.

Regarding Lay's Chips logo, about 95% of boys recognized the logo in comparison to 97% of girls, while 42% of boys recognized Hookah logo that was much lower in girls 34%.

Discussion

In this survey, the results of awareness to tobacco brands and logos among 1st grade primary school children in the kingdom of Saudi Arabia were investigated. It was observed that the majority of 1st grade school children were familiar with tobacco brands. This could be attributed to several factors such as seeing in the home or neighborhood, or through print and electronic media, or other acquaintances. Multiple studies have reported a significant relationship between children's viewing of tobacco advertisements and their positive attitude towards consumption of such products that they are too young to use. A study on grade 6 and 7 students (age 10–12 years) showed that majority of children when shown the advertisement of a cigarette brand had more positive opinion of the user as compared to those who were shown the picture of the same brand of cigarette [13]. For example, when shown the Benson & Hedges cigarette pack, 18% children thought the user to be interesting, which increased to 44% when shown the advertisement for the same. This rise in numbers was seen in a range of categories. Similarly, studies employing pictures of logos and brand names have reported that children as young as 3 years old could correctly identify logos and advertisements. A study in the United States showed that the three most heavily advertised brands, Camel, Marlboro, and Newport were preferred by 86% of children who smoked [14]. Another study reported that in a survey of 3–6-year-old children, approximately 91.3% of 6-year-old children correctly matched Old Joe with a picture of a cigarette compared with 30% of 3-year-old children [9].

The reason for influence of advertisements on children could be attributed to their lack of understanding of the persuasive intent of the advertisement and lack of awareness leads to higher trust in advertisements and there are some companies of tobacco products consumed millions for advertisement to gain this trust. For example, Arnett and Terhanian [15] reported that advertisement most prevalent among adolescent are for two of the brands they are destined to smoke— Marlboro and Camel. More than 95% of 534 adolescents between 11-18 years old had seen an advertisement shows Joe Camel or the Marlboro Man at least once, and more than 50% had seen these advertisements six or more times. Also, they reported that advertising budgets for the brands as follow 84$ million for Marlboro and 40$ million for Camel.

We found an overall recognition rate of tobacco reaching 53% which was much lower than other products like chips and Pepsi. What is noteworthy is that children were able to recognize the names of cigarette brands, even though tobacco is supposedly an adult product and all forms of media advertising have been controlled in Saudi Arabia. This is a high level of awareness for adult products supposedly not marketed to the survey group. Higher brand recognition rates of up to 95.2% for Samsun (a Turkish cigarette brand) were reported by Emri et al., Recognition rates for other cigarette brand names and logos ranged between 95.2% and 80.8% [16]. This large difference between the recognition rate of cigarettes brand between the Saudi and Turkish children may be related to the unrestricted tobacco advertising and promotion in Turkish media, which have been more controlled in the Saudi channels, due to religious consideration.

Moreover, we observed variability in recognition rate across gender. Boys showed a significantly higher recognition rate to cigarette brands than girls (67.2% vs. 41.4%, respectively). The possible explanation of this might be that boys usually spend most of their time outside their homes and thus are exposed to people who use indigenous tobacco products as compared to girls, who spend most of their time at home. Both boys and girls exhibited similar awareness of logos of other commercial products. Both boys and girls showed a very high recognition to food and drink logos, which indicated their ability to recognize tobacco products. Interestingly, boys seem to be familiar and exposed to Hookah compared to girls. It is not surprising that companies that invest large sums of money in advertising, such as Pepsi and Chips are recognized by almost all the children. One would expect young children to be able to identify such products because they use them. In primary school children, however, high awareness of L&M and Marlboro logo is likely to be due to the style and content of advertising and its appeal to children.

The results presented here support placing restrictions on the tobacco advertisement. Considering the established link between the exposure to tobacco marketing and the increased likelihood of starting to smoke, these findings should be considered to impose more restrictions on promotion, advertisement, and sponsorship of tobacco brands. The national tobacco control program of Saudi Arabia targets to assess the frequency of smoking and its adverse effects on health and economy. Additionally, many policies have been implemented to restrict smoking in educational institutions and banning tobacco advertisements [17]. This study's findings suggest that despite relatively comprehensive bans young children are still exposed to tobacco marketing.

Several studies have suggested the approaches required to reduce the reach of tobacco products from children [18]. For example, the sale of tobacco products should be discouraged near places that are frequently visited by children. Further, the brand logos

could be removed from cigarette packs, which could lessen the attractions towards children. Also, the reach of content non-suitable for children should be monitored to reduce the exposure. Parents or family members who smoke cigarettes should be careful not to smoke near children and children should also be counseled to not use or start using tobacco products. Moreover, health professionals should become more involved in efforts to restrict tobacco usage and implementing stronger control policies such as comprehensive ban on promotion and advertisement of tobacco products.

This study had a few limitations. First, the lower reading and writing skills of children in 1st grade limited the extent of questionnaire. The number of questions was limited and formulated to allow simple answers, thus in-depth study of associations could not be analyzed. Second, the study did not investigate the source of exposure, as having someone in the household who smoked or exposure to media and advertisements could also contribute to the knowledge of tobacco products. Third, the study did not investigate the effect of tobacco marketing and awareness in this age group.

To our knowledge, this is the first study to examine cigarette brand awareness among children in 1st grade school in the kingdom of Saudi Arabia. We found that 5 out of 10 children identified major tobacco brands, and the differences were significant across gender. The results of this study highlight that children in the <6 years of age should also be counseled to discourage use of tobacco products in future.

The study concluded that children in Saudi Arabia are still widely exposed to tobacco products and promotion and more effective regulations and awareness campaigns are needed to combat a generation of nicotine addicts.

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Original Article

The Relationship Of Tobacco Smoking To Depressive Symptoms Among Male Expatriate Workers In Saudi Arabia: A Cross Sectional Study.

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ABSTRACT:

Background & Aims: Mental health issues have been associated with tobacco smoking. Several studies conducted in large samples of general population found significant relationship between tobacco smoking and depressive symptoms. However, previous research conducted in Saudi Arabia reported high prevalence of depression and smoking among a small-scale sample of male expatriate workers but found no correlation. This study aims at investigating the association between self-reported tobacco smoking (cigarette and water pipe smoking) and depressive symptoms in a large representative sample of expatriate workers.

Methods: A cross-sectional survey involving face-to-face interviews of 4575 male expatriate workers in 270 businesses/companies in Riyadh, Saudi Arabia was conducted using a multi stage stratified cluster sampling technique to randomly select businesses/companies and participants. Trained research assistants used the Composite International Diagnostic Interview instrument applicable to clinical depression to assess DSM-IV for major depressive disorder and episodes among participants. Smoking was assessed using the WHO standard questions for assessing tobacco exposure and other covariates with a standardized questionnaire. The data were analysed using logistic regression.

Results: Current smoking is associated with significantly increased likelihood of depressive symptoms (Crude Odds Ratio=1.790 - 1.284) 1.516)). The association remained statistically significant after adjusting for age, self-reported health and income (Adjusted Odds Ratio=- 1.341) 1.590 1.886)).

Conclusions: This study provides new insights into the relationship between tobacco smoking and depressive symptoms. In expatriates, current smoking is associated with significantly increased risk of depressive symptoms. Future

الملخص

الخلفية والأهداف: ارتبطت قضايا الصحة العقلية بتدخين التبغ. وجدت العديد من الدراسات التي أجريت في عينات كبيرة من عامة السكان علاقة ذات دلالة إحصائية بين تدخين التبغ والأعراض الاكتئابية. لكن الأبحاث السابقة التي أجريت في المملكة العربية السعودية ذكرت ارتفاع معدل انتشار الاكتئاب والتدخين بين عينة صغيرة من العمال المغتربين الذكور ، لكنها لم تجد أي ارتباط. تهدف هذه الدراسة إلى التحقق من العلاقة بين تدخين التبغ المبلغ عنه ذاتياً (تدخين السجائر والشيشة) والأعراض الاكتئابية في عينة كبيرة من العمال المغتربين.

الطريقة: تم إجراء دراسة مقطعية مستعرضة تشمل مقابلات شخصية وجهاً لوجه لـ ٤٥٧٥ من العمال المغتربين الذكور في ٢٧٠ شركة / شركة في الرياض ، وقد أجريت المملكة العربية السعودية باستخدام تقنية العينة العنقودية متعددة المراحل لاختيار الأعمال / الشركات والمشاركين بشكل عشوائي. استخدم الاستطلاع Composite International Diagnostic Interview التي تنطبق على الاكتئاب السريري DSM-IV للاضطرابات الاكتئابية الرئيسية والحالات بين المشاركين. تم تقييم التدخين باستخدام الأسئلة القياسية لمنظمة الصحة العالمية لتقييم التعرض للتبغ والمتغيرات المشتركة مع استبيان موحد. تم تحليل البيانات باستخدام الانحدار اللوجستي.

النتائج: يرتبط التدخين الحالي بزيادة احتمالية حدوث أعراض اكتئابيّة (نسبة الأرجحية Crude Odds = ١,٥١٦ (١,٢٨٤ - ١,٧٩٠)). بقيت العلاقة ذات دلالة إحصائية بعد تعديل العمر ، الصحة والدخل المبلغ عنها ذاتيا (نسبة الأرجحية المعدلة = ١,٥٩٠ (١,٣٤١ – ١,٨٨٦)).

الاستنتاجات: تقدم هذه الدراسة رؤى جديدة في العلاقة بين تدخين التبغ

research is needed to clarify directionality and mechanism explaining the relationship. Health professionals and policy makers should be aware of the increased risk of depressive symptoms in expatriate workers who are tobacco smokers.
Key-words: Tobacco smoking, depressive symptoms, expatriates, tobacco control, mental health services

والأعراض الاكتئابية. في المغتربين ، يرتبط التدخين الحالي بزيادة خطر الإصابة بأعراض اكتئابية. هناك حاجة إلى بحث مستقبلي لتوضيح الاتجاه والآلية التي تشرح العلاقة. يجب أن يكون المهنيون الصحيون وصانعي السياسات على دراية بالخطر المتزايد للأعراض الاكتئابية لدى العمال المغتربين الذين هم مدخنون للتبغ.

INTRODUCTION

Globalization of the workforce has been described as one of the most significant trends that will affect workers especially expatriates. An expatriate worker can be considered an individual who is to be employed, is employed or has been employed in a salaried occupation in a country of which the individual is not a national [1]. The Kingdom of Saudi Arabia (KSA) is home to 10.4 million expatriates which constitute a third of the population [2] and they represent a significant potential in the context of labour and skill shortages. Previous research by Alkhamis, Hassan [3] suggests that expatriates have different health insurance plans that may affect the quality of care provided in KSA. Expatriate workers are expected to pay an average of 10% (specialist physician's fees) or 30% (consultant physician fees) of their salary to cover co-payments, excluding the cost of transportation and other expenses. The wages of Asians and non-Asian expatriate workers are lower when compared to that of the local workforce and expatriates are also willing to work longer hours [4]. The stress of expatriate work, in addition to cultural, professional and personal transitions may cause expatriates to smoke cigarette and tobacco related products to self-medicate anxiety. Tobacco smoking includes cigarette, cigar, pipe, hookah, shisha or water pipe and other tobacco products. Tobacco smoking is the number-one cause of preventable death and kills more than half of its users with more than 6 million deaths each year because of direct tobacco use [5]. Smoking is decreasing globally and in many countries, but the prevalence of tobacco smoking appears to be increasing in the WHO Eastern Mediterranean Region. The WHO report claims if tobacco prevention programs in Saudi Arabia continue at the same pace, the projection is that by 2025 approximately 6,268,400 individuals, about 24% of the population will be smokers [6]. It is well established that there is no safe level of tobacco use. Smoking as few as one to four cigarettes per day increases the risk of cardiovascular disease and other chronic conditions[7]. This indicates tobacco smoking causes significant socioeconomic costs due to increased absenteeism, deteriorating general health status and reduced productivity in the workforce.

A recent study that involved a cross sectional survey of 400 expatriate workers in one company in Al-Qassim, KSA using the Center For Epidemiological Studies Depression scale (CES-D) found depression prevalence of 20% which was considerably high in the small scale non-representative study sample [8]. Duration of stay, living condition, current cigarette smoking were not significant corre-

lates of depression but age, stress, and self-reported health status. However, previous research [9-12] and the report from the United States Department of Health (Surgeon General) [13] have shown significant relationship between tobacco consumption and depression. Yet the association of tobacco smoking and depressive symptoms has not been comprehensively investigated among a large representative sample of expatriate workers in KSA. This study, consequently aimed to extend the previous research using data from a cross sectional study and add to the evidence base. The Saudi Arabia general population or health professionals, particularly those not involved in tobacco and health, still do not commonly know the relation between smoking and depressive symptoms. Research in this area is important to effectively focus potential preventative efforts on this population that is frequently underserved, vulnerable and often experience significant health disparities, for example, lower income, high co-payments for medical care and cultural minority status. This study investigates expatriates tobacco smoking and expected that it would have a negative relation with depressive symptoms.

MATERIALS AND METHODS

A cross-sectional survey of 4,575 male expatriates was conducted among expatriate workers in businesses/companies that were identified from the Saudi Ministry of Labour database (sampling frame). Riyadh City, the capital of Saudi Arabia, was selected as the setting for the study because the Riyadh region contains more than one-third of expatriates and one-fourth of the Saudi population [14]. This study was part of a main study that investigated expatriates access and barriers to healthcare and the study methods have been described elsewhere [15, 16].

A stratified multi-stage business/company systematic selection design with an equal chance of each expatriate worker being selected from the target population was used in this survey. Participants businesses/companies were identified from the Ministry of Labour database and were stratified based on location, business type, company size, and number of employees. To estimate the sample size with 95% confidence and 2% margin of error, 2,000 expatriates were required, but was multiplied by the design effect of 2 because cluster sampling was employed, resulting in an initial sample size of 4,000 expatriate workers. The calculation was done in Epi-Info 3.5.1. In order to determine how many samples for each economic sector and company size, we divided 4,000 (the sample size) by the total number of companies (102,495) in Riyadh. The fraction was used to multiply the total number of companies in each economic sector, to determine the number of companies to be selected from each economic sector. Each company was assigned a minimum of 30 samples to be surveyed during the selection process. If the company had less than 30 workers, another randomly selected company with a similar size was studied to reach the 30 workers representing both the sector and company size. However,

more companies were added to some sectors to have a minimum of four companies covering all four different sizes of companies. Due to this adjustment, the sample size required was 4,629. Based on their size and economics sectors, companies were selected from the database by systematic random sampling. This was done using the Statistical Package for the Social Sciences (SPSS) software, companies' names and any related information were concealed and the means of identification was the company's code number known only to the manager of the Statistics Department at the Ministry of Labour.

Employees in the selected organizations were approached after obtaining due approval from the company owner and/or general manager of the company. The human resources department of large businesses/ companies provided a list of expatriate staff from which participants were randomly selected. To be eligible for survey, participants must be 18 years or over and non-Saudi nationals. Expatriates workers who refused to sign the inform consent form were excluded. Participants were approached for interviews during break/lunch time or at the close of work. The purpose of the study was explained to all participants. In addition, anonymity and confidentiality were assured and the right to refuse participation without affecting their healthcare plan and employment was explained. Ethical approval was obtained from the Institutional Research Board of King Abdullah International Medical Research Centre.

This current study reports on the aspects of the survey that determined the association between tobacco smoking exposure and depressive symptoms in a large representative sample of expatriate workers. To ensure uniform data collection, ten research assistants' from the dominant languages of expatriate workers were recruited. The research assistants were trained on interview techniques, skills on how to advertise the importance of the survey and educating selected participants. To test the questionnaire and procedure, it was piloted in Al Batha, a well-known gathering area for expatriate workers with a sample of 150 participants.

The main independent variable of interest was whether or not an individual reported tobacco smoking. The three recommended basic questions by WHO that must be included in all surveys that measure tobacco exposure were used to assess participants' exposure to tobacco smoking (17). Participants were asked if they smoke cigarette, moasel or hubble-bubble (water pipe) based on three topics: 1. Current tobacco smoking status 2. Past daily smoking status (for current less than daily smokers) 3. Past smoking status (for current non-smokers). Those who responded that they have no lifetime history of smoking were categorized as never smokers and those who indicated they smoke everyday were classified as everyday smokers. Participants who reported smoking at least once a week in the last 30 days were grouped as occasional smokers and those who indicated previous history of smoking but have not smoked in the last 30 days were classified as

ex-smokers. The rationale for assessing self-reported tobacco smoking use was based on previous research that suggests self-reports of tobacco smoking are rather reliable, particularly in observational studies [18, 19]. Other covariates included were age < 30, 30 – 49, ≥ 50), income (≤2000SR, 2001-6000SR, > 6000SR) and self-reported health status. To assess their health status, participants were asked to rate their overall health status with five response options; excellent, very good, good, fair and poor. The variable used in this analysis had two categories after merging very good, good with excellent, and fair with poor (good and poor). Age and self-reported health status were found in previous research conducted in KSA to be associated with depression among expatriates workers and hence were considered potential confounders in this current study analysis. Income was included as a potential confounder in the analysis because existing studies suggest that low socioeconomic status (SES) is generally associated with high psychiatric morbidity and poorer access to health care and income-related inequality was more pronounced in mental health than in general health [20, 21]21. These covariates were assessed using the validated Medical Expenditure Panel Survey (MEPS) questionnaire [22].

The main outcome variable of interest was depressive symptoms. The Composite International Diagnostic Interview (CIDI) instrument [23] applicable to clinical depression was used to assess DSM-IV symptom criteria for major depressive episodes and symptoms (24) using the full range of questions on depression, for the past 12 months. The CIDI is a valid standardized structured diagnostic interview instrument designed for assessment of mental disorders worldwide by trained lay interviewers. Participants' responses were grouped into two categories based on the summation of their responses (yes vs no) to the individual symptom item [25, 26]. The outcome variables of interest were (1. No, depressive symptoms and 2. Yes, had depressive symptoms). Therefore, the category depressive symptoms based on the DSM-IV criteria consists of participants with major depressive disorder and episodes.

