VOLUME 9 ISSUE 2 DECEMBER 2015

University of Duhok
College of Medicine

Duhok Medical Journal

The Official Journal of Duhok College of Medicine

ISSN: 2071 - 7326

Photo on the cover page

Kamaka Mountain Overlooking Duhok Lake

The journal is also available at the college website (Online ISSN 2071-7334)

http://web.uod.ac/academic/colleges/college-medicine/duhok-medical-journal/

VOLUME 9 ISSUE 2 DECEMBER 2015

University of Duhok
College of Medicine

Duhok Medical Journal

The Official Journal of Duhok College of Medicine

Duhok University Press ISSN: 2071 - 7326

This page is left intentionally

Duhok Med J

EDITORIAL BOARD

Submission of Manuscript:

Manuscripts should be submitted to:
The Editor,
Duhok Medical Journal,
Duhok College of Medicine,
Post address: Nakhoshkhana Road 9, 1014, AM, Duhok, Iraq.
Telephone No.: 00964-62-7224268 EXT 115
E-mail: dmj@uod.ac
Electronic submission of articles is also accepted

Duhok Med J

ADVISORY BOARD

This page is left intentionally

Duhok Med J

INSTRUCTIONS FOR AUTHORS

Aims and Scope Duhok Medical Journal is a peer reviewed journal issued bi – annually by Duhok College of Medicine. Scientific and clinical researches are the main issues. The journal also publishes short articles, letters to editors, review articles and case reports.

General The Duhok Medical Journal is a signatory journal to the uniform requirement for manuscripts submitted to biomedical journals, February 2006 [updated 2009] (http://www.icmje.org).

To present your original work for consideration three manuscript copies written in English together with Kurdish and Arabic abstracts should be submitted to the editor. All authors are required to provide the manuscript on a CD labeled with the name and title of the paper.

Preparation of the manuscript The manuscript should be typed double spaced as normal text on one side of the paper in single column format, font size 14 pt, paper type A4, 1″ margin at each side and each of the following sections should begin on a new page in the following sequence:

1- **Title page**; should include the following: title, font size 16 pt, each author's full name, academic degree(s), scientific title (if available), institutional affiliation, full contact information including emails. If there are more than one author, article should include author to whom correspondence should be addressed including the scientific title (if available), institution affiliation, address, email, telephone.

2- **Structured abstract**; of no more than 250 words including background and objectives, methods, results, and conclusions.
3 – 10 keywords or phrases should be put at the end of each abstract (Printed in bold font; size12 pt).

3- **Body of the text**; structured in an IMRAD style;
(Introduction, Methods, Results and Discussion).

4- **Acknowledgment** (if any.)

5- **References.**

6- **Tables with legends**.

7- **Illustrations with legends**.

8- **Structured Kurdish abstract including title in Kurdish.**

پێشەکی و ئارمانج، ڕێکێن ڤەکولینێ، ئەنجام، دەرئەنجام

9- **Structured Arabic abstract including title in Arabic.**

خلفية و اهداف البحث، طرق البحث، النتائج، الاستنتاجات

Tables Each table must be typed on separate page and should follow the reference list. All the tables must be numbered consecutively in the order of their first citation in the text. Supply a brief title for each on top and place explanatory matter in foot notes not in the heading (if needed). Tables should be simple and not duplicated in the text. Percentages are included with numbers in the same cells but in brackets.

Illustrations Graphs, line drawing, photographs, printed x rays and other illustrations are accepted only if they add to the evidence of the text. They should be of a high quality and suitable for reproduction. They should be numbered consecutively according to the order in which they have been first cited in the text. Supply a brief title beneath each illustration. Graphs should have white background; should be colored and non 3-dimensional figure; and should have labels for X and Y axis.

Numbers and Units Measurements of length, height, weight and volume should be reported in metric units. Temperature in degrees Celsius, blood pressure should be expressed in mmHg and all hematologic and clinical chemistry measurements in SI units.

Abbreviations should be defined on first use and then applied consistently throughout the article. Avoid abbreviations in the title and abstract.

References should be numbered both in text and in the list of references in the order in which they appear in the text. The punctuation of the Vancouver style should be followed; if the original reference is not verified by the author, it should be given in the list of references followed by (cited by) and the paper it was referring to. The titles of journals should be abbreviated according to the style used in Index Medicus. This can be obtained from website (http://www.nlm.nih.gov/). The author is responsible for the accuracy of references. The following are examples of the three most common types of citations:
The article citation: if six authors or fewer list all; if seven or more authors list the first six and then add "et al":
1- Nuwayhid IA, Yamout B, Azar G, Kambris MA. Narghile (hubble bubble) smoking, low birth weight, and other pregnancy outcomes. Am J Epidemiol. 1998;148(4):375-83.
Book citation, noting chapter and authors:
2- Arevalo JA, Nesbitt TS. Medical problems during pregnancy. In: Taylor RB, editor. Family medicine: principles and practice. 6th ed. New York: Springer – Verlag; 2003. p. 109-16.
Electronic source:
3- Garfinkel PE, Lin E, Goering P. Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? Br J Psych [Internet]. 1996 [cited 1999 Aug 17];168(4):500-6. Available from: URL:http://biomed.niss.ac.uk

Authorship and consent form All authors must give signed consent (Form No.1- Submission Form), which should accompany the manuscript. The letter should say "this manuscript is an unpublished work, which is not under consideration elsewhere in the record. Authors are requested to state an approximate estimate of their contribution in the study, sign the form and send it with the manuscript.
Authors must declare if they have any competing interests in the study and to specify any funds given to conduct the study.

Ethical considerations When experiments on humans are being reported the whole work in the manuscript should conform to the ethical standards of the responsible committee on human experimentation.

Submission of manuscript

Manuscripts should be submitted to:
The Editor,
Duhok Medical Journal,
Duhok College of Medicine,
Post address: Nakhoshkhana Road 9, 1014, AM, Duhok, Iraq.
Telephone no.: 00964-62-7224268 EXT 115
E-mail: dmj@uod.ac
Electronic submission of articles is also accepted

N.B.

* Accepted manuscripts may be altered by the editorial board of Duhok Medical Journal to conform to details of the journal publication style.

** The Editorial Board of Duhok Medical Journal accepts no responsibility for statement made by authors in articles published by the journal.

Duhok Med J

CONTENTS

This page is left intentionally

VITAMIN D STATUS AND METABOLIC ABNORMALITY PROFILE AMONG SIBLINGS OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

DHIA J. AL-TIMIMI, MPhil, PhD*
SARAH H. HAZIM, MSc**
IDRIS H. AHMED, MD***

Submitted 15 May 2015; accepted 9 September 2015

ABSTRACT

Background: Cross-sectional data provide some evidence that circulating 25-hydroxyvitamin D is inversely associated with metabolic syndrome components. Reported data in populations at high risk for type 2 diabetes mellitus (T2DM), however, are contradictory. In this study we measured 25-hydroxyvitamin D [25(OH) D], glucose, triglycerides, HDL-cholesterol and insulin in siblings of patients with T2DM.

Methods: Body weight, height, waist circumference, blood pressure, glucose, insulin, triglycerides, HDL-cholesterol, and 25(OH) D were measured in 184 apparently healthy individuals, siblings of patients with T2 DM, with age range 20-40 years. Study participants were categorized into 2 groups: a metabolically obese, normal weight (MONW) group and non-MONW group. The association between components of metabolic syndrome and serum 25(OH) D levels was examined.

Results: Participants categorized as MONW group were 155(84.2%) ,exhibited lower serum 25(OH) D levels than did the non-MONW ($p<0.01$). Significantly higher prevalence of vitamin D insufficiency (36.1% vs. 20.7%, $p<0.05$) and severe deficiency (8.4% vs. 3.5%, $p<0.05$) were found in MONW compared to non-MONW group. MONW group had higher mean age, body mass index and waist circumference than non-MONW group. MONW had also higher mean values for HMOA-IR, triglycerides, but lower HDL-cholesterol concentrations. In MONW group, negative correlations of 25(OH) D were observed with waist circumference and triglycerides ($p<0.001$ and $P<0.01$, respectively) and a positive correlation was observed with HDL-cholesterol ($p=0.015$)

Conclusion: Our data showed a low vitamin D status among siblings of T2DM patients, particularly among MONW individuals, suggested that siblings of T2DM are at increased risk of future metabolic disease.

Duhok Med J 2015; 9 (2): 1-9.

Keywords: Vitamin D, siblings of diabetics, metabolic health status

Vitamin D deficiency and lower concentrations of serum 25(OH) D might be associated with a higher risk of diabetes and glucose intolerance[1,2]. The relationship between vitamin D and metabolic health status is controversial. Several studies have reported that vitamin D may have protective effects against metabolic syndrome (MS)[3,4], a condition that is highly prevalent in the world[5]. More

* *Professor of clinical Biochemistry; Department of Clinical Biochemistry, College of Medicine, University of Duhok, Duhok, Iraq.*
** *Specialist, Teaching Laboratories, Azadi Teaching Hospital, Duhok, Iraq.*
*** *Specialist, Duhok Diabetes Center, Azadi Teaching Hospital, Duhok, Iraq.*
Correspondence author: Prof. Dhia J. Al-Timimi. Email:altmimidj@yahoo.com

than 30 years ago, it was suggested that there are individuals who are not obese on the basis of body mass index, but who like people with overt obesity, are hyperinsulinemic with insulin-resistance (IR). They are predisposed to T2DM, hypertriglyceridemia, and premature coronary artery disease[6,7]. It is well established that first-degree relatives of T2DM patients are a high risk category for developing T2DM which may potentially be MONW individuals[8].

Vitamin D deficiency has recently been implicated as a possible risk factor in the etiology of numerous diseases, including diabetes[9]. Despite evidence suggestive of possible widespread vitamin D deficiency in Iraqi population[10], attempts to assess vitamin D status in the first degree relatives of patients with T2DM have been few. Given this existing data, it is reasonable to hypothesize that low vitamin D status in siblings of patients with T2DM may predispose them to insulin resistance and metabolically unhealthy status. Reports on this issue are limited and the prevalence of this entity has not been established in the siblings of patients with T2DM who are inherently at high risk for T2DM. Therefore this preliminary study aimed to investigate whether vitamin D status is associated with metabolic health status in a sample of siblings of patients with T2DM in Duhok Diabetes Center (Duhok, Iraq).

MATERIALS AND METHODS

Study population

Across-sectional study was carried out during the period from April to October 2014.One hundred and eighty four apparently healthy subjects, siblings of patients with T2DM were included (87 males and 97 females).. Protocol involved that: all patients diagnosed as T2DM or being treated as such who visited the Duhok Diabetes Center; during the period of the study (n=5783) were interviewed and informed about the nature of the study, and then asked to bring their siblings who are at the age range of 20-40 years in fasting state .At the beginning, a total of 286 were participated in the study. After exclusion of 102 responders who were with BMI >27 or <20 Kg/m2 , non-fasting ,and women with pregnancy, the reminders were enrolled in this study. The study protocol was approved by the ethical committee of the General Directorate of Health, and informed consent was obtained from all the participants at the start of study.

Data Collection: Data were collected from subjects interviewed by special questionnaire form. Included data were demographic information about the individual (age and sex), personal history of DM., coronary heart disease (angina,

myocardial infarction), hypertension, weight gain (after 18 years in women, 21 years in men), low birth weight (<2.5 Kg), and gestational DM. and menstrual irregularities (oligomenorrhea or amenorrhea) in women, and family history of T2DM, premature coronary heart disease (CHD), essential hypertension (<60 years) and hypertriglyceridemia.

Then physical activity was assessed by asking about the physical activity (work, leisure, and travel) in a typical week. History of hypertension was defined as blood pressure > 140/90 mm Hg or being on an antihypertensive medication. Family history of premature CHD was defined as definite MI or sudden death in a first degree relative before 60 years of ages. MONW or non-MONW individual was define according to the scoring method for identifying an MONW individual represented by Ruderman et al8. The proposed scoring value for identifying an MONW individual was > 7.