The data were analyzed using the Statistical Package for the Social Sciences Windows Version 24.0. Data were processed using descriptive statistics and logistic regression. Prevalence estimates were calculated and described for never smokers, current smokers and ex-smokers. Associations between depressive symptoms and all potential predictors were analysed in univariate regression followed by multivariate logistic analysis using backward stepwise method. The covariates were entered into the logistic regression as categorical variables, indicator and first. Statistical significance was based on two-tailed tests and level of significance was set at 0.05. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated for each variable.

RESULTS

In this study, all participants who an-

swered the tobacco smoking and depression questions were included (n=4575) which is a response rate of 98.83%. There are no missing data. Table 1, displayed detailed sociodemographic and workplace characteristics of the study participants. The majority of the samples were in the age category 30-49 years (69.4%). The prevalence of depressive symptoms, the crude odds ratio and adjusted odds ratio between depressive symptoms with smoking status (Never smokers, ex-smokers and current smokers (which collapsed occasional smokers because the small numbers prevented its separate analysis)) are listed (see table 2). Hence, current smokers refer to participants who smoked at least once in the 30 days before the survey. The highest prevalence of depressive symptoms was reported by current smokers (19.85%) followed by ex-smokers (18.45%) and never smokers (15.14%). Current smokers compared to never smokers were associated with statistically significant increased risk of depressive symptoms (OR=1.516 (1.284, 1.790)). However, the association between previous history of self-reported smoking but not currently smoking and depressive symptoms (OR=1.347 (.971, 1.869)) was not statistically significant in the final model (p>0.05). In the multivariate logistic regression, the association between self-reported current smoking and depressive symptoms remained statistically significant after adjusting for age, income and self-reported health (AOR=1.590 (1.341,1.886)).

Table 1. Sociodemographic and workplace characteristics of study participants.

Variable	Number of study participants, n (%)
Nationality	
India	1100 (24.0%)
Bangladesh	1159 (25.3%)
Pakistan	498 (10.9%)
Egypt	819 17.9%)
Philippine	200 (4.4%)
Yemen	234 (5.1%)
Others	565 (12.3%)
First Language	
Arabic	1480 (32.4%)
Urdu	949 (20.7%)
Hindi	443 (9.7%)
Malayalam	171 (3.7%)
Bengali	1111 (24.3%)
Tagalog	182 (4.0%)
Others	239 (5.2%)
Age category (Years)	
< 30	1014 (22.2%)
30 - 49	3176 (69.4%)
≥ 50	385 (8.4%)
Education	
Primary school or less.	1331 (29.1%)
Elementary or high school completed.	1654 (36.1%)
Diploma or university degree	1590 (34.8%)
Income (monthly)	
≤ 2000SAR	3085 (67.4%)
2001 - 6000SR	1342 (29.3%)
> 6000	148 (3.2%)

Marital Status	
Single/Divorced.	842 (18.4%)
Married, family in KSA.	750 16.4%)
Married, family outside KSA.	2983 (65.2%)
Duration of stay (years)	
<1	818 (17.9%)
1 - 5	2233 (48.8%)
> 5	524 (33.3%)
Occupation group	
Specialist/Professionals.	1189 (26.0%)
Manual workers.	2064 (45.1%)
Unskilled workers.	1322 (28.9%)
Smoking status	
Non-smokers Current smokers Ex-smokers	3308 (72.3%) 1046 (22.9%) 221 (4.8%)
Self-reported physical health	
Very good	4424 (96.7%)
Poor	151 (3.3%)

DISCUSSION

To the best of our knowledge, this is the first study that investigated the relationship between self-reported smoking status and increased risk of depressive symptoms in a large representative sample of male expatriate workers in KSA. The similarities and representativeness of our study sample characteristics to the expatriate population have been described elsewhere [15]. Our study found current smoking is associated with significantly increased risk of depressive symptoms that persisted after adjusting for age, income and self-reported health and high prevalence rate of depressive symptoms among current smokers. The current findings are consistent with a recent study conducted by the British Heart Foundation (BHF) that found tobacco smokers were 70% more likely to suffer from anxiety and depression overall compared to non-smokers [27,28]. Moreover, our findings are similar to previous research among the general population samples that found tobacco smoking is significantly associated with in-

Table 2: Prevalence and logistic regression of smoking status and depressive symptoms.

Smoking status	Total (%) N=4575	Depressive symptoms	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Never Smokers	3308 (72.3%)	590 (15.14%)	1	1
Current Smokers	1046 (22.9%)	259 (19.85%)	1.516 (1.284, 1.790)*	1.590 (1.341,1.886)*
Ex-smokers	221 (4.8%)	50 (18.45%)	1.347 (0.971,1.869)	1.181 (0.843,1.654)

CI (Confidence Interval), * p<0.001 Adjusted for age, income and self-reported health.

creased risk of clinical depression and depressive symptoms [26, 29].

This evidence that smoking is associated with significantly high levels of risk for depressive symptoms among expatriate workers is open to alternative explanations based on our study' cross sectional design and findings from existing work. First, tobacco smoke is a complex brew containing more than 7,000 compounds including more than 70 known compounds or toxins that can cause cancer [30]. Recent studies [30, 31] demonstrate tobacco smoking damages deoxyribonucleic acid (DNA) in cellular tissues directly exposed to smoke as well as speeds up mutational cellular processes in organs that are both directly and indirectly exposed to smoke. As a result, one possible explanation for the observation noted here is that tobacco smoking causes distortion in the brain cellular processes in a way that results in the depletion of serotonin, norepinephrine and dopamine leading to increased risk of depressive symptoms through neurologic pathways.

Second, research suggests expatriate workers are prone to anxiety and depressive symptoms due to professional and personal transitions. Evidence shows that migration is a risk factor for depressive symptoms in some individuals and married expatriate workers living without their families in the host country are at higher risks of smoking [16, 32] 32 Therefore, another explanation could be that individuals with depressive symptoms are at increased risk of smoking. In addition, existing study[33] reported a shared genetic predisposition to smoking and mental illness. However, other important clinical evidence suggests that after a few weeks of quitting smoking, mood improves above that reached when the individual was smoking [34]. A recent meta-analysis that investigated changes in mental health after smoking cessation reported that quitting for at least six weeks is associated with reduced depression, anxiety and stress, improved positive mood and quality of life compared to individuals with mental disorders who continued to smoke [35].

Interestingly, large longitudinal research [26, 36-38] that found smoking was associated with mental health disorders have enabled researchers to account for previous history of mental illness as a confounder in their analyses.

The possible alternative explanations for this association have potential important clinical implications. On one hand, it provides evidence that targeting smoking (tobacco cessation) among expatriate workers could reduce the risk of depressive symptoms. On the other hand, it implies a comprehensive healthcare program delivery with smoking cessation programs integrated with mental health services may be a suitable approach among this group. This approach will promote smoking cessation and improve mental health status. Thus, there is a need for a future study comparing a (usual) smoking cessation intervention with a smoking cessation intervention integrating mental health evaluation/ services. This study has a number of limitations. First, the cross-sectional study design

limits the authors' ability to make causal inference. The cause–effect relationships are not well known; additional research that includes using cellular or genetic information to determine the causal relationship between smoking and depressive symptoms is needed to understand the direction and pathophysiologic mechanisms of association. Second, the findings cannot be generalized to the female expatriate population as we focused on the male expatriate population. Nonetheless, compared to male, female constitute a small proportion of smokers (1.1%) in the general population [39]. Additionally, there are few female expatriate in the private sector work and most of them are in healthcare and as housemaids [15, 40]. Segregation in the workplace would have made it difficult to access them. Third, participants may have underreported their smoking habits due to social desirability. However, a recent cross sectional study of a representative sample of the general population conducted in KSA reported a current smoking male prevalence of 21.5% (39). Our study found a comparable prevalence of 22.9%. For that reason, the high prevalence of current smoking reported by participants makes it unlikely there was underreporting due to social desirability. Fourth, there is a possibility that smoking is a confounder that is, related independently to a third factor that is the real cause of the depressive symptoms. Lastly, the study only focused on major depressive disorder and episodes. We did not account for other mood disorders such as bipolar disorders, anxiety and stress that could be potential confounders or effect modifiers in this study. However, longitudinal studies [36, 37] that accounted for history of mental illness in their analyses found tobacco-smoking increases the risk of depression. The strength of the current study is the representativeness of our study sample who are the main expatriate groups in Saudi Arabia.

In summary, this research is important showing smoking is associated with significantly increased risk of depressive symptoms among expatriate workers. Nonetheless, the use of a cross-sectional design in this study does not allow a temporal relationship to be established between smoking and depressive symptoms. Regardless of the direction of association between smoking and depressive symptoms, the findings suggest the need for anti-tobacco interventions among this group to reduce the risk of depressive symptoms and the integration of tobacco smoking cessation and mental health services. Health policy makers and healthcare professionals should consider this possible pathway when designing smoking cessation programs for expatriate workers in Saudi Arabia. More research is required to clarify directionality and mechanism explaining the relationship. In addition, future study comparing a (usual) smoking cessation intervention with a smoking cessation intervention integrating mental health evaluation/services is needed. This will ensure that healthcare programs implemented on tobacco cessation and preventative mental health are relevant and effective.

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Competing interests

The authors declare no conflicts of interest.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethical Review Board at King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Saudi Arabia. Written consent to participate was obtained from all participants. All participants signed a consent form and freely agreed to participate in this study. All participants were asked for permission to publish the study findings and assured of anonymity and confidentiality.

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Original Article

Prevalence of Work-Related Low Back Pain among Health Care Professionals in Tabuk, Saudi Arabia

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ABSTRACT

Background and Aims: Low back pain (LBP) is common among health care professionals (HCPs). The aim of this study was to analyse the prevalence and selected risk factors of LBP among HCPs in different medical institutions in Tabuk, Saudi Arabia.

Methods: Using convenience sampling, 160 subjects (28 physical therapists, 52 physicians, and 80 nurses) were included in this study. Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) and self-assessment back pain information sheet were administered. Descriptive analysis was used to study the general characteristics of the participants. Relationship between LBP and selected risk factors were tested using Chi-square and ANOVA. Data was analysed using SPSS ver. 20.0.

Results: The one-week prevalence of LBP was found 57% among nurses, 50% among physicians and 36% among physical therapists. Many risk factors were found to have significant relationship with LBP ($p<0.05$) such as occupation, severity of pain, gender, education status, activities of daily living, limitation of activities in lifting and prolonged standing. The results also revealed a statistically significant difference among nurses, physicians, and physical therapists with respect to pain scale ($p = 0.002$). In particular, the pain level was higher in nurses (M= 4.55) than in physicians (M= 3.31). No significant differences were found between physical therapists (M= 3.75) and nurses or physicians with respect to mean score of pain scale.

الملخص

الأهداف: آلام أسفل الظهر هي من الحالات الشائعة بين الممارسين الصحيين، لذلك هدفت هذه الدراسة لدراسة انتشار آلام أسفل الظهر والعوامل المؤدية إليه بين الممارسين الصحيين في مؤسسات طبية مختلفة في منطقة تبوك، المملكة العربية السعودية.

الطريقة: باستخدام أسلوب العينة المريحة، تم إدراج ١٦٠ مشارك (٢٨ أخصائي علاج طبيعي و ٥٢ طبيب و٨٠ ممرضًا) في هذه الدراسة. طبقت عليهم استبانة كورونيل لقياس عدم الراحة العضلية الهيكلية (Cornell Musculoskeletal Discomfort Questionnaire) واستبانة تقييم ذاتي لآلام الظهر. لتحليل البيانات، تم استخدام الإحصاء الوصفي لوصف الخصائص العامة للمشاركين، ولتحليل العلاقة بين آلام أسفل الظهر وعوامل الخطر فقد تم استخدام اختبار مربع كاي (Chi-square) للمتغيرات المصنفة واختبار تحليل التباين للمتغيرات الكمية (ANOVA). تم تحليل البيانات باستخدام برنامج (SPSS ver. ٢٠,٠).

النتائج: أظهرت النتائج ان نسبة انتشار آلام أسفل الظهر في الاسبوع الواحد هي ٥٧٪ بين الممرضين و ٥٠٪ بين الأطباء و٣٦٪ بين أخصائي العلاج الطبيعي. كما أظهرت النتائج علاقة ذات دلالة إحصائية ($p < ٠,٠٥$) بين العديد من العوامل وآلام أسفل الظهر مثل المهنة، مستوى الألم، الجنس، المستوى التعليمي، مستوى الأنشطة في الحياة اليومية، محدودية الأنشطة في الرفع والوقوف لفترات طويلة. كما أظهرت النتائج فروق ذات دلالة إحصائية ($p < ٠,٠٠٢$) بين الممرضين والأطباء وأخصائيي العلاج الطبيعي فيما يتعلق بمستوى الألم. على وجه الخصوص، كان مستوى الألم أعلى بين الممرضين (المتوسط ٤,٥٥) من الأطباء (المتوسط ٣,٣١). لكن لم تظهر النتائج فروق ذات دلالة إحصائية بين أخصائيي العلاج الطبيعي (المتوسط ٣,٧٥) والممرضين أو الأطباء في مقياس الألم.

الخلاصة: تشير نتائج الدراسة ان معدل انتشار آلام أسفل الظهر بين الممرضين

Conclusions: Nurses are found with more prevalence rate of LBP than physicians and physical therapists. This might be due to adoption of poor ergonomics and it requires preventive and appropriate treatment measures to improve their quality of life and work productivity.

Keywords: Low back pain, Health care professionals, Occupational risk, Prevalence, Saudi Arabia.

أعلى من الأطباء وأخصائيو العلاج الطبيعي. وقد يعزى ذلك لبيئة العمل الغير مناسبة مما يتطلب إجراءات وقائية وعلاجية ملائمة لتحسين نمط الحياة والانتاجية في العمل لدى هذه الفئة.

الكلمات الدالة: آلام أسفل الظهر، الممارسون الصحيون، المخاطر المهنية، معدل الانتشار، المملكة العربية السعودية

INTRODUCTION

Low back pain (LBP) is one of the most common work-related musculoskeletal disorders (MSDs) among health care professionals (HCPs).[1] Work-related MSDs are defined as a subset of MSDs that arise from occupational exposures.[2] Work-related MSDs refer to non-traumatic inflammatory or degenerative disorders of the musculoskeletal structures of the neck, back, upper or lower extremities, and they develop over time and arise when the adaptive and repair capacities of affected structures have been exceeded.[3]

LBP is defined as pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica).[4] The prevalence of LBP in the adult general population as published in 2000 shows point prevalence of 12–33% and 1-year prevalence ranging between 22% – 65%, and life time prevalence up to 84%.[5] LBP is one of the important problems for occupational health care workers such as physical therapists,[6] physicians[7] and nurses.[8] Work-related LBP causes disability and affects the health care, workers' activities of daily living (ADL),[9] and work productivity.[10] MSDs are more common among HCPs due to exposure of wide range of work-related risk factors that may results in various types of occupational disorders.[11]

Proper ergonomic practices could reduce the severity of MSDs.[12] The studies emphasizes that mechanisms leading to the work-related musculoskeletal pain are multifactorial.[13] The main risk factors of LBP are bad postures, bending, twisting and frequent lifting.[14] It is generally accepted that the physical posture of the HCPs, while having ultimate care, should be relaxed, the entire muscles are in good balance and any weakness outside of this neutral position for a prolonged period of time will cause musculoskeletal discomfort.[15]

A few studies have been conducted to understand the prevalence and risk factors of work-related LBP among the HCPs in Saudi Arabia. However, no such studies in the combination of physical therapists, nurses and physicians were done in the hospital setting. Therefore, the purpose of this study was to analyze the prevalence and selected risk factors of work-related LBP among HCPs in various hospitals and polyclinics in Tabuk, Saudi Arabia. To our knowledge, this is the first study to analyze the prevalence and selected risk factors of LBP among HCPs in different hospitals in Tabuk, Saudi Arabia.

MATERIALS AND METHODS

Study Design: A cross-sectional design was utilized in this study.

Study setting and Participants

In this study, a total of 175 participants from six hospitals and four polyclinics in Tabuk were included using convenience sampling method. The sample size was determined using the prevalence of LBP in study population. This was calculated by using a power of 80% and $\alpha = 0.05$ to detect a difference of 20%. Accordingly, a total sample size of at least 160 was determined. Participants were included based on the following criteria: has to be in direct contact with patients, work as physical therapists, nurses or physicians, work in both government and private hospitals or polyclinics. Subjects were excluded if they worked part time, pregnant or currently on leave from their duties (e.g., maternity or sick leave).

This study was approved by the Research Ethics Committee, University of Tabuk, Tabuk, Saudi Arabia. The participants were invited to take part in the study on voluntary basis. They received written informed consent explaining the aims of the study. The participants' confidentially were protected at all time.

Questionnaires

The main aim of this study was to measure the one-week prevalence rate of LBP among HCPs utilizing the Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) for Male and Female[16] (Appendix A1 and A2). All other MSDs were captured as well using the same questionnaire. The CMDQ is a 54-item questionnaire containing a body map diagram and questions about the prevalence of musculoskeletal ache, pain or discomfort in 18 regions of the body during the previous week. Respondents indicate frequency of discomfort on an ordinal scale from 0 (none) to 4 (daily) and severity of discomfort from 1 (slightly uncomfortable) to 3 (very uncomfortable). The level at which the discomfort interfered with work was scored from 0 (no interference) to 2 (substantial interference). Test-retest reliability for a group completing the CMDQ at a 3-week interval found a 7% difference in responses for upper body parts and a 1% difference for lower body parts.17

A self-assessment LBP information sheet (Appendix B) was used to record the respondents' demographic information and selected risk factors of LBP. The sheet consists of five sections: (1) demographic information, such as age, gender, marital status, educational level, height, weight and body mass index (BMI); (2) lifestyle information, such as smoking habits and working hours; (3) the numerical pain rating scale (NPRS) score; (4) information about the duration of LBP, effects of LBP on ADL and work activities, medications intake and history of LBP surgery; (5) perceived stress level in work environment and previous back care education about LBP.