Anthropometric measurements

Waist circumference (WC) was checked by using a plastic metric tape applied midway between the lower costal margin and the iliac crest. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting systolic and diastolic blood pressure(BP) was measured by using random zero sphygmomanometer and cuffs appropriate for arm size.

Biochemical measurements

Biochemical blood measurements were determined by a standard laboratory procedure using Cobas 6000. Roche/Hitachi. Serum concentration of insulin and 25(OH)D were measured by enzyme linked immunosorbent assay (ELISA) method. The homoeostasis model assessment estimates insulin resistance (HOMA-IR) was calculated using the following formula (Glucose [mg/dl] × Insulin [uU/ml]) / 405.

Assessment of vitamin D status

Vitamin D status was assessed as follow: Severe vitamin D deficiency (serum 25(OH) D <10 ng /ml), insufficiency (10-29.9ng/ml), sufficient 30-150 ng/ml and toxic >150 µg /dl).A cut off point of < 25ng/dl of 25(OH) D was used to classify individuals as on low vitamin D status.

STATISTICAL ANALYSES

All data was analyzed using the statistical package for Social Sciences (SPSS); version 21.0. Independent t-test was used to assess differences in serum analyte among groups. Categorical variables were analyzed by Chi square tests.

RESULTS

Subjects consisted of 87 men (47.3%) and 97 women (52.7%), their mean age was 28.9±5.21year and BMI 20-27Kg/m^2 (23.9±1.56). The prevalence of MONW

among the study subjects was 84.2% . The vitamin D status of all study subjects was: severe deficiency (7.6%), insufficiency (33.7%) and sufficient (58.7%).

Table 1 shows the baseline characteristics of the study subjects. A significantly lower mean 25(OH) D level was found in the MONW group compared with non-MONW group (P<0.01). As expected, the comparison between MONW and non-MONW subjects showed higher frequency of some classical risk factors among siblings with MONW compared to non-MONW.

Table1- Baseline Characteristics of All Study Subjects

Characteristics	MONW (n=155)	non-MONW (n=29)	*P*-value
Age (years)	29.2±5.2	26.9± 4.7	<0.05
Systolic BP (mmHg)	113.1± 9.3	112.3± 6.1	0.199
Diastolic BP (mmHg)	74.3 ±7.7	72.5± 7.0	0.294
BMI (Kg/m^2)	24.0± 1.7	22.8 ±1.6	<0.01
Waist Circumference (cm)	87.2 ±7.6	75.8±8.7	<0.05
Fasting serum glucose (mg/dl)	102.1 ±17.8	99.2± 12.3	<0.05
Serum insulin (uIU/ml)	7.42±4.12	6.32±3.71	<0.05
HOMA-IR	1.87±0.42	1.54±0.08	< 0.01
Triglycerides (mg/dl)	146±39.9	78.6±35.7	< 0.01
HDL-Cholesterol (mg/dl)	43.5±12.0	47.8±13.1	<0.05
25(OH) D(ng/ml)	35.8±19.3	44.4± 22.3	< 0.05

The Prevalence of vitamin D and metabolic abnormalities in MONW and non-MONW subjects is presented in Table 2. Significantly higher prevalence of low vitamin D status [(25(OH) D <25 ng/ml] (29.6% vs. 17.2%; OR 2.81, p= 0.05) was observed in MONW group compared to those with non-MONW. MONW group showed a higher prevalence of vitamin D insufficiency (36.1% vs. 20.7%; OR 2.16, p<0.05), and severe vitamin D deficiency (8.4% vs. 3.5%; OR 2.56, p<0.05) than non- MONW group. MONW group had higher mean age, BMI, WC than non-MONW group. MONW had also higher mean values for HMOA-IR, triglycerides, but lower HDL-ch concentrations

Table 2- Prevalence of vitamin D and metabolic abnormalities in MONW and non-MONW subjects
MONW (n=155) non-MONW (n=29)

Variable	n (%)	n (%)	OR	*p*-value*
Waist Circumference (cm)				
male>86.4, female71.1	99(63.8)	3(10.3)	15.3	<0.001
Blood Pressure>140/90 (mmHg)	11(7.1)	3(10.3)	0.66	0.21
Glucose>110(mg/dl)	31(20.0)	3(10.3)	1.28	0.09
Triglyceride>150(mg/dl)	48(30.9)	1(3.4)	12.5	<0.001
HDL-ch <35(mg/dl)	39(25.1)	5(17.2)	1.60	<0.05
25(OH) D <25(ng/ml)	46(29.6)	5(17.2)	2.81	
Vitamin D status				
25(OH) D <10 (ng/ml)	13(8.4)	1(3.5)	2.56	<0.05
25(OH) D 10-29.9(ng/ml)	56(36.1)	6(20.7)	2.16	<0.05
25(OH) D 30-150(ng/ml)	86(55.5)	22(75.8)	0.39	<0.05

*Chi-square test

The relationship between 25(OH) D and metabolic syndrome components in MONW and non-MONW groups is presented in Table 3. On using the Spearman's correlation coefficient (P), the results in MONW group showed, 25(OH) D correlated negatively with WC and triglycerides ($p<0.001$, $p<0.01$).However, in the non-MONW group, no significant correlation was found.

Table 3: Spearman's correlation coefficient *(p)* between 25(OH) D and metabolic syndrome components in MONW and non-MONW subjects.

Variable	MONW		non-MONW	
	P	p	*P*	p
WC	**-0.612**	**<0.001**	**0.182**	**0.139**
BP	**-0.08**	**0.712**	**-0.131**	**0.351**
Glucose	**-0.075**	**0.682**	**0.193**	**0.146**
Triglycerides	**-0.551**	**<0.01**	**0.212**	**0.273**
HDL-cholesterol	**0.452**	**0.015**	**0.159**	**0.224**

DISCUSSION

This study has provided definitive evidence that siblings of patients with T 2 DM had low vitamin D status. The best relationship of low 25(OH) D levels was with obesity waist circumference, and hypertriglyceridemia. It is noteworthy that 41.3% appear at risk for vitamin D insufficiency or severe deficiency and most of them were MONW individuals. Several metabolic abnormalities are associated with vitamin D status. Of these, insulin resistance, T2DM and obesity are with the most marked negative effect on serum 25(OH) D concentrations 11 .Hence, vitamin D status may associate with metabolic unhealthy status in those with positive family history of DM.. In this study, lower concentrations of serum 25(OH) D and high prevalence of low vitamin D among MONW siblings is of potential concern and ever reported widely. In fact, this study confirms that low vitamin D status (serum 25(OH) D <25 ng/ml) is highly associated with the metabolically unhealthy status in siblings. It is noteworthy that the prevalence of MONW individuals among the siblings of patients with T 2 DM was 84.2 % and most of these individuals (63.8%) was with obesity waist circumference (>86.4 cm for males, and >71.1 cm for females). Moreover, they had higher means of HOMA-IR than non-MONW group, while the level of serum 25(OH) D was lower in those with high levels of triglycerides. Thus, this observation implied more susceptibility to low vitamin D status among MONW group, and reflect the association between vitamin D status and the high prevalence of MONW individuals among siblings of T2DM patients. This is in resonance with a study carried out by Liu,2005 3 as well as with a separate study, in which Reis and coworkers 12

reported a strong inverse relationship between 25(OH) D levels and prevalent metabolic syndrome that is independent of important confounders. The mechanism(s) by which low vitamin D could be associated with MS remain to be elucidated. A research among humans suggests that low 25(OH) D levels are associated with glucose intolerance and insulin resistance 13. However, our finding is a positive step towards further research to determine if vitamin D supplementation in siblings of patients with T2DM may reduce the risk of developing diabetes, this withstanding that 34/184(18.5%) of the study siblings was pre-diabetes or diabetes(FBG>110 mg/dl) and 26.6% had hypertriglyceridemia .

There have been reports of prevalence of MONW in general population, which ranges from 5-45%. But, however none of these reports directly related the prevalence of MONW among siblings of patients with T2DM Thus, we carried out this cross-sectional study on three identities; MONW, vitamin D, and siblings of patients with T2DM. The prevalence of metabolic abnormalities for MONW was significantly higher than that of non-MONW. For example, MONW individuals had higher mean age, body mass index, obesity waist circumference than non-MONW group. MONW individuals had also higher mean values of serum triglycerides, but lower HDL-cholesterol and serum 25(OH) D concentrations. This finding agrees with trials performed in general population 14as well as in our population 15

This study has few limitations, first we conducted this present study in Duhok Diabetes Center which is a health facility and health facility based studies are more likely to be biased than population based randomized studies regarding sampling. Second, our study is a cross-sectional study and a cross-sectional analysis has limitations as research methodology as it lacks follow up so the data presented are less likely to be representative of the general population actual data and of the same individual at other times. Third, some of the variables present in the study were depending on history taking and this carries an inherent risk of bias. Despite these limitations, our descriptive study interpreted with suitable caution can offer some useful insight to complement the data from the forthcoming studies using randomization

CONCLUSIONS

A low vitamin D status is present in one third of the siblings of patients with T2DM, particularly among MONW individuals; this finding may have clinical implications due to the increased risk of future metabolic disease. A large prospective study is needed to confirm our

observation, and experimental data may further elucidate the biological mechanism of the associations.

REFERENCES

1. Adams JS, Hewison M. Update in vitamin D.J Clin Endocrinol Metabol 2010;95:471-8.
2. Dalgard C, Petersen MS,Weihe P, Grandjean P.Vitamin D status in relation to glucose metabolism and type 2 diabetes in septuagenarians. Diabetes care 2011; 34:1284-8.
3. Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older US women. Diabetes care 2005; 28:2926-32.
4. Johnson T, Avery G, Byham-Gray. Vitamin D and Metabolic Syndrome. Topics in Clinical Nutrition 2009; 24:47-54.
5. Park JS, Park HD,Yun JW,Jung CH, Lee WY, Kim SW. Prevalence of the metabolic syndrome as defined by NCEP-ATPIII among the urban Korean population. Korean J of Medicine 2002;63:290-298.
6. Ruderman N, Berechtold P, Schneider SH. Obesity-associated disorders in normal-weight individuals: some speculations. Int J Obes 1981; 6:151-7.
7. Ruderman N, Schneider SH, Berechtold P. The "metabolically-obese", normal-weight individual. Am J Clin Nutr 1981; 34:1617-21.
8. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider SH. The metabolically obese; normal-weight individual revisited. Diabetes 1998;47:699-713.
9. Davies JS, Poole CD. Vitamin D: too much of a good thing?. Br J Gen Pract 2014; 64:8-9.
10. Al-Timimi DJ, Ali AF. Serum 25(OH) D in diabetes mellitus type 2: Relation to glycemic control.J Clin Diagn Res 2013; 7(12): 2686-8.
11. McGill AT, Stewart JM, Lithander FE, Strik CM, Poppitt SD. Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. Nutr J 2008;7:4-
12. Reis JP, Von Muhlen D, Miller ER. Relation of 25-hydroxyvitamin D and parathyroid hormone levels with metabolic syndrome among US adults. Eur J Endocrinol 2008; 159:41-8
13. Talael A, Mohamadi M, Adgi Z. The effect of Vitamin D on insulin resistance in patients with type 2 diabetes. Diabetology and Metabolic Syndro2013;5:8.
14. Succurro E, Marini MA, frontoni S, Hribal ML, Andreozzi F, Lauro R, et al Metabolically healthy but obese individuals. Obesity 2008;16:1881-6.
15. Al-Timimi DJ, Mustafa AH. Prevalence of metabolically obese, normal–weight individuals among first degree relatives of patients with type 2 diabetes. JABHS 2012;13(3): 2-8.