Data Analysis

Data was analyzed using Excel and Statistical Package of Social Studies (SPSS, Windows Version 20.0) for descriptive (mean, range, percentage and standard deviation)

and inferential statistics. In inferential statistics, Chi-square test was used for categorized variables and ANOVA for the numerical variables. A $p < 0.05$ was identified as statistically significant for all statistical tests used.

RESULTS

Out of 175 respondents, 160 respondents (66 males and 94 females) with mean age of 35.5 ±12.4 years completed the two questionnaires. Fifteen respondents were excluded due to incomplete questionnaire. Response rate was observed as 91.4% (Figure 1). The description of the subjects included in the final analysis is shown in Table 1. Overall mean BMI of subjects was found as slightly overweight (25.82 kg/m2). The BMI of physical therapists, physicians and nurses were observed as 25.87 kg/m2, 28.77 kg/m2 and 23.90 kg/m2, respectively. The average NPRS score of subjects having only LBP was found 4.01.

Figure 1. Flow diagram for participants recruitment.

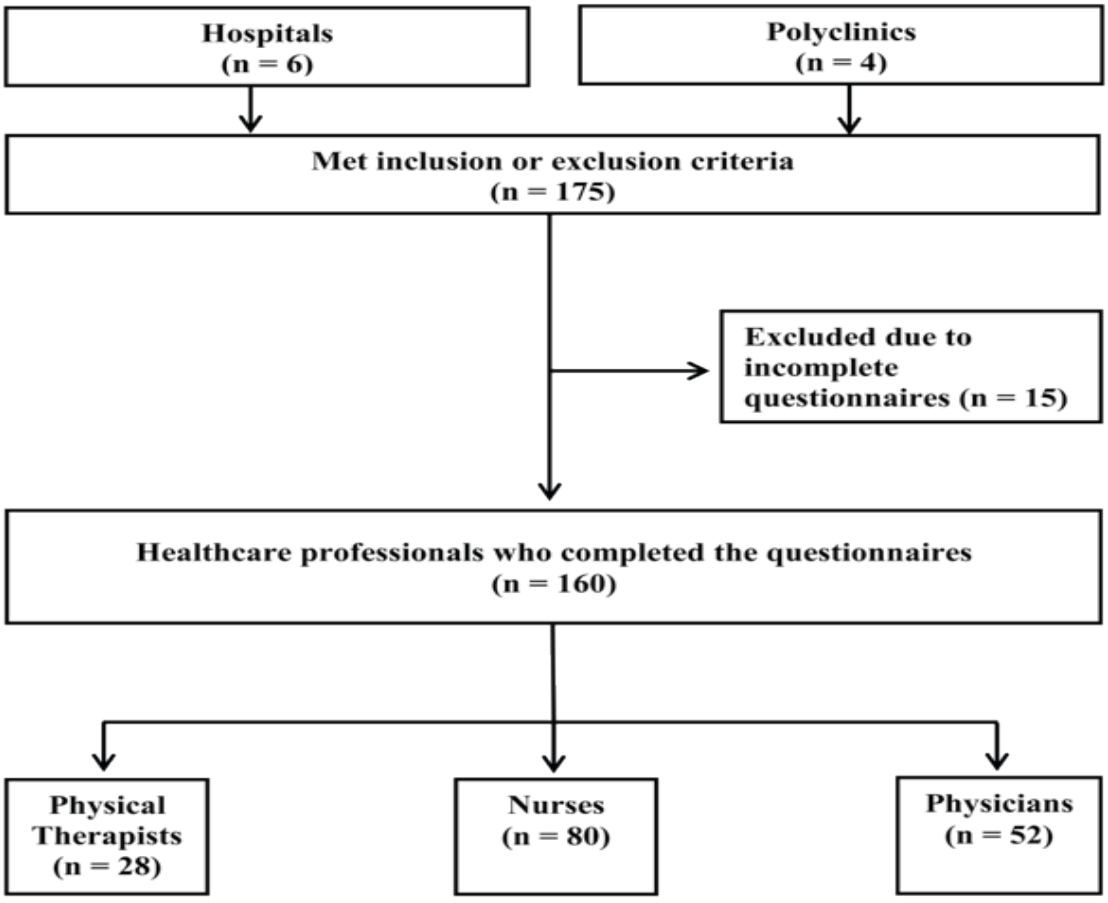


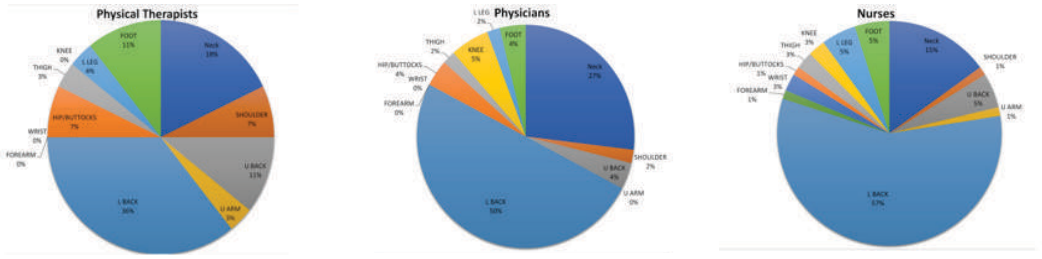
Table 1 Characteristics of the participants

Occupation Mean		Age (yrs)		Height (cm)		Weight (kg)		BMI (kg/m^2)		Pain scale	
		S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	
PT n=28	Male (12)	30.17	7.41	170.75	3.55	76.83	21.73	26.27	7.11	2.67	1.44
	Female (16)	31.19	7.10	158.87	5.34	64.50	9.51	25.58	3.77	4.56	1.55
	Total	**30.75**	**7.11**	**163.96**	**7.54**	**69.79**	**16.77**	**25.87**	**5.35**	**3.75**	**1.76**
Physician n=52	Male (41)	48.46	13.04	171.26	8.11	87.54	16.98	28.92	4.29	3.07	2.09
	Female (11)	39.91	15.27	160.00	6.16	74.82	17.30	28.18	4.73	4.18	2.64
	Total	**46.65**	**13.90**	**168.88**	**8.97**	**84.85**	**17.67**	**28.77**	**4.35**	**3.31**	**2.24**
Nurses n=80	Male (13)	29.23	5.12	166.08	8.83	73.46	19.04	26.44	5.71	5.00	2.52
	Female (67)	30.23	7.44	156.53	6.44	57.60	12.72	23.41	4.57	4.46	1.77
	Total	**30.01**	**7.06**	**158.08**	**7.68**	**60.18**	**14.99**	**23.90**	**4.86**	**4.55**	**1.90**
Total N=160	Male (66)	41.35	14.25	170.14	7.82	82.82	19.04	27.95	5.24	3.38	2.21
	Female (94)	31.53	9.13	157.33	6.31	60.79	13.95	24.33	4.71	4.45	1.84
	Total	**35.55**	**12.46**	**162.61**	**9.40**	**69.88**	**19.50**	**25.82**	**5.23**	**4.01**	**2.06**

PT: Physical Therapists, BMI: Body Mass Index

Out of 160 respondents, 28 were physical therapists (17.5%), 52 were physicians (32.5%) and 80 were nurses (50%). Among physical therapists, the highest one-week prevalence of work-related MSDs was found for LBP (36%), followed by neck pain (18%), then upper back pain and foot pain with 11% prevalence rate. The rest of MSDs had 7% or less prevalence rate (Figure 2A). For physicians, LBP was also found the most common complaint during the last week with 50% prevalence rate. This was followed by neck pain and knee pain with 27% and 5% prevalence rate, respectively (Figure 2B). In nurses, 57% reported LBP over the last week, 15% had neck pain and 5% constituted of pain in upper back, lower leg and foot regions (Figure 2C).

Figure 2. One-week prevalence of musculoskeletal disorders among participants:



[2A]: Physical Therapists. [2B]: Physicians [2C]: Nurses

Table 2 shows the association between the selected risk factors and LBP level, as measured by NPRS, using chi-square test. The analysis revealed significant association between gender and severity of pain ($p = 0.002$), where 60% of females had moderate to severe pain. Contrary to this, 47% of males experienced moderate to severe pain.

While analyzing the education level, a significant association was found between educational background and severity of pain ($p = 0.008$), where 63% of bachelor's degree holders are prone to moderate to severe pain. Likewise, a significant association was observed between the type of occupation and severity of pain ($p = 0.012$), where 61% of nurses experienced moderate to severe pain in comparison to 53% of physical therapists and 48% of physicians.

Furthermore, 72% of subjects with moderate to severe LBP indicated that his/her pain interferes with ADL. A significant association was also found between limitation of activities such as lifting (70%) and prolonged standing (69%) with respect to severity of pain ($p = 0.001$ and 0.008, respectively). Nevertheless, severity of pain perceived by the subjects showed no significant association towards marital status, working hours, smoking habit, medications intake, prior exposure to surgery, perceived stress at work environment and patient education ($p > 0.05$).

It should be noted that the severity of pain (mild – moderate – severe) was categorized based on the NPRS score. Zero score in the NPRS represents no pain, while 10 indicates worst pain imaginable. The NPRS score is often used to divide patients into groups who are in need of pain treatment (moderate and severe pain) and those who are not (mild pain). According to Diane C. Zelman et al.18, a NPRS score of 0–3 is categorized as mild pain, 4–6 moderate pain and a score ≥ 7 as severe pain. In this study, severity of pain was categorized based on the same categorization method.

The results of the one-way ANOVA revealed statistically significant difference among nurses, physicians and physical therapist with respect to pain level, $F(2, 157) = 6.39$, $p = 0.002$. In that case, a Scheffe's test was conducted to examine the difference among professions. The Scheffe's post hoc tests showed that the pain level was signifi-

Table 2 Association between selected risk factors and low back pain level

Category			*df*	*Chi-square value*	*p-value*
Gender	Male (n =66)		3	15.199	0.002*
	Female (n =94)				
Marital status	Single (n =65)		3	7.047	0.070
	Married (n =95)				
Education level	Doctorate (n =15)		9	22.240	0.008*
	Master (n =20)				
	Bachelor (n =108)				
	Diploma (n =17)				
Occupation	Physical Therapists (n =28)		6	16.259	0.012*
	Nurses (n =80)				
	Physicians (n =52)				
Working hours	Less than 30 hours (n =38)		6	2.686	0.847
	30 to 40 hours (n =46)				
	More than 40 hours (n =76)				
Smoking	Yes (n =15)		3	2.094	0.553
	No (n =145)				
Effects of LBP on daily activities	Yes (n =83)		3	13.805	*0.003
	No (n =77)				
Activities limited during LBP	Lifting	Yes (n =59)	3	16.058	*0.001
		No (n =101)			
	Pushing	Yes (n =26)	3	2.580	0.461
		No (n =134)			
	Patient handling	Yes (n =27)	3	2.904	0.407
		No (n =133)			
	Prolonged sitting	Yes (n =29)	3	1.302	0.729
		No (n =131)			
	Prolonged standing	Yes (n =60)	3	11.705	*0.008
		No (n =100)			
	Walking	Yes (n =26)	3	5.020	0.170
		No (n =134)			
Taking medications	Yes (n =36)		3	2.382	0.497
	No (n =124)				
Underwent prior surgery for LBP	Yes (n =15)		3	3.731	0.292
	No (n =145)				
Perceived stress level in work environment	Mild (n =71)		6	8.041	0.235
	Moderate (n =71)				
	Severe (n =18)				
Received education about LBP	Yes (n =95)		3	0.802	0.849
	No (n =65)				

LBP: low back pain, *Significant at 0.05 level

cantly higher in nurses (M= 4.55) than in physicians (M= 3.31). However, in this study, no statically significant differences were found between physical therapist (M= 3.75) and nurses or physicians with respect to mean score of pain scale (Table 3).

Table 3 Scheffe's post hoc test for mean score of pain scale among professions

Comparison	*Mean difference*	*F*	*p-value*
Physical therapists vs. Physicians	0.44	0.88	0.640
Physical therapists vs. Nurses	0.80	3.34	0.192
Physicians vs. Nurses	1.24	12.19	0.003*

*Significant at 0.05 level

DISCUSSION

In our study, 48% of participants had experienced LBP over last week. Nurses experienced more LBP than any other hospital workers. It has been previously reported that the lifetime prevalence of LBP among nurses ranged between 70% and 80%, annual prevalence ranged between 15% and 45% and point prevalence was 30%.9 In a study that was conducted in Italy to investigate the musculoskeletal problems among Italian nurses, they found that the 12-months prevalence of LBP ranged from 33% to 86%.[19] Another epidemiological study revealed that Greek nurses reported significantly more backof Lr studies using the Nordic Musculoskeletal Questionnaire (NMQ), on which the CMDQ is based, reported 7-day prevalence rates complaint (75%) than Dutch nurses (62%) in the past 12 months.20 Other studies reported 69% one-week prevalence for neck, shoulder, upper and LBP among Swedish nurses21 and 61.2% back pain among nurses in Germany,22 which is similar to our results.

Physicians were observed as the second common HCP with the prevalence of LBP (50%). This is consistent with the findings by Karen et al.[7]. The occurrence of MSDs among hospital physicians is due to multiple physical exposures23 or duration of keeping awkward postures or because of walking distance during work.[24] These factors may lead to different complaints of the musculoskeletal system that are known to be related to hospital work.

In this study, LBP was found to be common among physical therapists, but comparatively less than nurses and physicians. This may be due to small sample size of physical therapists used in this study. A recent study reported 35.6% point-prevalence of LBP among physical therapists.[25] Another study by Salik and Oczan[26] reported the occurrence of LBP as 26% among physical therapists (n =120) in Izmir-Turkey. These prevalence rates, although with different time lines, are comparable with our findings.

Risk factors like smoking, high BMI, advancing age, female gender, inactivity, long standing time, and perceived stress were significantly associated with the presence of LBP worldwide and in Saudi Arabia.[27-32] But in our study, there is no association found between severity pain and marital status, work-

ing hours, smoking habits, limitation of activities such as pushing, prolonged sitting and walking, medication intake, history of LBP surgery, job stress and perceived education. This is consistent with results by Landry et al.33 which states that there is no association between LBP and common risk factors such as age, sex, professional experience, smoking and exercise.

In our study, some of the risk factors were found to have significant relationships with LBP such as ADL, limitations of activities in lifting and prolonged standing among HCPs. The above findings are consistent with other studies that targeted physical therapist2 nurses and physicians.11 Other studies report that the occurrence of LBP is due to frequent patient transfer and repositioning.34,35 In order to avoid work-related LBP among HCPs, posture training, patient handling, ergonomics and back care education program should be introduced during their undergraduate study courses. This would give them the opportunity to learn how to use their postures without putting too much effort on the body and use their forces efficiently and effectively. It has been recommended that frequent workshops and seminars should be organized for physical therapists and other HCPs who are handling the patients frequntly.2 Hospitals and other health care facilities need to be prepared with the necessary equipment that would assist to minimize work-related MSDs among HCPs (e.g., patient lifter, frames to sit and stand, sliding boards, suspension frame, adjustable beds, walking frames). The administration facility should report LBP incidence rates36 and comprehensive, safe patient handling methods need to be developed.

CONCLUSION

Nurses have more prevalence rate of LBP (57%) than physicians (50%) and physical therapists (36%). Insufficient ergonomic knowledge and extreme postures sustained for prolonged periods and their repetitiveness may contribute to this occurrence. Preventive measures are necessary to reduce the role of work-related LBP such as adequate relaxation, back care education program and ergonomic advices. Ergonomic assessment of work place risk factors and the greater use of back care interventions are recommended.

LIMITATIONS

A limitation of this study is the relatively small sample size, which was also limited to one region in Saudi Arabia. This may limit the generalizability of our findings. Another limitation is the limited risk factors investigated in this study. Wider range of potential work-related risk factors should be included in future studies.

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LIST OF ABBREVIATIONS:

LBP: low back pain; MSD: musculoskeletal disorder; HCP: health care professional; ADL: activities of daily living; CMDQ: Cornell Musculoskeletal Discomfort Questionnaire; BMI: body mass index; NPRS: numerical pain rating scale.

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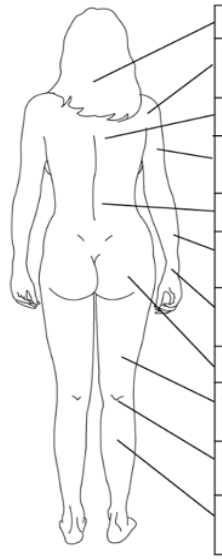
Appendices

Appendix A1: Cornell Musculoskeletal Discomfort Questionnaire – Male

Appendix A2: Cornell Musculoskeletal Discomfort Questionnaire – Female

The diagram below shows the approximate position of the body parts referred to in the questionnaire. Please answer by marking the appropriate box.	During the last work week how often did you experience ache, pain, discomfort in:					If you experienced ache, pain, discomfort, how uncomfortable was this?			If you experienced ache, pain, discomfort, did this interfere with your ability to work?		
	Never	1-2 times last week	3-4 times last week	Once every day	Several times every day	Slightly uncomfortable	Moderately uncomfortable	Very uncomfortable	Not at all	Slightly interfered	Substantially interfered
Neck	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shoulder (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shoulder (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Back	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Arm (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Arm (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Back	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Forearm (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Forearm (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wrist (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wrist (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hip/Buttocks	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thigh (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thigh (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knee (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knee (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Leg (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Leg (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



The diagram below shows the approximate position of the body parts referred to in the questionnaire. Please answer by marking the appropriate box.	During the last work week how often did you experience ache, pain, discomfort in:					If you experienced ache, pain, discomfort, how uncomfortable was this?			If you experienced ache, pain, discomfort, did this interfere with your ability to work?		
	Never	1-2 times last week	3-4 times last week	Once every day	Several times every day	Slightly uncomfortable	Moderately uncomfortable	Very uncomfortable	Not at all	Slightly interfered	Substantially interfered
Neck	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shoulder (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Shoulder (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Back	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Arm (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Upper Arm (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Back	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Forearm (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Forearm (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wrist (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Wrist (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hip/Buttocks	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thigh (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Thigh (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knee (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Knee (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Leg (Right)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lower Leg (Left)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix B: Self-assessment back pain information sheet

SELF-ASSESSMENT BACK PAIN INFORMATION SHEET

Age: _____ years Gender: ☐ Male ☐ Female

Marital Status: ☐ Single ☐ Married Occupation: _____

Education level: ☐ Doctorate (PhD) ☐ Masters ☐ Bachelor ☐ Diploma

Height: _____ centimeters Weight: _____ Kilograms BMI: _____

Experience: _____ years Working Hours: ☐ > 30 ☐ 30-40 ☐ <40

Smoking: ☐ Yes ☐ No ☐ Blood Pressure: _____ / _____mmHg

Pain scale (NPRS):

Duration of LBP: _____ years/months/weeks

Effects of LBP on daily activities: ☐ Yes ☐ No

Activities limited during LBP:
☐ None ☐ Lifting ☐ Pushing ☐ Patient handling ☐ Prolonged sitting
☐ Prolonged standing ☐ Walking ☐ Others

Taking Medications: ☐ Yes ☐ No Underwent Surgery for LBP: ☐ Yes ☐ No

Perceived stress level in work environment: ☐ Mild ☐ Moderate ☐ Severe

Received Education about LBP: ☐ Yes ☐ No

Note: LBP: Low back pain, BMI: Body Mass Index, NPRS: Numerical Pain Rating Scale.

Name: _____ ***Signature:*** _____ ***Date:*** _____

Original Article:

Medical Students' Accountability, Preferences and Satisfaction with Team- Based Learning

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ABSTRACT

Background: The study aimed to assess Team Based Learning (TBL) as an instructional method using a validated and reliable TBL-Student Assessment Instrument (TBL-SAI) from female medical students' perspective during their pre-clinical phase (1st, 2nd and 3rd years).

Methods: A cross sectional descriptive design was applied in this study, and a comprehensive sample (n=93) was taken. The TBL-SAI, used to collect data, consists of 33 items and was divided into 3 subscales, namely, Accountability, Preference for Lecture or TBL, and Student Satisfaction. A -5graded rating scale was used, where 1= Strongly Disagree and 5= Strongly Agree.

Results: The students' response rate was 75.26% (n=70). Overall, 77.27% of the students preferred TBL over lectures. This represented 78.94% , 82.75% and 77.27% of the first, second and third-year students, respectively. In addition, 80% of the students expressed a high level of satisfaction

الملخص

خلفية: أصبح لطريقة التعلم القائم على العمل في فرق شعبية كبيرة في التعليم الطبي؛ بسبب قدرته على تعزيز التعلم النشط ومهارات حل المشكلات والاتصال والعمل الجماعي. تهدف الدراسة لمعرفة مسؤولية طالبات كلية الطب وتفضيلاتهم ومدى رضاهم عن التعلم القائم على الفريق.

المنهجية: تم إجراء دراسة وصفية لقطاع من الطالبات بكلية الطب البشري بجامعة الجوف بالمملكة العربية السعودية. تم أخذ عينة شاملة من الطالبات في المرحلة ما قبل السريرية (السنة الأولى والثانية والثالثة) بقسم الإناث وعددهن ٩٣ طالبة. تم استخدام استبيان موثق لجمع البيانات.

النتائج: بلغ معدل الاستجابة لدى المشاركات ٧٥,٢٦٪ (عدد = ٧٠). أظهرت النتائج أن ٧٧,٢٧٪ من الطالبات يفضلن التعلم القائم على العمل في فريق مقارنةً بـ ١٣,٦٨٪ يفضلن المحاضرة كوسيلة للتعلم. بالإضافة إلى ذلك، ٨٢,٧٥٪، ٧٨,٩٤٪ و٧٧,٢٧٪ من طلاب السنة الأولى والثانية والثالثة على التوالي يعتبرن التعليم القائم على العمل في فريق تجربة ممتازة للتعلم؛ و٨٠٪ من الطالبات أبدين مستوًى عال من الرضاء عن هذه الطريقة. أظهرت النتائج أيضاً أن متوسط (± معدل انحراف معياري) الرضا العام في الثلاث سنوات

with TBL, even though there were statistically significant differences between the three-year students (P = 0.004).

Conclusion: According to the findings obtained from the study, the majority of pre-clinical years students are accountable to TBL, preferring it over lectures, and are satisfied with their teamwork experience of TBL activities.

Keywords:

Students' assessment instrument, Accountability, Preference, Team based learning.

هو: ١١٥,٠٧ ± ١٧,٩١، ١٠٣,٢٥±١٢,٠٧ و١٠٢,٥٠ ± ١١,٤٧ لطالبات الفرقة الأولى والثانية والثالثة على التوالي. هناك فروق ذات دلالة إحصائية بين الثلاث سنوات (P = ٠,٠٠٤).

الخلاصة: خلصت الدراسة إلى أن الغالبية العظمى من الطالبات بكلية الطب البشري في جامعة الجوف أبدين مسؤولية تجاه الاستعدادات المطلوبة لطريقة التعلم في فريق من تحضير للمواد وفهمها واستيعابها من قبل جلسة العمل في الفريق. علاوةً على ذلك، فإنهن يفضلن هذه الاستراتيجية على طريقة التعلم عن طريق المحاضرة، وهن راضيات عن تجربتهن من خلال العمل الجماعي في فريق، ويجدنه أكثر إفادة من طريقة التعلم التقليدية.

INTRODUCTION

Team-based learning (TBL) is an instructional strategy that is being implemented increasingly in many medical schools. TBL is defined as a method of active student learning in small-groups; every student is responsible for his/her learning as well as his/her group. It can be described as an expert-led, interactive and analytical teaching strategy.1

The College of Medicine, Jouf University (COM-JU), adopts innovative integrated educational active-learning strategies, and pedagogical approaches that enable students to transition from dependent to self-directed, lifelong learners, that include: Problem-Based Learning, Team-Based Learning, Community-Oriented Education, Student-centered seminars, interactive lectures, and, Simulation-Based Learning (SBL) and early hands-on training in a safe learning environment through the clinical skills laboratories.

In Problem-Based Learning (PBL) system at COM-JU, students use scenarios to define their own learning objectives. Students think critically about the nature of the problem, generate ideas, and acquire the knowledge and skills required to become a doctor.2

Lecture based learning (LBL) at COM-JU is an efficient and organized method for delivery of a large body of knowledge, lecturers use power point presentations to deliver information to many students in a relatively short period. Lecturers try to make it more interactive; they activate the involvement and participation of the audience by questioning them, providing quizzes and short answers and using audience responses.

TBL in the College of Medicine, Jouf University (COM-JU), Kingdom of Saudi Arabia (KSA) is a part of a hybrid teaching method that enhances the learning quality by using high-performing learning teams. TBL appears to improve academic performance and students' attitudes toward teamwork.3, 4 Also; it improves student performance and increases student engagement and satisfaction.5

TBL effectively uses the time of its session to stress on applying the learned concepts.6

The main challenges are successfully planning for TBL session and providing a timely and active constructive feedback to students to ensure learning. 7, 8

In TBL, only one single instructor can

manage multiple students' small groups simultaneously in one classroom. The principle behind team-based learning is that students working together as a team can achieve a higher level of learning than individual students alone can achieve.3

TBL has three steps:

Step one: students should pass through study in advance assignment defined by faculty, learners read and study material independently outside class. 4

Step two: faculty should be sure that his students have already studied and understood the assignment by making learners demonstrate knowledge through individual readiness assurance tests (IRATs), then pre-assigned teams of 5–7 learners re-take the same test, forming a consensus about each answer in group readiness assurance tests (GRATs) 4, These answers are scored for immediate feedback. In TBL, there is peer evaluation by students and their colleagues' learners; they assess the contribution of peers within their group.

Step three: students start application of knowledge when learners apply course concepts to solve realistic, authentic problem designed by faculty and analyzed by teams. 4

Teams also work on group application exercises (GAE), solving the problems before engaging in inter-team discussion and debate on finding solutions.

There is a flexibility of implementing TBL in medical education; instructors can use selectively one or more of the phases, depending on the contextual demands of the course or session. Unlike the role of tutor in Problem based learning, instructor in TBL work as a facilitator as well as a subject area expert. He helps students to apply the knowledge learned to solve the problem. 9

Leadership roles in TBL session:

Each team member is required to assume each role at least once, after which teams will have the freedom to manage leadership roles as they wish.

- accurately record GRAT answers;
- coordinating team's submission of GRAT appeals;
- facilitating intra-team GAE discussion;
- serving as a team spokesperson in the inter-team discussion of GAE problems;
- leading a team huddle to debrief group performance; and
- Collecting and returning of materials. 10

The challenge that faces all of us as medical educators is to enhance medical students higher order cognitive skills by moving from traditional, passive methods of teaching to more active methods.11 TBL helps to prepare medical students to be effective health care providers in the healing environment such as the clinical training setting. 2

A number of studies providing empiri-

cal evidence of students' benefits from TBL such as increased student engagement and higher-quality communication processes.4

Our school has successfully implemented Team-Based Learning in all our preclinical blocks and most of our clerkships.

Although TBL was introduced as a medical education strategy in 2001, a few studies in the Middle East have explored its impact on learning outcomes. As medical educators considering implementing TBL, we need supporting evidences of its educational effectiveness. This study aimed to assess Team Based Learning (TBL) as an instructional method using a validated and reliable TBL-Student Assessment Instrument (TBL-SAI) from female medical students' perspective during their pre-clinical phase (1st, 2nd and 3rd years).

MATERIALS AND METHODS

Setting and participants

This study was conducted in the COM-JU, KSA in 2018, and adopted the descriptive cross section survey research design. A total number of 93 female students (30, 28 and 35 students from the 1st, 2nd, and 3rd years, respectively) participated in this study. To select study groups from the target population, purposive sampling (non-probability sampling (was used, the individuals are selected deliberately based on the main criteria which are assumed by the researcher to be representative of the population. The main criteria consisted of: 1-being a female medical student, 2-being at the basic sciences phase (1st, 2nd and 3rd years), 3-using TBL as instructional method in their educational courses and 4—having consent to be enrolled in the study.

This study was expected to measure the female students' perception towards TBL as a method for teaching. The study is expected to answer the questions; Are female students in COM-JU accountable to TBL? Do they prefer TBL or lecture-based learning (LBL)? Are they satisfied with TBL? Female students are novice; they graduated from high school as passive learners, who lack experience of students centered educational strategies, that enable them to be active learner participating in their learning process. The alternative hypothesis is "female students in COM-JU are satisfied with TBL, and they consider it a rich learning experience, it enhances their learning, they are accountable to TBL, and prefer it over LBL".

Data collection & Statistical Analyses:

The validated TBL-Student Assessment Instrument (TBL-SAI) was used to collect data, it consists of 33 items, and is divided into 3 parts: First part: Accountability subscale, which assesses students' preparation for class and contribution to the team. Second part: preference for lecture or TBL subscale, which assesses student ability to recall material and student attention level in lecture and TBL. Third part: Student Satisfaction Subscale, which assesses students' satisfaction with TBL. The rating scale ranges from 1 to 5 where 1= strongly disagree and 5= Strongly Agree.

Data were collected anonymously, and the study was approved by the Permanent Bioethical Committee of JU with an approval number of 5-16-8/39. Statistical analyses of the TBL-SAI were calculated in accordance with the guidelines given by the developer of the instrument. Descriptive statistics were used for each component, and comparative statistics were undertaken to compare statistically significant differences between the three years. Data generated was analyzed using percentage, mean and standard (SD). Null hypotheses were tested using One-Way Analysis of Variance (ANOVA) test with Post-Hoc Test. A p value <0.05 was considered statistically significant, and consequently reject the null hypothesis. The desired level of confidence will be 95%.

RESULTS

In the academic year of 2018, 70 out of 93 students of the female students in the 1st, 2nd and 3rd year consented to participate in the TBL-SAI survey. Response rate was 75.26% (70/93); distributed as 96.7% (29/30), 67.85% (19/28) and 62.85% (22/35) from the 1st, 2nd and 3rd year students, respectively.

The TBL-SAI consists of 33 questions using a 5-option symmetric disagree-agree rating scale. Percentages of students' responses of "agree and strongly agree", "neutral", and "disagree and strongly disagree" options were calculated.

Concerning female students' accountability for TBL, Table 1 shows that 79.31%, 42.1% and 77.27% of the students in the 1st, 2nd, and 3rd year, respectively, are accountable for TBL.

Table 2 shows that the mean scores in the three subscales and the overall for all three years are 25.7, 49.54, 31.7 and 106.94, respectively.

Regarding students' preferences for LBL or TBL, Figure 1 shows that 72.4%, 84.2% and 77.3% prefer TBL compared to 17.2%, 10.5% and 13.6% of the 1st, 2nd and 3rd-year students, respectively, prefer lecture.

Regarding students' favorable experience with TBL, Figure 2 shows that 82.8%, 78.9% and 77.3% of the 1st, 2nd, and 3rd year students, respectively, have favorable experience with TBL. Most of the female students in basic sciences phase have favorable experience with TBL activities.

Concerning overall satisfaction with TBL as an educational method, Figure 3 shows that 80% of the participants have a higher level of satisfaction with TBL.

Regarding the participants' accountability for TBL, Table 3 shows that the mean ± SD for the 1st, 2nd and 3rd-year students, respectively, is 27.34±6.95, 23.77±5.34 and 26.16±3.58. There are no statistically significant differences between the three years.

Regarding female students' preference, for Lecture or TBL, Table 3 shows that mean ± SD for students' preference is 52.76±9.39, 50.45±4.05, and 45.41±6.44 for the 1st, 2nd, and 3rd year, respectively. There are statistically significant differences between the three years (P = 0.003).

Regarding female students' Satisfac-

tion with TBL, Table 3 shows that mean ± SD for students' Satisfaction is 34.97±7.51, 29.32±8.45, and 31.10±5.40 for the 1st, 2nd, and 3rd year, respectively. There are statistically significant differences between the study years (P = 0.025).

In terms of the overall satisfaction with TBL, Table 3 reveals that the mean ± SD for that scale is 115.07±17.91, 103.25±12.07 and 102.50±11.47 for the 1st, 2nd, and 3rd year, respectively. There are statistically significant differences between them (P = 0.004)

RESULTS

Table 1: Assessment of the accountability for Team-Based Learning.

Accountability Subscale level	First Year %	Second Year %	Third Year %	Total	% of Total
Low	13.79%	52.63%	9.09%	16	22.85
Neutral	6.89%	5.26%	13.63%	6	8.57
High	79.31%	42.1%	77.27%	48	68.57
Total	100%	100%	100	70	100

Table 2. TBL-SAI Survey Result.

Subscales	Possible Range	Neutral Point	Mean	SD	p
Accountability	8-40	24	25.75	5.29	
TBL vs. lecture	16-80	48	49.54	6.62	
Satisfaction	9-45	27	31.70	7.12	*0.000
Overall	33-165	99	106.94	13.81	
Grand mean	11-55		35.66	12.38	

* p<0.05 indicates statistically significant differences. SD = Standard deviation. TBL-SAI = Team-based learning student assessment instrument

Table 3: Comparing the accountability, preference, satisfaction and overall satisfaction of participants for TBL based on the year of study

Subscale	1st year (n = 29)	2nd year (n = 19)	3rd year (n = 22)	Grand Mean (n = 70)	P value
Accountability	27.3 ± 7.0	23.8 ± 5.3	26.2 ± 3.6	25.8 ± 1.8	0.107
Preference of lecture over TBL	52.8 ± 9.4	50.5 ± 4.1	45.4 ± 6.4	49.5 ± 3.8	0.003
Satisfaction with TBL	35.0 ± 7.5	29.3 ± 8.5	31.1 ± 5.4	31.8 ± 2.9	0.025
Overall satisfaction with TBL experience	115.1 ± 17.9	103.3 ± 12.1	102.5 ± 11.5	106.9 ± 7.1	0.004

Data are expressed as Mean ± SD. P value by One-Way ANOVA. * p<0.05 indicates statistically significant differences.
TBL = team-based learning,

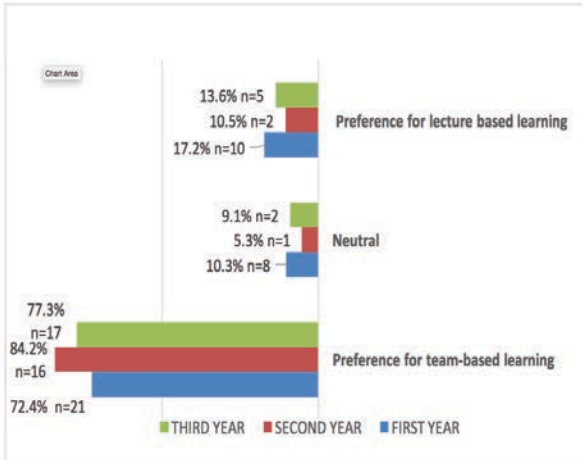

Figure 1: Frequency distribution of female students' preference for Lecture or Team-Based Learning

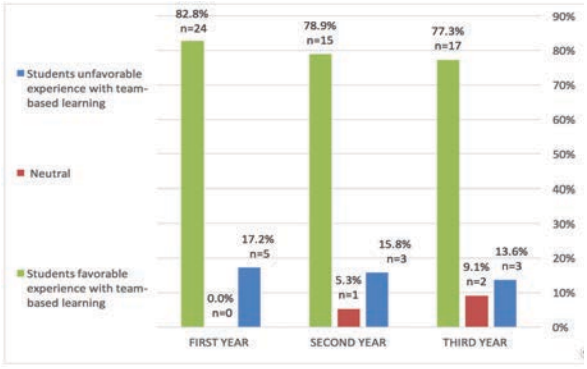

Figure 2: Frequency distribution of female students' favorable experience with Team-Based Learning.