پوختە

ئاستێ ڤیتامین د و دوسیا شزوزا میتابولزمێ لدەف کەسوکارێن نەخوشین شەکرێ جورێ دووێ

ئارمانج: ڤەکولینا cross section پیزانینێن بەرجاڤ دان کو ئاستێ 25 (OH) D دناف خوینێدا پەیوەندیەکا هەڤدژ یا هەی دگەل پیکهاتێن ئێشا میتابولزمێ. پێزانینێن دیارکری لدەف جڤاکێن رێژەیا بلندتر یا مەترسیێ بو نەخوشیا شەکرێ جورێ دووێ، دگەل هندێ هەڤدژن. دڤێ ڤەکولینێدا پشکنینا 25 (OH) D، گلوکوز، بەزێ سیانی، کولیسترولێ HDL، و ئەنسولین لدەف کەسوکارێن نەخوشین شەکرێ جورێ دووێ هەی هاتنە ئەنجامدان.

ریکێن ڤەکولینێ: هەژمارتنا کێشا لەشی، بلندایی، درێژاییا دورماندوری سکی (WC)، فشارا خوینێ، گلوکوز، بەزێ سیانی وکولیسترولێ HDL و 25 (OH) D لدەف ١٨٤ کەسێن بسەرڤە دساخلەم، کەسوکارێن نەخوشین شەکرێ جورێ دووێ هەی، دگەل ژیێ دناڤبەرا 40-20 سالان. بەشداربو هاتنە دابەشکرن ل سەر دوو گروپان: گروپێ MONW و گروپێ non-MONW. پەیوەندی دناڤبەرا پیکهاتێن ئێشا میتابولزمێ و ئاستێ 25 (OH) D دناف خوینێدا هاتە پشکنینکرن.

ئەنجام: گروپێ MONW (84.2%) 155 دیارکر ئاستەکێ نزمتر یێ 25 (OH) D بەراوردی کرن دگەل گروپێ non-MONW (P<0.01). هاتە دیتن بشێوەکێ بەرجاڤ رێژەیەکا بەربەلاڤبونێ یا بلندتر یا نە بەسیا 25 (OH) D (36.1% vs. 20.7%, P<0.05) و کێمبونا دژوار (8.4% vs. 3.5%, P<0.05) لدەف گروپێ MONW بەراوردی کرن دگەل گروپێ non-MONW. لدەف گروپێ MONW رێژەیا بلندتر یا تیکرایێ ئاستی هاتە دیتن دگەل ژیی، هیمایێ کێشا لەشی (BMI)، و WC. و هەروەسا رێژەیا بلندتر یا تیکرایێ ئاستی لدەف گروپێ MONW دگەل HOMA-IR، بەزێ سیانی، بەلێ رێژەیەکا نزمتر یا تیکرایێ ئاستی دگەل کولیسترولێ HDL. لدەف گروپێ MONW پەیوەندیەکا هەڤدژ هاتە دیتن دناڤبەرا 25 (OH) D و بەزێ سیانی و WC (P<0.001 وP<0.01 لدویف ئێك) و پەیوەندیەکا وەك هەڤ دگەل کولیسترولێ HDL (P=0.015).

دەرئەنجام: پیزانینێن مە دیارکر ئاستەکێ نزمتر یێ ڤیتامین د لدەف کەسوکارێن نەخوشین شەکرێ جورێ دووێ و بتایبەتی لدەف کەسێن MONW هەی، پیشنیار دکەت کو کەسوکارێن نەخوشین شەکرێ جورێ دووێ رێژەیەکا بلندتر یا مەترسیێ یاهەی بو ئێشین میتابولزمێ دپاشەروژێدا.

الخلاصة

حالة الفيتامين د وملف الشذوذ الايضية بين اقارب مرضى السكري من النوع الثاني

الخلفية والاهداف: دراسة مقطعية زودت بمعلومات مشهودة بأن مستوى 25 (OH) D في الدم له علاقة عكسية مع محتويات المتلازمة الايضية. المعلومات المدونة في المجتمعات التي لديها نسبة خطورة اعلى للنوع الثاني من مرض السكري, مع ذلك, تناقضية. في هذه الدراسة تم قياس 25 (OH) D, الكلوكوز, الشحوم الثلاثية, كوليسترول الHDL والانسولين في اقارب مرضى السكري من النوع الثاني.

طرق البحث: تم قياس وزن الجسم، الارتفاع، محيط الخصر، ضغط الدم، الكلوكوز، الانسولين، الشحوم الثلاثية، كوليسترول الـHDL و25 (OH) D في ١٨٤ افراد أصحاء ظاهرياً، اقارب مرضى السكري من النوع الثاني، مع عمر يتراوح بين ٢٠–٤٠ سنة. المشاركين في هذه الدراسة تم تقسيمهم الى مجموعتين: مجموعة السمناء أيضياً، اوزانهم طبيعية (MONW) ومجموعة الـ(non–MONW). تم فحص العلاقة بين محتويات المتلازمة الايضية ومستوى الـ25 (OH) D في الدم.

النتائج: مجموعة الـ(MONW) كانوا (84.2%) 155، بينوا مستوى 25 (OH) D أقل من مجموعة الـ(non–MONW) ($p<0.01$). وجد بشكل ملحوظ نسبة انتشار أعلى من عدم كفاية الـ25 (OH) D (36.1% vs. 20.7%, $P<0.05$) والنقص الشديد (8.4% vs. 3.5%, $P<0.05$) في مجموعة الـ(MONW) مقارنة بمجموعة الـ(non–MONW). كان لدى مجموعة الـ(MONW) معدل قيمة اعلى من بمجموعة الـ(non–MONW) بالنسبة للعمر، مؤشر كتلة الجسم ومحيط الخصر، وكذلك معدل قيمة أعلى في مجموعة الـ(MONW) للـHOMA–IR، الشحوم الثلاثية، ولكن معدل قيمة اقل بالنسبة لكوليسترول الـ HDL. في مجموعة الـ(MONW) لوحظ علاقة عكسية للـ25 (OH) D مع الشحوم الثلاثية ومحيط الخصر ($P<0.001$ و $P<0.01$ على التوالي) وعلاقة طردية مع كوليسترول الـ HDL ($P=0.015$).