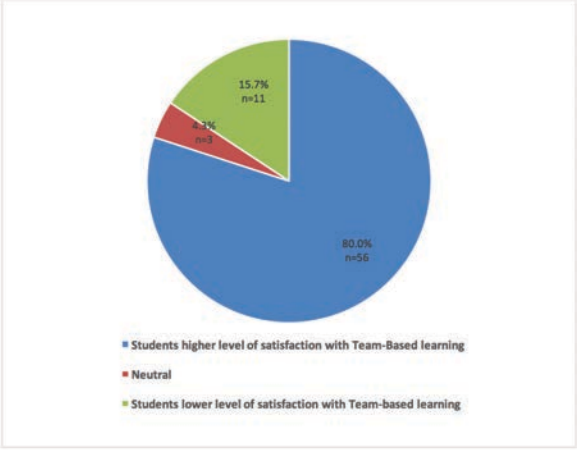

Figure 3: Frequency distribution of the overall Satisfaction with Team-Based Learning.

Discussion:

Although team-based learning (TBL) is widely used in medical education, evaluation of students' accountability, preference and satisfaction with it needs further assessment. The main aim of this study was to assess the implementation of TBL in newly established female section at COM-JU using TBL-SAI survey. As male section in the same college was found before and TBL was implemented for a long time, college was receiving feedback from male students but female students were not investigated before about this point. TBL-SAI measures female students' responses in three categories: their accountability, preference for lecture or TBL and their satisfaction with it. Assessment results showed that 80% of our students surveyed had favorable experience with TBL which is in keeping with the study held by Chao & Mott (2015), they found that over 86% of students surveyed using the same tool had favorable experience with TBL. 3

Concerning female students' accountability for TBL, our results showed that 79.3% and 77.3% of the First-year and Third-year students, respectively, are accountable for TBL compared to the second-year students where 52.6% showed low accountability for TBL as shown in table 1. In COM-JU, the First-year and Third-year students were more responsible and motivated to their own learning through individual preparation, such as spending time in preparing for the course and immersion in understanding of the material, team work and students' engagement in the development of a high-quality team.

First-year students showed a high degree of accountability, as it was their first time to be exposed to such an innovative educational strategy. They felt more motivated to TBL than their colleagues in the second year who apparently lost their motivation due to burning out during the 1st year and dependence on each other on group work, or secondary

to acquisition of score-oriented character as TBL being assessed formatively rather than summative. First-year students showed more interest in favor of TBL, their role as only passive recipient of information has dramatically changed with provision of frequent feedbacks from quiz performance, peers and faculty. This allows a constant cycle of identifying knowledge gaps, addressing these deficits and thereby fostering abilities for self-assessment.

In the first year, teams tend to be politer and cooperative because of their new constitution (i.e., at the forming stage of group dynamic cycle). Over time, in the second year, teams are likely going to face more conflict, which may negatively affect their perceptions of TBL. We recommend giving more instruction and guidance in conflict resolution and the use of constructive feedback. In the third year, they may regain their motivation and build up more self-confidence because of their progression in their study.

In a study held by Su Allan (2007), he explored the impact of teacher grading methods on students' attitudes towards TBL and revealed that students tend to project a more positive attitude toward TBL when the contingent grading method was used.13

Second-year students didn't perceive the value of TBL. Mean ± SD (23.8±5.3) for the second-year accountability subscale was near the neutral point (i.e., 24) as shown in table 3. In a study held by Feingold et al. (2008), they stated that "students appreciated the need for increased individual accountability for learning and identified value in learning through discussion".14 Also, in a study held by Nagaswami et al. (2009), they documented that students resisted implementation of TBL or any type of active learning as it's a shift from the passive process of lecture-based settings.15 Britta et al., 2007 stated that "Students spent most of TBL classroom time in discussion, analysis and problem solving». The instructor must organize the session with no problems like social idling.16

Comparing female students' preference for Lecture or Team-Based Learning, figure 1 showed that 72.4%, 84.2%, and 77.3% of the 1st, 2nd and 3rd-year students, respectively, preferred Team-Based Learning to lectures; students in lecture play passive role whereas team interactions in TBL allow more active student participation that fosters both activation of prior knowledge.17 and active knowledge construction.18

In a study held by Tracy et al. (2015), their results found there is significant differences between TBL and traditional lecture (p=0.001).19

This study results indicated that 82.75%, 78.94% and 77.27% of the 1st, 2nd and 3rd-year students, respectively, have favorable experience with TBL as shown in figure 2.

In a study held by Chao & Mott (2015), they found that mean score of accountability, TBL vs. LBL, preference, satisfaction and overall satisfaction subscales for their study sample were 30.7, 48.6, 33.3 and 112.6, respectively 3. We can notice that our students less accountable for TBL than their sample

population. Student accountability should increase significantly from year to year because students must work independently to prepare for team sessions, in which they will work to solve problems with their teammates.20 Second step of TBL process "Readiness Assurance" is the one that test students' accountability to TBL, faculty should be sure that his students are ready, study and understand the assignment.21, 22

One of the potential limitations of this study is that it did not determine whether student performance on examinations is affected by participation in TBL and whether TBL benefits lower or higher performing students. This needs to be addressed in future studies. In addition, male students were not involved in the study, which negatively affects the generalizability of the results of this study, although it applies to communities of similar situations. Furthermore, this study did not rationalize the low accountability of the second-year students for TBL and did not evaluate the positive impacts of TBL on students' learning experience, grades and educational outcomes.

In conclusion, most pre-clinical years students included in this study are accountable to TBL, preferring it over LBL, and are satisfied with their teamwork experience of TBL activities. Further studies on TBL involving larger numbers of both male and female students in both the clinical and pre-clinical years with longitudinal arm looking at their performance in exams are warranted and recommended.

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Original Article:

Optical Coherent Tomography (OCT) Helps In Predicting Visual Outcomes Of Eyes Treated With Intravitreal Bevacizumab For Macular Edema Due To Non-Ischemic Branch Retinal Vein Occlusion (BRVO)

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ABSTRACT

Background: Optical Coherence Tomography (OCT) has been used to evaluate the impact of Anti – VEGF agents in cases of macular edema due to retinal vein occlusion. This study is to associate the visual outcomes to the type of edema, reflectivity and macular thickness on OCT.

Method: Patients who were to undergo intravitreal bevacizumab (IVB) injection for treating macular edema secondary to non-ischemic branch retinal venous occlusion (BRVO) were included in our study. The OCT findings were analyzed to assess the visual potential in these eyes. This cohort study was undertaken in 18-2016. Medical retina specialist examined all eyes. Best corrected visual acuity (BCVA), status of anterior and posterior segment of eyes were noted. OCT findings focused on type of edema, central retinal thickness (CRT) and reflectivity of fluid in front and within retinal layers. Macular edema was treated with IVB. On 1st follow up (6-4 weeks), BCVA, reduction in central retinal thickness and absorption of retinal fluid were noted.

Results: Our cohort had 61 eyes of 60 patients. In 32 eyes with Cystoid macular edema (CME), vision improved with an average of two lines or more. In 14 eyes with sub-retinal fluid vision was stable on 1st follow up. In 35 eyes with good

الملخص

الخلفية: يستخدم تصوير التماسك البصري المقطعي (OCT) لتقييم تأثير العوامل المضادة للـ VEGF في حالات الوذمة البقعية بسبب انسداد أوردة الشبكية. تهدف هذه الدراسة إلى ربط مدى تحسن البصر بنوع الوذمة والانعكاسية وسمك البقعة على OCT.

الطريقة: في دراستنا تم تضمين المرضى الذين كانوا يخضعون لحقن بيفاسيزوماب (IVB intravitreal) لعلاج وذمة البقعة الصفراء الناتجة من انسداد فروع أوردة الشبكية (BRVO) بسبب غير نقص التروية. تم تحليل نتائج OCT لتقييم تحسن البصر في هذه العيون. وقد أجريت هذه الدراسة الجماعية في عام ٢٠١٦-٢٠١٨. قام أخصائي شبكية العين الطبي بفحص جميع العيون. سجلت أفضل حدة بصرية مصححة (BCVA) وحالة الجزء الأمامي والخلفي من العيون. ركزت نتائج OCT على نوع الوذمة، سمك الشبكية المركزي (CRT) وانعكاسية السائل في الأمام وداخل طبقات الشبكية. تم علاج الوذمة البقعية بواسطة IVB. عند المتابعة الأولى (٤-٦ أسابيع)، لوحظ BCVA والانخفاض في سمك الشبكية المركزي وامتصاص السوائل داخل الشبكية.

النتائج: مجموعة الدراسة احتوت على ٦١ عين من ٦٠ مريضا. في ٣٢ عين من التي تعاني من وذمة البقعة الصفراء الكيسية (CME)، تحسنت الرؤية بمتوسط خطين أو أكثر. في ١٤عين من التي تعاني من سوائل تحت الشبكية

reflectivity (pretreatment OCT), visual improvement was significant compared to those 26 eyes with poor reflectivity. The mean CRT declined from 373 micron to 215.5 micron. However, it was not associated with improvement of visual acuity on follow up. None of the eyes had increased intraocular pressure on 1st follow up.

Conclusion: OCT can guide to the prognostic outcome of patients with macular edema secondary to venous occlusion to be treated with IVB in non-ischemic branch venous occlusion.

Key words: Retinal vein occlusion, Macular edema, Intravitreal bevacizumab injection, Vision

كانت مستقرة في المتابعة الأولى. في ٣٥ من العيون التي كانت الانعكاسية بها جيدة (في تصوير التماسك البصري المقطعي قبل المعالجة)، كان تحسن الرؤية كبيرا مقارنة بتلك العيون ال ٢٦ ذات الانعكاسية الضعيفة. انخفض متوسط سماكة الشبكية المركزي من ٣٧٣ ميكرون إلى ٢١٥,٥ ميكرون. بالرغم من ذلك لم يكن مرتبطا بتحسين حدة البصر عند المتابعة. لم تسجل أي من العيون ارتفاع في ضغط العين عند المتابعة الأولى.

الخلاصة: يمكن لتصوير التماسك البصري المقطعي ان يكون دليلا لتوقع النتائج في المرضى الذين يعانون من وذمة البقعة الصفراء الثانوية لانسداد فروع أوردة الشبكية (BRVO) بسبب غير نقص التروية.

INTRODUCTION

Retinal venous occlusion (RVO) is the second most common retinal vascular disease, following diabetic retinopathy. Macular edema is one of the major causes for vision loss in various types of retinal vein occlusions. Anti – VEGF agents (bevacizumab, ranibizumab and Macugen) have been reported to be effective in treating macular edema. [1-3] On resolution of macular edema after successful treatment, most patients have satisfactory visual recovery. Unfortunately, some patients have poor vision despite complete resolution of the macular edema. The clinicians therefore, experience dilemma while explaining to patients the prospects of visual recovery following such expensive interventions. Optical Coherence Tomography (OCT) has been used to evaluate the impact of intervention in cases of macular edema associated with Diabetes, retinal vein occlusion etc. [4-6] However, to the best of our knowledge, different parameters of OCT are yet not investigated as tools to predict the outcomes of treatment of macular edema due to non-ischemic BRVO. Therefore, we conducted a study to associate the visual outcomes to the type of edema, reflectivity and macular thickness that we noted on OCT before intervention.

METHODS

The ethical and research committee of Retina Foundation, Ahmedabad permitted us to undertake this study. It was conducted between June 2016 and June 2018. Informed consent was taken from all patients. We hypothesized that in 75% of our patients, OCT findings would help us in predicting the visual outcomes in eyes with non-ischemic BRVO induced macular edema treated by intravitreal injection of bevacizumab (IVB). To calculate the sample size of a cohort study with 95% confidence interval and 90% precision, we needed to treat at least 46 eyes with macular edema. (Raosoft sample size calculator) To compensate for the loss of data in a longitudinal study, we increased the sample by 20%. Thus, the final sample size was 56 eyes.

Patients aged 18 years and older presenting to our clinic, were our study popula-

tion. Those with vision less than 0.1 (6/60) and diagnosed to have macular edema secondary to non-ischemic BRVO were included in our study. We excluded cases that had evidence of ischemia, any other retinopathy or had taken treatment in the past like laser, intravitreal injection and ocular surgery.

The demographic profile of patients like age, sex, eye involved, interval between RVO and presentation to our clinic were documented. Other systemic co morbidities including; presence of diabetes, hypertension, hyperthyroidism and other cardio vascular pathology were noted. Diabetes was defined as person with fasting blood sugar more than 7 mmol/L. If person was already taking treatment for diabetes, he/she was defined as diabetic irrespective of the blood sugar level. If systolic and diastolic blood pressure were more than 120 and 80 mmHg respectively, the patient was defined as hypertensive. If patient was already taking treatment for hypertension, patient was labelled as hypertensive irrespective of his/her blood pressure level. The best visual acuity (BCVA) was noted using ETDRS projection distant vision chart. Anterior segment was examined using slit lamp bio-microscope (Topcon, Japan). Ocular pressure was measured using applanation tonometer attached to the bio-microscope. After dilatation of pupil, posterior segment was examined with the help of indirect ophthalmoscope (Keeler, UK) and +20D Volk lens. For Optical Coherence Tomography we used Stratus OCT (Carl Zeiss Meditec – Germany). Fluorescein fundus angiography (FFA) was also performed if needed. The macular edema was divided into; Cystoid macular edema (CME) or sub-retinal fluid (SRF), combination of both or undetermined. Based on the status of the third high reflectance band (HRB) in the OCT before treatment, the eyes were grouped into those with high reflectivity and those with poor reflectivity. The central thickness of macula was also noted from OCT investigation reports.

The first high reflective band in OCT corresponds to the external limiting membrane and outer high reflective band corresponds to the pigment epithelium. For analysis, we accounted for the first high reflective band. We did not account for second and the third reflective band in OCT in our study. The second band corresponds to the boundary of the inner and the outer segments of photoreceptors and the third reflective band corresponds to an ensheathment of the cone outer segments by apical processes of the retinal pigment epithelium.

The eyes were treated with 1.25 mg of intravitreal bevacizumab injection (IVB) under all aseptic precautions in the operation theatre. The treatment was repeated at 4 weeks intervals if macular edema did not reduce.

The follow up examination was carried out between 4 to 6 weeks after treatment. It included OCT, BCVA and ocular pressure measurement.

The data was compiled and analyzed using SPSS version 20 software. For the qualitative variables like type of edema, reflectivity, etc we calculated frequency and propor-

tion percentage and for quantitative variables like central retinal thickness, age, best corrected visual acuity (decimal) we used mean and standard deviation. Before undertaking univariate analysis, we confirmed that they have normal distribution by using histogram. For correlating quantitative variables (difference of CRT and BCVA after and before intervention), we calculated mean and standard deviation for each eye. Then for subgroups like type of edema and reflectivity, we calculated the difference of mean with their 95% confidence intervals and two tailed p value by Two-Sample Independent t Test and using analysis facilities of Statistical Package for Social Studies (SPSS 20). For two continuous variables namely central retinal thickness and improvement in BCVA, we compared the means by using one-way Analysis of Variance (ANOVA).

The identity of the patients was delinked form the other findings to maintain confidentiality. If a patient did not respond to one IVB, he/she was given another IVB at concession rate.

RESULTS

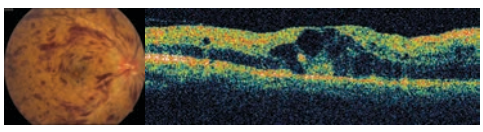
Our cohort included 61 eyes of 60 patients with macular edema due to RVO. 36 (60%) were male and 24 (40%) were female patients. The mean age of the cohort was 55.7 years (± 13.31 years). In 34 patients only, right eye was having macular edema and in 26 patients left eye was involved. In one patient both eyes were involved. The average interval between symptoms of RVO and presentation for treatment was 14.6 days (ranging from first day to 30 days).

Twenty-four patients had systemic hypertension, four were with diabetes and 11 had both hypertension and diabetes. One patient presented with CVS pathology and another had hyperthyroidism. Twenty patients had no systemic disease. Among our cohort, 56 eyes were phakic and five eyes were pseudophakic. The average IOP was 16 mm Hg (± 3.85 mm Hg).

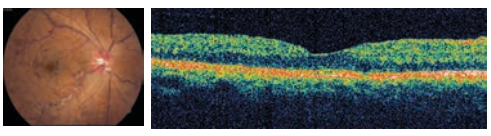
The fundus images and OCT images in different conditions are given in Figure 1, 2, 3 and 4.

Figure: 1 Fundus photograph and optical coherent tomography of an eye with cystoid macular edema (CME) due to branch retinal vein occlusion that had anatomical and visual recovery four weeks after intravitreal injection of bevacizumab.