الاستنتاج: معلوماتنا وضحت حالة فيتامين د اقل بين اقارب مرضى السكري من النوع الثاني، وخصوصاً بين أفراد الـMONW، مما يقترح بأن اقارب مرضى السكري من النوع الثاني لديهم نسبة خطورة أعلى للامراض الأيضية مستقبلاً.

BLOOD LEAD AND ORAL HEALTH STATUS AMONG SECONDARY SCHOOL STUDENTS IN DUHOK, KURDISTAN REGION, IRAQ

ALI H. AL-DOSKY*

Submitted 11 March 2015; accepted 1 July 2015

ABSTRACT

Background and objective: It has long been believed that air, water and place have a direct bearing on human health. In recent years there has been growing interest in understanding the exact role played by lead on oral health status. The wide inconsistencies about the subject and the paucity of local studies in this context mandated the conduct of this study. The objective was to investigate the relationship of blood lead with oral health status.

Methods: A cross sectional designs enrolling eight secondary schools in Duhok city has been adapted from 15th April to 15th June 2013. The sample comprised 280 (188 males and 92 females) apparently healthy students aged 18-23yrs. A questionnaire was used to obtain information on age, gender, drug history, acute and chronic illness. This was followed by clinical dental examination to assess two standard oral health indices, namely, Decayed, Missing, Filled Surfaces (DMFS) and gingival index (GI) for each student.

Results: The mean blood lead was (4.4 ± 1.8 µg/dl), the value was higher in males than in females ($p < 0.001$).The mean DMFS was higher in females than in males (12.08 ± 5.52 vs. 10.37 ± 5.84 $P < 0.05$), respectively while the mean GI was higher in males than in females (0.94 ± 0.77 vs. 0.49 ± 0.58 $p < 0.001$), respectively. Blood lead was positively correlated with both DMFS and GI, the correlation was stronger with GI scores ($r = 0.832, p < 0.001$) than with DMFS scores($r = 0.543$, $p < 0.001$),

Conclusions: Different levels of blood lead relate variably to oral health status. Blood Lead correlates positively with both DMFS and GI scores.

Duhok Med J 2015; 9 (2): 10-17.

Keywords: Blood lead, Oral health

Environmental contamination from heavy metals has been a matter of great concern in many countries for several decades. Various epidemiological studies have shown that the occurrence of dental decay varies from one country to another and from one region to another in the same country.[1] Tissues of the oral cavity may be affected by toxic agents through systemic exposure as poisoning with heavy metals e.g. lead. Teeth, periodontal tissue, lips, tongue, mucous membrane, salivary glands and jaw bones may be affected depending on the type of exposure.[2,3] Lead is one of the most toxic elements which may cause acute, sub acute or chronic poisoning through environmental or occupational exposure.[4]

Lead is present in water, air and soil. From there, they may be taken up into plants, accumulate in the human food chain and affect humans health.[5,6] Lead is one of the first discovered and most widely used metal in human history and one of the most commonly encountered metal in the environment.[7]

*Lecturer,Department of Clinical Biochemistry, College of Medicine, University Of Duhok, Kurdistan Region, Iraq Correspondence to Ali H. Al-Dosky Email : Alidohuk@yahoo.com

METHODS

The study was conducted at Duhok city which lies in the far north–west of Iraq and forms the western city in Iraqi Kurdistan Region. A cross sectional study design was conducted on 280 secondary schools students (188 males and 92 females). The period of data collection extended from 15th April-15th June 2013.. Exclusion Criteria included history of any systemic disease, current treatment, the presence of fixed or removable orthodontic appliance in the mouth or other appliances. A study questionnaire was designed to obtain information on age, gender, medical history and drug history. The clinical dental examination took place during school hours in the classroom on comfortable chair, the intra oral examination was performed for all students to assess the main outcome measures, namely, (DMFS) and (GI).

Clinical examination

The clinical examination took place during school hours in the classroom on comfortable chair. The ultimate goal of clinical examination was to assess main outcome measures, namely (DMFS) and (GI). Examiner reliability in calculating both DMFS and GI indices was assessed with a sample of fifteen subjects, the results showed no statistically significant difference neither for DMFS nor for GI. ($p = 0.75$ and $p = 0.63$) respectively (Table 1) .Blood samples have been collected and blood lead was estimated for all students8

Statistical analyses were performed using SPSS software. The results were then tabulated and statistical significance was inferred at $P < 0.05$.

Table1: Summary Statistics Assessing Measurement Reliability of DMFS and GI Values

Examiner	No.	Mean DMFS		P value*
Investigator	15	20.3	11.2	0.75
Specialist	15	18.8	9.73	
		Mean GI	SD	P value*
Investigator	15	0.37	0.46	0.63
Specialist	15	0.28	0.35	

* Based on paired t- test

RESULTS

Those aged 18 years of the study sample constituted the biggest proportion (51.43%). Student's age ranged between 18 and 23 years with a mean of 19.16 ±1.49. Their blood lead ranged from 2.0-8.9 µg/dL with a mean of 4.4+1.8). A significant different in blood lead level, were found between males and females. The mean blood lead in males was 5.2 µg/dL compared to 3.16 µg/dL in females, $p < 0.001$(Table 2). Assessment of DMFS scores revealed higher mean values in females than in males (12.08 vs. 10.37, p= 0.02) respectively (Table 3). Assessment of Gingival Index scores revealed higher mean values in males than in females (0.94 vs. 0.49 $p < 0.001$) respectively. (Table 4). In both males and females, DMFS score levels gets worse as blood lead increases. ($r = 0.543$; $p < 0.001$).As shown in Table 5 and Figure1.In both males and females, gingival index gets worse as blood lead increases, $r=0.832$, $p<0.001$(Table 6 and figure 2).