Fig. 1:



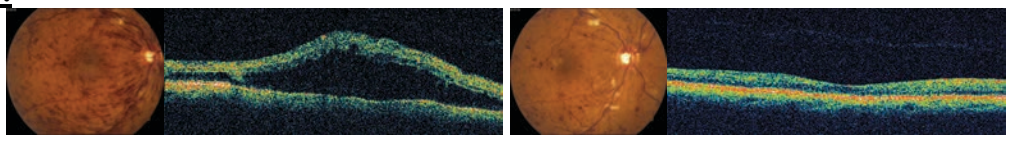
Vn – 6/24 Pre Avastin
OCT – CME pattern



Vn.- 6/6p Post Avastin 1 month
Resolution of edema with return of normal foveal contour

Figure: 2 Fundus photograph and optical coherent tomography of an eye with sub retinal fluid (SRF) due to branch retinal vein occlusion that had anatomical recovery and stable vision four weeks after intravitreal injection of bevacizumab.

Fig. 2:

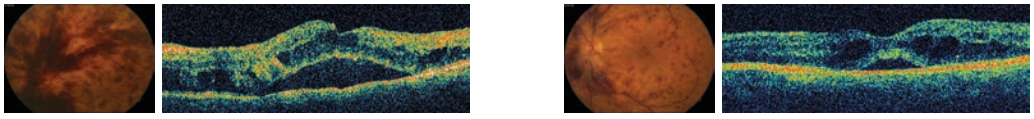


Vn – 6/60 pre Avastin
SRF presentation on

Vn – 6/60 post Avastin 1 month Resolution
of edema with normalisation of foveal

Figure: 3 Fundus photograph and optical coherent tomography of an eye with central retinal edema due to branch retinal vein occlusion that had High Reflectance Band but had persistent edema, but good reflectivity four weeks after intravitreal injection of bevacizumab.

Fig 3:

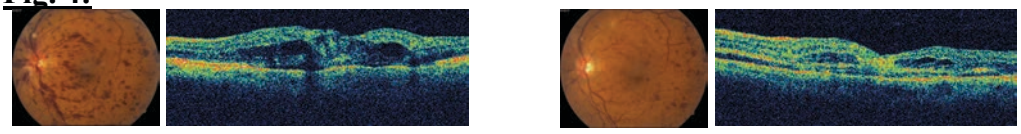


Vn. – 6/60 Pre avastin
OCT – Good HRB

Vn. – 6/24, 2 months Post Avastin
Persistant edema, but good reflectivity

Figure: 4 Fundus photograph and optical coherent tomography of an eye with central retinal edema due to branch retinal vein occlusion that had poor Reflectivity but had poor visual recovery and reduced edema, four weeks after intravitreal injection of bevacizumab.

Fig. 4:



Vn.- 6/60 pre treatment
OCT – poor reflectivity from HRB

Vn. – 6/36p 1 month post Avastin
OCT – macular edema reduced

The BCVA at 4-6 week follow up was compared to pre-treatment BCVA for each eye. For different types of macular edema, we compared the mean using independent t test in SPSS. (Table: 1) The patients with CME improved with an average of two lines or more on the visual acuity chart while those presenting with SRF remained stable within a line of initial presentation. None of the eyes in our cohort have shown intraocular pressure higher at 4-6 week follow up compared to that noted before intervention.

Table: 1 Best visual acuity before and four weeks after intravitreal injection of bevacizumab to treat macular edema due to retinal vein occlusion by type of macular edema.

Type of macular edema	eyes	Mean difference of Improved BCVA	95% Confidence Interval	Two tailed P value	t value
Cystoid edema	18	0.297	0.28 – 0.31	<0.0001	15.8
Sub-foveal fluid	14	0.095	0.05 – 0.14	0.0001	
Mixed	14	0.176	0.11 – 0.24	0.00002	
Undetermined	15	0.116	0.004 – 0.23	0.06	
All eyes with macular edema	61	0.171	0.14 – 0.20	<0.0001	

The BCVA at 4-6 week follow up was compared to pre-treatment BCVA for each eye. We calculated the mean and standard deviation by type of reflectivity noted on pre-treatment OCT and performed student's independent t test. (Table: 2).

Table: 2 Best corrected visual acuity (BCVA) before and four weeks after intravitreal injection of bevacizumab to treat macular edema due to non-ischemic retinal vein occlusion by type of reflectivity on Optical Coherence Tomography.

Type of HRB* (Reflectivity)	No. of eyes	Mean of the improvement of BCVA	(95% CI)	P value	t test value
Good	35	0.214	0.206 – 0.222	<0.0001	20.4
Poor	26	0.071	-0.0002 – 0.14	0.05	

* HRB = High Reflectance Band

The mean central retinal thickness (CRT) before treatment was 551.5 micron (±174.3 micron). On 1st follow up the mean CRT was 226.4 micron (± 107.12 micron). Thus, intervention reduced CRT significantly [difference of mean 325.1-micron (95% CI 273.2 – 377) p <0.0001] F = 12.4.

We compared the decline in CRT to the

improvement of BCVA 4-6 weeks following intravitreal bevacizumab in eyes with non-ischemic BRVO. We used two sample t test and found that the association was not statistically significant. (F= 3.31, p = 0.097)

DISCUSSION

Optical coherence tomography (OCT) is an effective tool for measuring quantitative and qualitative parameters of the macula, such as thickness, intraretinal abnormalities and the reflectivity from vital layers of the retina namely the ILM and RPE-photoreceptor complex. [7, 8] The reliability of anatomical correspondences of 1st and 4th bands of reflectivity to the outer limiting membrane and pigment epithelium respectively had been documented by Spaide RF et al. [9] The positive impact of IVB in both anatomical and physiological reversal of damage due to non-ischemic BRVO was apparent in our study and it matched with the findings of many other studies. [4, 6, 10, 11, 12]

We noted that the eyes with intraretinal edema regained vision better than those with subretinal fluid (SRF). Perhaps, presence of SRF might have negatively affected the viability of ILM and RPE complex resulting in less effect of IVB in absorption of edema and improving nutrition to the outer layers. 13 It could also be possible that the intravitreal route may be more effective in reducing edema nearer to the internal limiting membrane than that near RPE.

We found significant association of vision improvement and good reflectivity on pre-treatment OCT. This result is like other studies which show improved visual acuity with high reflectivity pattern on OCT. (14,15) However, to the best of our knowledge, there is no study correlating reflectivity to visual outcomes in macular edema due to non-ischemic BRVO. It is therefore suggested that clinicians should closely monitor pretreatment OCT to review OHRBT in cases of macular edema due to non-ischemic BRVO.

Many studies have documented reduction in central retinal thickness following IVB. [4, 6,10,11,16] We also noted marked decline in CRT. But improvement of vision was not consistent with the reduction of CRT in different studies. Perhaps difference in duration between IVB and follow up OCT in different studies could be responsible for this observation.

Thus, in our study, we found that the type of edema and reflectivity of macular lesion following non-ischemic BRVO are associated with the visual improvement and thus OCT findings would help vitreo-retinal surgeons to predict outcomes of IVB to treat retinal edema following non-ischemic BRVO. It is crucial that prompt intervention is planned for the patients with non-ischemic BRVO so that there are better chances of visual recovery. Counseling would be easier if clinicians can predict visual outcomes prior to commencing treatment

Our study had some limitations. All participants after first follow up did not visit the clinic. Hence, we had studied only short-term visual outcomes. Further studies are therefore recommended to evaluate the as-

sociation of visual outcomes at six months and one year after IVB and pretreatment OCT findings. Reexamining eyes 4 to 6 weeks after intervention, could be too early to have positive effects of intravitreal bevacizumab in all cases. This could have resulted in underestimates of success rates.

CONCLUSION

Optical coherence tomography is a spectacular tool in the vitreo retinal surgeon's armamentarium and assists VR surgeons to better predict the location of pathology in layers of retina and predict the anatomical outcome of treatments. [17] It is suggested that there should be wider use of this instrument to facilitate better understanding of the disease process, predicting the disease outcome, follow up of treatment results and involving the patient in decision making and becoming an important part of his/her own treatment process.

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Review Article

Tale of Two Non-Discogenic Pains, Sacroiliac Joint and Piriformis Syndromes – A Less Travelled Clinical Entities

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ABSTRACT

Both Sacroiliac Joint Syndrome (SIJS) and Piriformis Syndrome (PS) give rise to sciatica like symptoms and are the causes of low back pain due to its close proximity to the sciatic nerve. Clinical diagnosis of these two conditions are often compounded by the high degree of similarities in their clinical presentations making the diagnosis more speculative than confirmatory in our day to day practice. This is further complicated by non-availability of a reliable test that can confirm as well as distinctly distinguish the diagnosis of both the conditions.In the literature different theoretical basis are separatively given regarding causes of PS and SIJS, but are never discussed colectively which is usually seen in daily clinical practices. The review has emphasized to provide a bseline collective of most of pathogenetic and anatomic factors because of which one syndrome can give rise to another or vice-versa. Therefore the objective of the present review is to update what is known about the clinical characteristics and probable pathogenetic mechanisms of above syndromes for further understanding of the interrelations between PS and SIJS.

Keywords: low back pain, sacroiliac joint syndrome, sciatica, piriformis syndrome.

الملخص

كل من متلازمة المفصل العجزي الحرقفي (SIJS) ومتلازمة الكمثرية (PS) يؤدي إلى عرق النسا وأسباب آلام أسفل الظهر بسبب قربها من العصب الوركي. غالبا ما يضاعف التشخيص السريري لهاتين الحالتين من الدرجة العالية في أوجه التشابه في الأعراض السريرية مما يجعل التشخيص غير حقيقي اكثر منه تشخيصا تأكيديا في الممارسة اليومية. كما أصبح التشخيص اكثر تعقيدا بسبب عدم توفر الاختبارات الموثوقة التي تؤكده فضلا عن التمييز بوضوح بين تشخيص كل من الحالتين.

تعطي الأدبيات البحثية المختلفة أساسا نظريا حول أسباب متلازمة المفصل العجزي الحرقفي (SIJS) ومتلازمة الكمثرية PS))، ولكن لا تناقش ابدا بشكل مكثف الممارسات السريرية اليومية. ركزت مراجعة الأدبيات على اعطاء خطوط عريضة في الأساسيات الخاصة بالعوامل التشريحية والمرضية لأن أحدهذه المتلازمات يمكن أن يؤدي ال الآخر والعكس.

الهدف من هذا الدراسة هو تحديث ما هو معروف عن الخصائص السريرية وطرق الامراض المحتملة لمتلازمة المفصل العجزي الحرقفي (SIJS) ومتلازمة الكمثرية (PS) , ولمزيد من الفهم للعلاقات المتبادلة بينهما.

INTRODUCTION

Chronic low back pain (LBP) and understanding its etiologies has been a matter of studies since antiquity and arriving at a definitive diagnosis has always been a clinical challenge. Different components of the body such as muscles, joints, fascia and ligaments have been incriminated as the probable cause associated with such clinical condition.[1] Many other synonyms such as lumbar pain, spinal pain have been referred to as low back pain with various terms, coined by different authors.

Low back pain can further be categorized to lumbar spinal pain and sacral pain where lumbar pain is the pain that is perceived in the area between an imaginary line at the spinous process of T12 and S1 with a lateral extension by erector spinae whereas sacral pain is the pain perceived in the sacral area falling within the boundaries demarcated by the posterior-superior iliac spine and posterior-inferior iliac spine.[2,3] Among the various known causes of low back pain such as spondylosis, herniated disc, spondylolisthesis, spinal fracture, spondylolysis, spinal tumor, sacroilitis, sacroiliac joint dysfunction, piriformis syndrome, and pregnancy; sacroiliac Joint syndrome and Piriformis Syndrome are the two important causes of sacral pain. Clinically arriving at a correct diagnosis of sacral pain is often difficult, because it has often been better observed that two or more overlapping symptoms may manifest simultaneously in the patient mimicking symptoms of each syndrome. In this context, in the present article attempt has been made to highlight both anatomical and pathophysiological findings of Sacroiliac Joint syndrome and Piriformis Syndrome, where a muscle and a joint are primarily involved in producing overlapping clinical symptoms lead to a diagnostic dilemma. Furthermore, it is often difficult to distinguish which precedes the other.[4-7]

Sacroiliac Joint and Sacroilliac syndrome:

The Sacroiliac Joint (SIJ), an axial joint is surrounded by a fibrous capsule. There is a dorsally extended sacro iliac ligamentous structure that helps to limit the movement in three different planes.[8,9] The ligamentous structure is relatively weaker in females compared to male.[10] Various muscles such as piriformis, biceps femoris and gluteus maximus are connected to this ligament and do have a role related to the mobility of the sacro-illiac joint.[11]

The SIJ pain is commonly prevalent as low back pain in approximately 15% of the population.[9] Pain in the sacro iliac joint is often idiopathic, however two reasons i.e. either due to dysfunction and/or due to some underlying pathological conditions have been attributed. Joint dysfunction can occur due to various isolated or combined functional anomalies of muscular imbalance, locking of the joint and possibly due to pelvic rotation.[12] With reference to pain associated with dysfunction of sacro-iliac joint, Vleeming et al described "self-locking mechanism" of SIJ,

and have attributed to four integrated components. These components are formed closure, force closure, motor control and emotion and awareness. The failure of muscles and ligamentous "self-bracing mechanism" at lumbosacral junction, can lead to low back pain.[13-15] Pathological basis of pain in this joint can also be attributed to prior trauma to associated ligaments and bones outside the joint besides osteoarthritis within the joint and spondyloarthropathies.[16] In fact, John Cowan (1923) based on his study concluded that the arthritis of sacro-illiac joint could be one of the causes of sciatica.[17]

Association of Sciatica in sacro-illiac syndrome

Sciatica refers to musculoskeletal pain in the back and hip. This pain often radiates to the area that is supplied by the sciatic nerve.[18] Till late 1920s sacro-illiac joint was considered to be the important cause of sciatica. Barre & Duprez et al (1920) were the first to coin the term Sacro-Iliac Sciatica. They were of the opinion that lumbosacral plexus is lying immediately in front of SIJ just separated by Piriformis Muscle (PM), so SIJ could be included in one of the causes of sciatic nerve compression.[17] Schwarzer AC et al in their study found out that sometimes tears of ventral capsule of sacro-iliac joint have been seen in arthrograms of patients with SIJ-related pain.[19] Fortin et al stated that SIJ dysfunction could produce pain resembling sciatica and was very similar to PIVD (Prolapsed Intervertebral Disc). It was suggested that this pain could be a result of L5-S1 neural insult caused by SI capsular irritation and released cytokines. [20,21] Fortin et al stated that SIJ dysfunction could produce pain resembling sciatica and was very similar to PIVD (Prolapsed Intervertebral Disc). [21] Slipman et al found out 18 different pain referral patterns after studying 50 patients with SIJ and concluded that pain was referred mainly into two regions, one around the lumbar region and other in the lower extremity. In the lumbar region, most common pain referral areas were buttocks, lower lumbar and groin, and the least common was upper lumbar and abdomen. In contrast, the lower extremity pain referral patterns were observed only in 50% of the patients and the pain patterns were limited to the lateral or posterior thigh. SIJ compressing sciatic nerve can produce sciatica like symptoms but without any neurological signs. [22]

Diagnosis of SIJS

According to Cusi et al assessment of sacro-illiac syndrome may be done by careful history taking, clinical examination besides relevant imaging studies. While taking history, most of the patients complain of unilateral low back pain and also indicating pain directly to SI joint (Fortin's Finger Test).[13]

Various maneuvers have been tried for clinical diagnosis of sacro-illiac syndrome such as thigh thrust test, Gillet test, Active straight leg raise test, Patrick's Fabere, Gaenslen's tests, palpation of long dorsal SI ligament test, standing flexion test, sitting posterior-superior iliac spine palpation, su-

pine long-sitting test, prone knee flexion test, distraction test, compression test and sacral thrust. Amongst the cluster of all these tests, some researchers are of the opinion that a combination of positivity of three provocative tests without any centralization or decentralization of symptoms being evaluated by McKenzie evaluation, are suggestive of SIJ dysfunction pain.[3,13,22,23,24]

Imaging investigations like X-Ray, Computed Tomography (CT) & Magnetic Resonance Imaging (MRI) are must be done to rule out the other diseases simulating SIJ symptomatologies. Use and validity of intra-articular SI joint blocks to diagnose SIJ pain still remains debatable.[13,21,25,26,27]

PIRIFORMIS SYNDROME

The sciatic nerve passes below the flat pyramidal shape muscle known as Piriformis muscle.[28,29] Due to close juxtaposition of nerve and the muscle, there is some amount of constant developmental and functional interrelationship between the two structures. [30] The function of PM is dependent mostly on the different movements of the hip joint. During extension, the muscle helps to rotate the hip joint externally where as in flexion it abducts the hip joint.[31] The piriformis muscle has a close proximity with SIJ because this is the only muscle that bridges the joint.[28] Yeoman et al were the first to describe the role of anatomic relations of sciatic nerve and piriformis muscle in causing the hip pain. [4] Further, Freiberg and Vinke proposed that pain could be due to priformis muscle causing compression of the sciatic nerve that passes below it.[5] Later on, the hypothesis of Freiberg and Vinke was reinforced by Robinson and a clinical entity of piriformis syndrome (PS) was known to medical literature.[6] The term PS has been debatable due to inclusion of different entities viz i) damage to the sciatic nerve by adjoining tumors, fibrosis, hematomas, endometriosis etc. ii) possible compressive damage to the sciatic nerve due to piriformis muscle. iii) damage to sciatic nerve by piriformis muscle or adjoining tissues due to trauma. iv) Chronic buttock pain with no evidence of sciatic nerve damage. However, in all these entities, the primary symptom will be of buttock pain often with sciatica, without any neurological deficits. Depending on the availability of definitive diagnostic tests, the incidence rates of piriformis syndrome may vary from 33 to 36%. [32]

Sciatica & Piriformis Syndrome (PS)

The causal etiologies of PS can be categorized into two types i.e. primary and secondary. The primary PS may include intrinsic anatomical variations, myofascial pain, hypertrophy, myositis ossificans or direct trauma to the pelvis or buttock whereas secondary PS may occur due to sacroiliac joint dysfunction, facet syndrome, trochanteric bursitis, PIVD.[33]

Sciatic pain can be caused by the piriformis muscle was suggested in a rationale hypothesis given by Yeoman et al[4] and by Freiberg and Vinke.[5] In addition, inflammatory degeneration of muscle and its fascia,

spasm and hypertrophy of piriformis muscle and prior trauma may also be responsible for pain.[34,35] Pecina et al, in one of their study reported that possibly there are two different passages of sciatic nerve or its branches through PM. The first one through the belly of the muscle and the other through tendinous portions of the muscle. If the nerve passes through the muscle, the contraction of muscle fibers during external rotation of thigh may not be able to exert enough pressure on the nerve fibers and the resulting damage is not of great magnitude, and this condition can be managed conservatively. However, if the nerve or its branch passes through the tendinous portion of the piriformis muscle, it can produce significant morbidity (ishchalgia) due to compression of a nerve or its branches during inward rotation of thigh causing passive stretching of the piriformis muscle. It is also known that sciatica would not be caused because of muscular contraction during outward rotation of thigh. In such a case, ischalgia can be managed by cutting through one of the tendons of PM.[30] Pace & Nagle suggested that compression of the sciatic nerve by Piriformis muscle can produce sciatica like symptoms without any neurological deficits.[29]

Diagnosis of PS

In clinical settings, diagnosis of PS can be made by considering characteristic clinical symptomatology and by excluding other causes of sciatica or low back pain.

History of old trauma in the sacroiliac and gluteal region must be considered while diagnosing periformis syndrome. Moderate traction relieves the symptoms of pain in sacroiliac joint, greater sciatic notch and piriformis muscles. Pain which extends down the limb and causes difficulty with walking; acute exacerbation of pain caused by stooping or lifting also relives by traction. Other clinical signs like- a palpable sausage-shaped mass, tender to palpation, over piriformis muscle on the affected side; a positive Lasègue sign; and gluteal atrophy, depending on the duration of the condition should be seen while diagnosing periformis syndrome.[6,36]

Out of various tests proposed by different experts in the field , two tests are often preferred that is Freiberg and Pace. In our clinical experience, Freiberg was found to be more useful because in this test symptoms are produced due to compression of nerve by PM while Pace shows only weakness or loss of function of PM which may not mandatorily be caused by nerve compression.[18,29.34,37,38] It was proved by Martin et al in their study to get most accurate findings for identification of sciatic nerve entrapment in deep gluteal region combined results of the active piriformis and seated piriformis stretch tests can be used with sensitivity of 0.91, specificity of 0.80, positive likelihood ratio of 4.57, negative likelihood ratio of 0.11, and diagnostic odds ratio of 42.00.[39] For confirmed diagnosis, albeit it is expensive and not feasible at outpatient settings - muscle scans and electrodiagnostic studies, may be used.[31]

RELATIONSHIP BETWEEN SI JOINT PAIN AND PS

From the above appraisal on PS and sacroilliac syndrome, the commonality is sciatica like symptoms having no neurological deficit besides the referral patterns of the pain. Kirkaldy-Willis et al in their study concluded that the symptom complex of PS is similar to that of the sacroiliac syndrome.[40] This commonality of symptomatology often creates difficulty in arriving at a confirmatory diagnosis and the diagnostic dilemma prevails. Alfred in his study opined that muscular pain from piriformis, gluteus maximus, quadratus lumborum may co-exist with both the conditions and / or may have independent presentation.[12] However, by introspecting and revisiting the anatomical structure, we are aware that piriformis muscle lies in the close vicinity of sacro-illiac joint. And it is also intriguing to note that sacro-illiac syndrome can give rise to PS or vice-versa. In other words, we can say that out of these two clinical entities, it is often difficult to establish what overlaps the other.

However, there are some logical conclusions have been made regarding this. According to Bhojani et al, PS is not necessarily caused because of structural abnormality, as at times an unstable sacroiliac joint may result in a ligamentous strain that may be responsible for the spasm of piriformis muscle that can further lead to contracture, fibrosis, finally entrapping the nerve with other adjoining muscles in the sciatic notch.[7]

Although, Yeoman et al first reported that one of the causes of sciatica is due to sacroiliac periarthritis that involves the anterior sacroiliac ligament, the piriformis muscle and some of the adjacent branches of the sciatic nerve.[4] Subsequently, Freiberg and Vinke considered that inflammation of the sacro-illiac joint may primarily affect piriformis muscle and its fascia leading to irritation of the overlying lumbosacral plexus.[5] Many other available literature provided the fact that PS can be caused by stimulating the nerve by causal agents, at two points. The first at the origin i.e. at sacroiliac joint by excitatory reflex spasm of the muscle due to stimulation, The second at the insertion by inflammation of trochanteric bursa as a result of general involvement of trochanter.[4-6,30,41,42]

CONCLUSION

With these above analysis, we are of the opinion that in most of the population, both SIJS & PS can co-exist or one can give rise to other. There are chances also that these can be found separately in patients. Clinically it has been observed, although not yet proven by research that most of the patients present signs and symptoms of both the conditions at the same time adding to diagnostic confusion and need treatment for both the conditions. So this article provides a platform to researchers for future clinical researches supporting or opposing the fact of coexistence of PS and SIJS.

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Case Report

Bilateral Idiopathic Retinal Vasculitis, Aneurysm And Neuro-Retinitis (IRVAN): A Case Report

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Abstract:

A teenage girl presented with posterior uveitis with retinal vasculitis, aneurysm and neuro-retinitis and a gradual decrease in vision bilaterally. There was peripheral vascular non-perfusion the aetiology of which was not found. Optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) pictures are presented. The treatment included intravitreal bevacizumab injection (IVBI), systemic steroid, cyclosporine and pan retinal photocoagulation. Subsequent prevention of relapse was achieved by mycophenolate mofetil (MMF). The vision improved to 30/20 and was stable 7 years after management. To the best of our knowledge, a case with seven years follow up has not been previously described.

Key Words: IRVAN, Retina, Steroid, Uveitis

الملخص

يصف هذا المقال حالة لمريضة في سن المراهقة مصابة بالتهابات في العينين حيث تبين بعد الفحص الإكلينيكي وجود تغيرات في شبكية العينين بصورة التهابات في الشبكية والأوعية الدموية لها وكذلك تغير في قوام الأوعية وذلك بصورة تمدد وضعف في اجزاء من الأوعية الدموية، كما بين الفحص وجود ترشح في مركز البصر في الشبكية مما أدى الى انخفاض في حدة الإبصار لدى المريضة، كذلك وجود نقص في التروية في أطراف الشبكية. وبعد عمل فحص التصوير المقطعي بالتماس البصري (OCT) وتصوير أوعية قاع العين بالفلوريسنت (FFA) شخصت الحالة: التهاب الأوعية الدموية بالشبكية مجهول السبب مع تمدد الأوعية الدموية والتهاب الشبكية العصبي

(Bilateral Idiopathic retinal vasculitis, aneurysm and neuro-retinitis (IRVAN

تم اعطاء المريضة حقن بيفاسيزوماب (IVBI) والستيرويد والسيكلوسبورين وتم التخثير الضوئي للشبكية

intravitreal bevacizumab injection (IVBI), systemic steroid, cyclosporine and pan retinal photocoagulation

بعد أن تلقت المريضة العلاج المناسب تحسن حدة النظرالى ٣٠/٢٠ وظلت الحالة مستقرة ما يقارب سبع سنوات

Introduction:

The prevalence of non-infectious uveitis in paediatric population in USA was 29 per 100,000 in 2012. The magnitude and the underlying causes differ in different parts of the world [1]. Even after extensive investigations, the cause remains obscure in nearly 25% of cases [2]. A study from western Saudi Arabia reported that 40% of cases had bilateral presentation and 46% were idiopathic anterior uveitis [3]. Various management mo-

dalities have been used for idiopathic posterior uveitis, however, the long-term benefit of systemic and local treatment is not very encouraging [4].

We present a case of idiopathic retinal vasculitis, aneurysm and neuro-retinitis (IRVAN) that was managed by intravitreal bevacizumab injection (IVBI), systemic steroid and cyclosporine and pan retinal photocoagulation (PRP). The case was managed with mycophenolate mofetil (MMF) without relapse for seven years.

Case report:

A 14 years old Saudi female presented with complaints of gradual dimness of vision bilaterally. She had no history of similar complaints, ocular surgery or ocular trauma. The vision was assessed with a Snellen chart at 6-meters distance and was recorded at 20/200 without correction and 20/100 in right eye and 20/160 in left eye with pinhole. Slit lamp examination (Topcon Corp, Tokyo, Japan) indicated a normal anterior segment. There was no evidence of corneal or lenticular pathology. The pupils of both eyes were normal in size, and responded briskly to light. Applanation tonometry measurements were 16 and 18 mmHg in the right and left eyes respectively. The posterior segment was evaluated using a binocular fundus camera (Canon Inc., Tokyo, Japan) after dilation of pupil with 0.5% tropicamide eye drops.

(Fig. 1 a & b) The patient was diagnosed with posterior uveitis. Subsequently, laboratory investigations ordered including, complete blood count (CBC), urea and electrolytes, liver function tests (LFT), purified protein derivative (PPD) skin test, venereal disease research laboratory (VDRL) test, angiotensin-converting enzyme (ACE) test, lysozyme, toxoplasmosis titre, Brucella titre, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor and antinuclear antibody (ANA) tests. All these investigations were within normal range. Computed tomography (CT) of the chest and magnetic resonance imaging (MRI) of the brain were normal. Optical coherence tomography (OCT) of both macula and fundus fluorescein angiography (FFA) indicated chorio-retinal inflammation and choroidal neovascular membranes (CNVM) at the macula, vasculitis and aneurysms in macular area and ischaemic changes in peripheral retina. (Fig. 1 c, d)

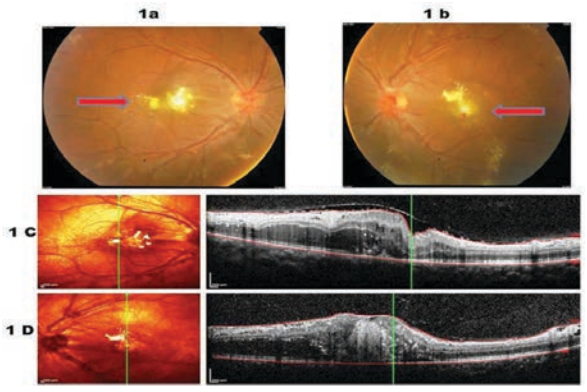

Fig. 1: Fundus photo of right eye (a) and left eye (b) shows elevated area of CNVM in the macula, also shows vasculitis with vascular sheathing. (c, d) Optical Coherence Tomography (OCT) of the same lesion both eyes.

The patient was diagnosed with IRVAN and treated with 35 mg oral prednisolone four times a day and cyclosporine 50 mg twice a day. Additionally, 0.05 mL solution contain-

ing 1.25 mg of bevacizumab was injected intravitreal.

At follow up, 6 weeks after treatment, vision was 20/160 in RE and 20/200 in the LE without correction and 20/80 in RE and 20/160 in LE with correction. FFA indicated an active leak in the macula of the RE and resolution of the macular lesion in LE. The OCT studies indicated signs of inflammation bilaterally. Hence, a second dose of intravitreal bevacizumab was delivered to both eyes and the systemic steroid was tapered. The patient was also prescribed mycophenolate mofetil (MMF) 500 mg tablets twice a day. The patient was monitored for side effects and this medication was continued as prophylaxis to prevent relapse.

At last follow up in 2017, the vision in both eyes was 20/30. The anterior segment was normal. There was evidence of PRP in both eyes. Macular scar was visible. There was no active lesion in the macula or other regions of the retina. The patient continued 500 mg MMF twice a day and lubricant eye drops four times a day. The retinal image of both eyes at last follow up is presented in Figure 2.

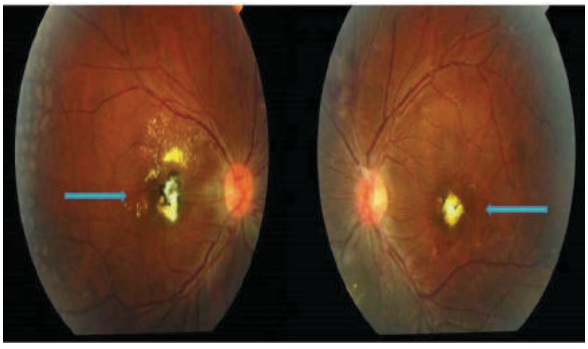

Fig. 2: Fundus photo of both eyes shows scar of cicatrized CNVM in the macula

Fundus exam shows bilateral diffuse retinal exudation more in the macular area, abnormal arterial structure in form of looping, kinging and saccular dilatation presenting aneurysmal dilatation, area of vascular sheathing in periphery (Fig. 3). Sequential fluorescein angiogaphy images of the left eye shows in the early arteriovenous phase. An early hyper fluorescence, however the vessel loops are not identified (Fig. 3a1, a2).

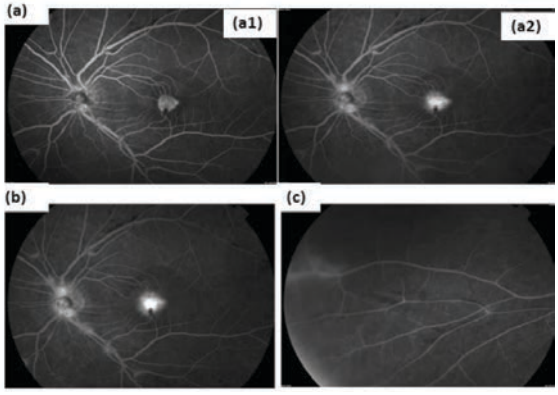

Fig. 3: Sequintional flurosceine angiogaphy images of the left eye. (a) Early hyperfluorescence; (b) Late phase hyperfluorescence; (c) Peripheral capillary drop out consisting with a wide area of non vasculrization.

In the late phase a clear leakage from the choroidal neovascularization were seen (Fig. 3b). Figure 3c shows the peripheral capillary drop out consisting with a wide area of non-vascularization.

In the early arteriovenous phase, the vessel network of the classic CNVM appears as an early well defined hyperflurescence, later there is a marked increase hyperflurescence in the area of the CNVM later the fluorescein is flowing out of the vessels and the area of increasing leakage extends beyond the vessel network that was visible in the early phase (Fig. 4).

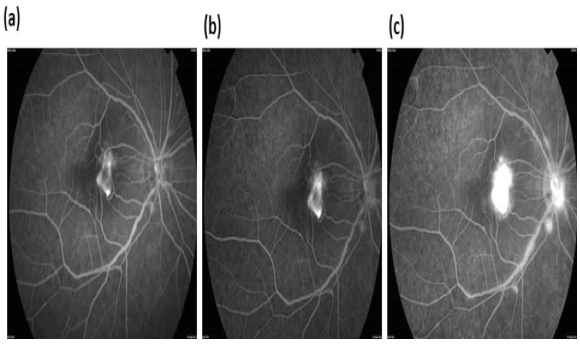

Fig. 4: (a) Early arteriovenous phase the vessel network of the classic CNVM; (b) Later arteriovenous phase of the CNVM; (c) The area of increasing leakage extends beyond the vessel network

Discussion

Reports of IRVAN have been published as early as in 1973 [5]. Although it is rare in the Asian population, there are cases reported in India and China in the last three years [6]. Hence, clinician should remain vigilant for cases of IRVAN and in order to detect it in the early stages.

Samuel et al have described the staging and criteria for the clinical diagnosis of IRVAN (7). Our case was classified as stage II IRVAN. Notably, a good outcome was achieved even 7 years after initial treatment. We believe this outcome can be attributed to early detection and management.

The laboratory investigations were normal in the current case. The patient did not have any systemic disease that could be associated to IRVAN. A case with similar presentation but associated with fungal sinusitis was described in Saudi Arabia [8]. A case of IRVAN in an adult was associated with antinuclear antibodies against WBCs [9]. However, the exact pathogenesis for the development of ocular changes in IRVAN remains unknown. Over time more investigative tools have become available (eg. OCT), but the underlying cause of IRVAN is a challenge for researchers.

The management of IRVAN has changed by time. A case in 2001 was treated with steroid and PRP and was reported as stable without remission after one year [10]. PRP in early stages is effective for addressing peripheral non-perfusion and preserving long-term vision in cases of IRVAN [11]. The successful use of intravitreal anti-vascular endothelial growth factor for treating IRVAN was documented by Karagiannis et al [12]. Slow release steroid implants in the vitreous cavity and systemic antimetabolites have been attempted for treating IRVAN [13].

MMF is used for immunosuppression mainly in cases of organ transplantation. However, it is also useful in managing uveitis as it reduces the dose of other antimetabolites used in combination and is considered a safe and effective treatment if used in suitably low doses for a prolonged time [14]. We found MMF was effective for managing IRVAN and preventing relapse without any side effects to date.

Periodic FFA and OCT is recommended of similar cases to monitor for retinal aneurysms [13]. All ocular investigations were repeated every 6 months in our patient.

The blood, renal and liver function tests were repeated at least every three months. No side effects were noted during 7 years of follow up. Use of systemic antimetabolites has been found to negatively affect renal func-

tions and the patient's quality of life especially mental health. Hence periodic investigations are recommended to rule out the side effects and a periodic mental health assessment is warranted [15].

This case of IRVAN was successfully treated with MMF for preservation of vision and halting active inflammation without relapse.