Table 2: Age, gender and Blood Lead level of the study sample

Age		Minimum	Maximum	Mean	Standard Deviation
		18	23	19.16	1.49
		2.0	8.9	4.40	1.80
Blood Lead	µg/dL	Male m (SD)	Female m (SD)	Independent t test	p. value
		5.2 (1.78)	3.16 (1.05)	0.396	< 0.001

Table 3: Study Sample by DMFS and Gender

DMFS	Total No (%)	Male		Female		p. value *
		No. (%)	m (SD)	No. (%)	m (SD)	
0	4 (1.4)	4 (2.2)	10.37 (5.84)	0 (0.0)	12.08 (5.52)	0.02
1-5	48 (17.2)	39 (20.7)		9 (9.8)		
6-10	98 (35)	65 (34.5)		33 (35.9)		
11-15	75 (26.8)	46 (24.5)		29 (31.5)		
16-20	34 (12.1)	22 (11.7)		12 (13.0)		
>20	21 (7.5)	12 (6.4)		9 (9.8)		

* Based on Independent t test.

Table 4: Study Sample by Gingival Index and Gender

GI	Total No. (%)	Male		Female		p. value *
		No. (%)	m (SD)	No. (%)	m (SD)	
Healthy (0)	43 (15.4)	28 (14.9)	0.94 (0.77)	15 (16.3)	0.49 (0.58)	< 0.001
Mild (0.1 - 1)	161 (57.5)	107 (56.9)		54 (58.7)		
Moderate (1.1 - 2)	62 (22.1)	42 (22.3)		20 (21.7)		
Severe (2.1 - 3)	14 (5)	11 (5.9)		3 (3.3)		

* Based on Independent t test

Table 5: DMFS by Gender and Blood Lead

DMFS	Total No (%)	Male		Female		p. value*
		No. (%)	Blood lead m (SD)	No. (%)	Blood lead m (SD)	
0	4 (1.4)	4 (2.2)	3.9 (0.35)	0 (0.0)	NA	NA
1—5	48 (17.2)	39 (20.7)	3.89 (0.31)	9 (9.8)	2.23 (0.39)	< 0.001
6—10	98 (35)	65 (34.5)	3.88 (0.29)	33 (35.9)	2.88 (0.76)	< 0.001
11—15	75 (26.8)	46 (24.5)	5.69 (1.99)	29 (31.5)	2.93 (1.01)	< 0.001
16—20	34 (12.1)	22 (11.7)	7.66 (0.45)	12 (13.0)	4.03 (0.93)	< 0.001
>20	21 (7.5)	12 (6.4)	7.75 (0.55)	9 (9.8)	4.64 (0.45)	< 0.001

*Based on Independent t test.

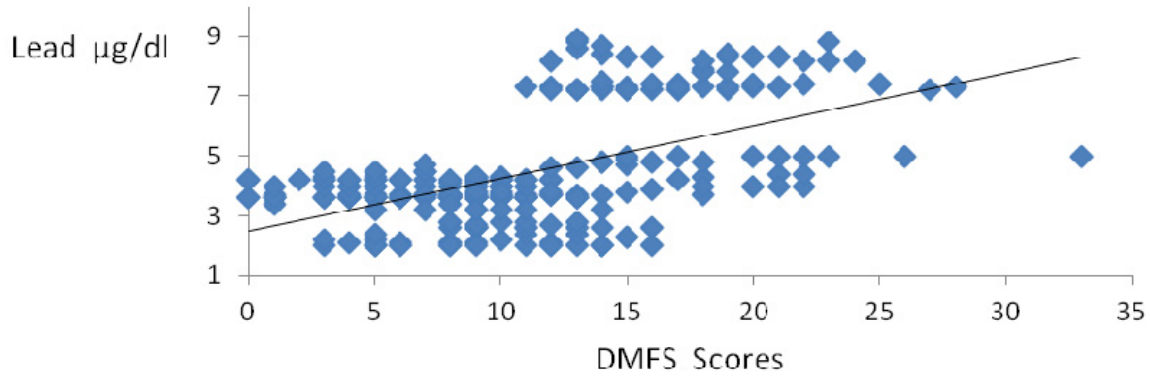


Figure 1: Correlation between DMFS Scores and Blood Lead Pearson Correlation Coefficient (r 0.543 ; p < 0.001)

Table 6: Gingival Index by Gender and Blood Lead

GI	Total No. (%)	Male		Female		p. value*
		No. (%)	Blood lead m (SD)	No. (%)	Blood lead m (SD)	
Healthy (0)	43 (15.4)	28 (14.9)	3.86 (0.30)	15 (16.3)	2.66 (0.98)	< 0.001
Mild (0.1- 1)	161 (57.5)	107 (56.9)	4.08 (0.86)	54 (58.7)	2.83 (0.85)	< 0.001
Moderate (1.1- 2)	62 (22.1)	42 (22.3)	7.43 (1.10)	20 (21.7)	4.29 (0.64)	< 0.001
Severe (2.1 – 3)	14 (5)	11 (5.9)	7.82 (0.64)	3 (3.3)	4.03 (1.19)	< 0.001

* Based on Independent t test.

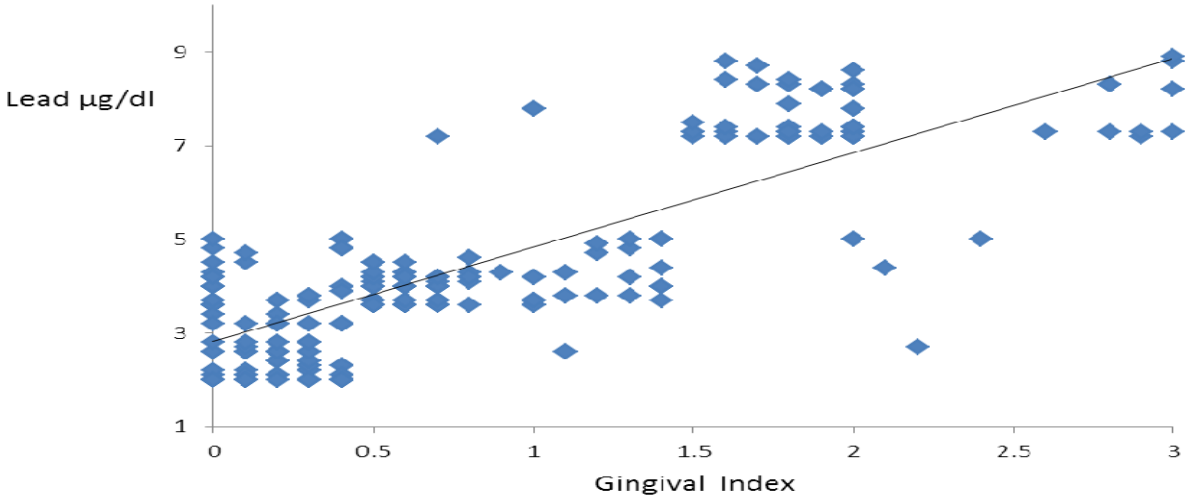


Figure 2: Correlation between Gingival Index and Blood Lead Pearson Correlation Coefficient (r 0.832; p < 0.001)