Conflict of interest:

The author declares that there is no conflict of interest regarding the publication of this paper.

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Case Report

Primary Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma Involving Cecum A Case Report From Saudi Arabia

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ABSTRACT

MALT Lymphoma is now recognized as a distinct subtype of non-Hodgkin's Lymphoma (NHL) with distinguishable immunopathological characteristics. MALT lymphoma of GI tract is rare and most of the cases are found in the stomach, other parts of GI tract are affected very rarely. Here we present a case of a sixty-four years old Saudi female diagnosed with cecal MALT lymphoma, presented to gastroenterology clinic with chronic mild nonspecific abdominal pain for several years. She was treated initially as irritable bowel syndrome, subsequently underwent CT abdomen and colonoscopy, which revealed subepithelial cecal mass. Biopsy and immunohistochemistry were consistent with cecal MALT lymphoma.

Key words: Cecal MALT Lymphoma, Extra nodal Non-Hodgkin's lymphoma, Intestinal Marginal Zone Lymphoma (I-MZL).

الملخص

يعتبر الآن سرطان الغدد الليمفاوية المرتبطة المخاطية الانسجة كنوع فرعي متميز من سرطانات الغدد الليمفاوية غير هودجكن مع خصائص مناعية مميزة. وهو من الأورام نادرة الحدوث بالجهاز الهضمي ومعظم الحالات وجدت في المعدة، تتأثر الأجزاء الأخرى من الجهاز الهضمي نادرا جدا. ونحن نقدم حالة من النساء السعوديات تبلغ من العمر ٦٤ سنة تم تشخيصها بسرطان الغدد الليمفاوية الشعير بالمعي الأعور، قدمت إلى عيادة أمراض الجهاز الهضمي مع ألم مزمن بالبطن غير محدد وبسيط استمر لعدة سنوات. عولجت المريضة في البداية كمتلازمة القولون العصبي، وخضعت في وقت لاحق لأشعة البطن وتنظير القولون، والتي كشفت عن كتله ورمية في القولون الأعور، وكانت نتائج الخزعة متسقة مع سرطان الغدد الليمفاوية الشعير.

INTRODUCTION

MALT Lymphoma is a sub type of Non- Hodgkin Lymphoma involving mucosa associated Lymphoid Tissue (MALT). It is labeled as a separate entity because it involves lymphoid proliferation in mucosa associated lymphoid tissue that lines the body organs or cavities rather than lymph nodes, this includes GI tract, lungs, eyes, skin, salivary glands, thyroid and breast. MALT lymphomas are usually indolent but with a potential to transform into a high-grade B cell lymphoma. MALT lymphoma represents only 5% of all non-Hodgkin lymphomas and majority of

Gastrointestinal MALT lymphomas affect the stomach. Intestinal lymphomas have not well investigated compared to stomach MALT lymphoma. Cecal MALT lymphoma is a very rare entity, we present a case of MALT lymphoma involving the cecum, probably the first case to be reported from KSA.

CASE REPORT

A 64-year-old Saudi female initially presented to a primary health clinic with chronic, mild and nonspecific abdominal pain and altered bowel habits for several years. Pain was relieved by defecation and not associated with other GI symptoms. She was treated as irritable bowel syndrome (IBS) initially, then she was referred to GI clinic for further evaluation. CT scan abdomen/ pelvis showed asymmetric circumferential wall thickening of the cecum measuring 3.1 X 4 cm (Fig.1). The Colonoscopy showed a subepithelial mass involving cecal base and appendicular orifice (Fig.2). histopathology and immunochemistry were consistent with diagnosis of MALT lymphoma of the cecum (Fig.3). We referred her to haemato-oncology team as a case of cecal MALT lymphoma for further management. They further investigated her with bone marrow aspiration which was normal. The consensus plan was closed observation and follow up, given that she has a limited disease (stage 1-2) with a potential plan to start chemotherapy if she develops invasive disease, becoming symptomatic or transformed to other type of lymphoma. Patient is being regularly followed with hemoto/ oncology for almost 2 years since the diagnosis and fortunately, the disease is still in same stage without progression.

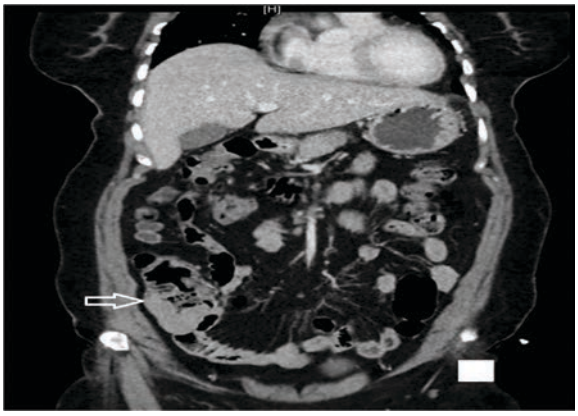

Fig (1) Abdomen

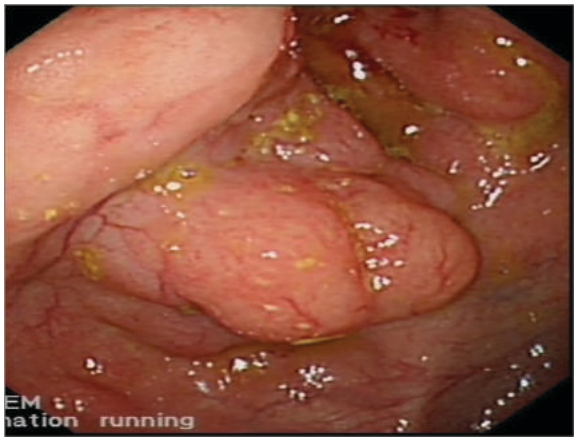

Fig (2) Colonoscopy

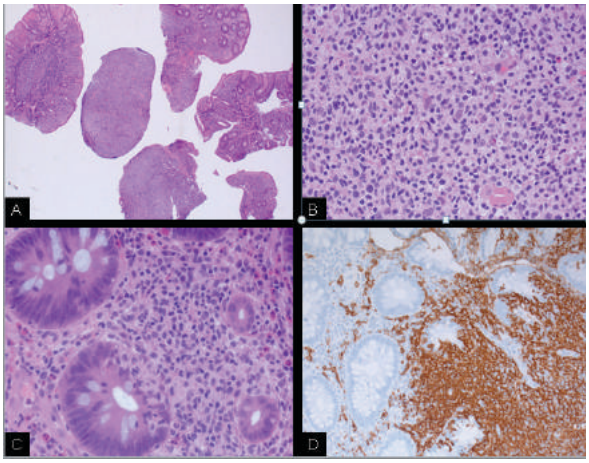

Fig (3) Histopathology

DISCUSSION

The concept of distinctive type of extra nodal B-cell lymphoma arising from MALT-derived lymphocytes in the gastro-intestinal tract was first time introduced in 1983 by Isaacson P and Wright DH [1]. MALT lymphoma is considered a sub type of non-Hodgkin lymphoma [2]. Mucosa-associated lymphoid tissue (MALT) is found along with the mucosal linings in the human body [3, 4]. MALT-type lymphomas are usually found in organs originally devoid of lymphoid tissue, which may be acquired by persistent antigenic stimulation by infectious or autoimmune processes [5].

MALT lymphoma is considered very rare and constitute only about 5% of all non-Hodgkin lymphoma [6]. In GI tract, two-thirds of all cases occur in stomach [7, 8] followed by small intestine, cecum, colon and rectum [9]. Increasing evidence suggests that etiology of MALT lymphoma may be related to chronic stimulation of infectious agents or autoimmune stimuli [10] Gastric MALT lymphomas are associated with H. Pylori infection in more than 90% of cases [11]. However, the etiology of non-gastric MALT lymphomas is not clear. The clinical presentation of MALT lymphoma is heterogeneous. It is quite nonspecific and is related to the organs involved. Pain, loss of appetite, and weight loss are the most common symptoms, while bleeding occurs more commonly with gastric involvement [12, 13]. Our patient initially presented with non-specific symptoms followed by altered bowel habits.

We searched the literature and found only few cases of MALT lymphoma involving cecum reported from different countries. This may be the first case of cecal MALT Lymphoma to be reported from Kingdom of Saudi Arabia. Previously few reported cases of cecal MALT lymphoma had various presentation notably with intestinal obstruction [14] and intussusception [15]. Our patient had just nonspecific symptoms and on further follow-up with haemato-oncology for approximately two years, she is asymptomatic without any specific treatment. It may reflect that her symptoms initially might be related to IBS and MALT lymphoma was just an incidental finding. The data about cecal and other part of the colon are scarce, and more data are needed to guide future management about this rare disease.

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Manuscripts submitted in this category are expected to be concise, well organized, and clearly written.
The maximum length is 5000 words, including the abstract, references, tables, and figure legends. The maximum length is 5000 words, including the abstract, references, tables, and figure legends.

- The structured abstract must not exceed 250 words.
- The title must not exceed 130 characters.
- A maximum of 4 tables and 4 figures is allowed.
- References should not exceed a maximum of 100.
- The abstract must be organized as follows:
- Background & Aims
- Methods
- Results
- Conclusions
- Do not use abbreviations, footnotes or references in the abstract.
- An electronic word count of the abstract must be included.
- Three to ten key words at the end of the abstract must be provided.

The manuscript must be arranged as follows:

- Title page
- Abstract
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Acknowledgements
- References
- Tables
- Figure legends
- Figures

Acceptance of original manuscripts will be based upon originality and importance of the investigation. These manuscripts are reviewed by the Editors and, in the majority of cases, by two experts in the field. Manuscripts requiring extensive revision will be at a disadvantage for publication and will be rejected. Authors shall be responsible for the quality of language and style and are strongly advised against submitting a manuscript which is not written in grammatically correct English. The Editors reserve the right to reject poorly written manuscripts even if their scientific content is qualitatively suitable for publication. Manuscripts are submitted with the understanding that they are original contributions and do not contain data that have been published elsewhere or are under consideration by another journal.

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- Review articles must be accompanied by a title page and a summary.

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Review articles are reviewed by the Editors and may be sent to outside expert reviewers before a final decision for publication is made. Revisions may be required.

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References must be in accordance with the Journal of Hepatology reference style. References are ordered as they appear in the text and citation numbers for references are placed between "brackets" ("[ ]") in the text as well as in the reference list.

Authors should be listed surname first, followed by the initials of given names (e.g. Bolognesi M). If there are more than six authors, the names of the first six authors followed by et al. should appear.
Titles of all cited articles are required. Titles of articles cited in reference list should be in upright, not italic text; the first word of the title is capitalized, the title written exactly as it appears in the work cited, ending with a full stop. Journal titles are abbreviated according to common usage, followed by Journal years, semicolon (;) before volume and colon (:) before full page range (see examples below).

All articles in the list of references should be cited in the text and, conversely, all references cited in the text must be included in the list.

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An example of how references should look within the text:

"HVPG was measured by hepatic vein catheterization using a balloon catheter according to a procedure described elsewhere [14, 15] and used as an index of portal hypertension [16]."

An example of how the reference list should look:

[14] Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology 1992;102:973-979.

[15] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280-282.

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- Photographs (scans, immunofluorescences, EM, and histology images) should be submitted as: 1. TIFF (*.tif) with a resolution of at least 300 pixels per inch, or
- Illustrator compatible EPS files with RGB color management (*.eps),
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1. 300 dpi for color figures
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- • Furthermore, panel lettering should be in Arial bold 14 pt, capitalized and no full stop (A, B) while lettering in figures (axes, conditions), should be in Arial 8 pt, lower case type with the first letter capitalized and no full stop. No type should be smaller than 6 pt.

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A maximum of 4 tables is allowed
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- Tables should be provided as Word files (*.doc) or Illustrator/InDesign (*.ai, *.eps, *.indd) compatible files. No TIFF and JPG files are acceptable for table submission.
- When submitting tables in Microsoft Word table function, no tab, space or colors should be used. Tables should contain a maximum of 10 columns.
- Tables submitted in landscape orientation will not be accepted. Tables should include a title, table legend, and if necessary footnotes.
- Include tables in the submitted manuscript as a separate section.

FIGURE LEGENDS

- Figure legends should be listed one after the other, as part of the text document, separate from the figure files.
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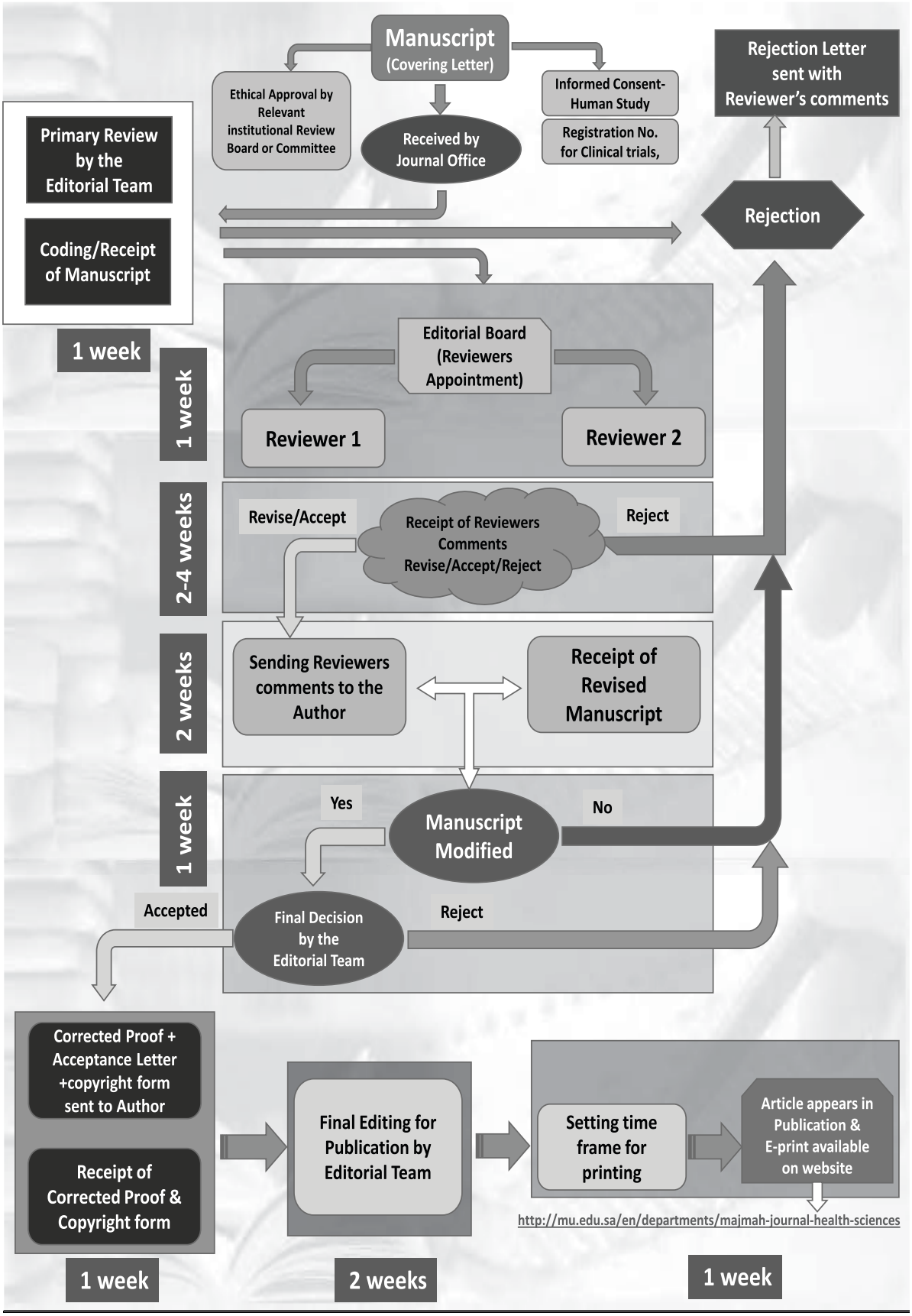
Methodological & Statistical instructions for Authors submitting manuscripts to the Majmaah Journal of Health Science

The manuscripts should include a complete and detailed description of what was done. This includes a description of the design, measurement and collection of data, the study objective and major hypotheses, type and source of subjects, inclusion and exclusion criteria and measures of outcome, number of subjects studied and why this number was chosen. Any deviation from the study protocol should be stated. The baseline characteristics of any compared groups should be described in detail and -if necessary -adjusted for in the analysis of the outcome.

For randomized clinical trials the following should also be clearly documented: treatments, sample size estimation, method of random allocation and measures taken for maintaining its concealment including blinding, numbers treated, followed-up, being withdrawn, dropping out, and having side effects (numbers and type). The statistical methods used should be relevant and clearly stated. Special or complex statistical methods should be explained and referenced.

Complex analyses should be performed with the assistance of a qualified statistician. Unqualified use of such analyses is strongly discouraged. The underlying assumptions of the statistical methods used should be tested to ensure that the assumptions are fulfilled.

For small data sets and if variable distributions are non-normal, distribution free (non-parametric) statistical methods should be used. The actual p values - whether significant or not - should always be presented (not NS). Confidence intervals convey more information than p values and should be presented whenever possible. Continuous variables can always be summarized using the median and range which are therefore preferred. Only in the infrequent case of a Normal distribution are the mean and standard deviation (SD) useful. Complex analyses (including Cox and logistic regression analysis) should be presented in sufficient detail: i.e. variable scoring, regression coefficients, standard errors and any constants. Odds-ratios or relative risks are not sufficient documentation of such analyses. The handling of any missing values in the data should be clearly specified. The number of statistical tests performed should be kept at a minimum to reduce spurious positive results. Explorative (hypothesis generating) analyses without confirmation using independent data are discouraged. Figures showing individual observations e.g. scatter plots are encouraged. Histograms may also be useful. Tables should indicate the number of observations on which each result is being based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