DISCUSSION

Dental caries and periodontal diseases are one of the most global oral health problems and most prevalent disease .9 There are many factors that can cause dental caries and the environment plays an important role in the health of oral cavity. 10 Heavy metals can be present in significant concentrations which affect the oral health of both adults and children.[11]

For many reasons Duhok city may present a higher level of lead contamination than other regions of Duhok Governorate and therefore, has a probable over exposure to the metal, considering that there are large numbers of vehicles and electric generators coinciding with the widespread use of leaded petrol. In addition, the geographical location of the city between two mountains and the location of industrial workshops within the city center contribute to an increased lead exposure12.This gender difference may be attributed to the increased outdoor activity and cigarettes smoking applicable to males . Increase in blood lead level could play a role in increasing the incidence of dental caries for many reasons since dental tissues such as teeth are very hard , allowing the heavy metals to be incorporated and stored in it.[13] Lead also has the ability to inhibit calcium uptake, lead ions replace calcium and phosphorus in bone minerals and, therefore, weaken the tooth.[14] The present study showed a moderate positive correlation between blood lead level and DMFS scores. Increase in blood lead level was associated with an increase in DMFS score which was statistically significant ($r = 0.543$ $p < 0.001$). The effect of blood lead on gingival health was also studied and the results showed a strong positive correlation between gingival index and blood lead. Increase in blood lead level correlates well with increase in GI score giving a correlation coefficient (r) of 0.832 with high statistical significance ($p < 0.001$). Increase in blood lead level could play a role in gingivitis since it affects the development and function of salivary glands and thus affecting the ability of the gland to produce adequate amounts of saliva which, in turn, leads to reduction in washing activity and increases bacteria and plaque.[15]

In conclusion, our study has demonstrated that the mean blood Lead was higher in males than in females. Blood lead was positively correlated with both DMFS and GI, the correlation being stronger with GI than with DMFS.

ACKNOWLEDGEMENT;

We acknowledge the support of the staff of Duhok secondary schools that provided the facilities for the interviews and the records.

REFERENCES

1. Amin W, Al Omoush S, Hattab F (2001). Oral health status of workers exposed to acid fumes in phosphate and battery industries in Jordan. Int Dent J; (51):169–74.
2. Peterson P, Gorment C (1991). Oral condition among German battery factor workers, JComm Oral Epidem; (19): 29 - 33.

3. Youravong N, Chonqsuvivatwong V, Greater AF, Dahlen G , Teanpaison R (2006). Lead associated caries development in children living in a lead contaminated area, Thailand. Sci Total Environ; (361):88– 96.
4. Hettmansberger T, Mycyk M (2002). Lead poisoning presents a difficult diagnosis, Am Fam Physician; (66): 1839-40.
5. Tvinnereim H, Eide R, Riise T (2000). Heavy metals in human primary teeth: some factors influencing the metal concentrations, Sci Total Environ; (255): 21–7.
6. Legind C, Trapp S (2009). Modeling the exposure of children and adults via diet to chemicals in the environment with crop-specific models, Environ Poll; (157): 778-85.
7. Stein J, Schettler T, Rohrer B, Valenti M (2008). Environmental Threats to Healthy Aging ,Boston, MA:GBPSR.
8. AL- Dosky AH, AL-Timim DJ, AL-DabbaghSA.Blood Lead Level and Kidney function among adolescents in Duhok.DMJ; 2014; 8(1)9-16
9. Petersen P (2003). The World Oral Health Report: continuous improvement of oral health in the 21st century – the approach of the WHO Global Oral Health Programme,Com Dent Oral Epidemiol; 31(1):3-23.
10. Anjos M, Barroso R, PerezC, Braz D, Moreira S, Dias K et al (2004). Elemental mapping of teeth using μSRXRF. Nucl Instrum and Meth; (213): 569–73.
11. Zhang M (2011). Mineral materials as feasible amendments to stabilize heavy metals inpolluted urban soils, Environ Sci; 23 (4):607–15.
12. AL–Dosky AH (2011).Lead exposure among the general population of duhok governorate, kurdistan region – Iraq. pepar. Thesis, University of Duhok, Collage of medicine. Iraq.
13. Martin RR, Naftel SJ, Nelson AJ, Feilen AB, Narvaez A (2007). Metal distributions in the cementum rings of human teeth: Possible depositional chronologies and diagenesis, J. Archaeology Sci; 34(6):936–45.
14. Niebyl JR, Simpson JL (2007). Drugs and environmental agents in pregnancy and lactation:embryology, teratology, epidemiology. In: Gabbe SG, Niebyl JR, Simpson JL(eds). Comprehensive Gynecology. 5th ed. Mosby Elsevier, Philadelphia, pp77-80.
15. Bowen WH (2001). Exposure to metal ions and susceptibility to dental caries. J Dent Educ ; 65 (10) :1046 – 53.

پوختە

رصاص وەك پیڤەرەك ل سەر ساخلەمیا دەڤ و ددانا ل دەف قوتابییێن قوتابخانێن ناڤنجی ل باژێرێ دهوكێ – هەرێما كوردستانێ – عیراق

پێشەكی و ئارمانج: ل سالێن دوماهیێ دا گرنگیەكا زێدە هاتیە دان ب تێگەهشتنا رولێ سەرەكی ب ئالاڤێن كارتێكەر لسەر ساخلەمیا دەف و ددانان وەكو توخمێ (رصاصی) ژبەر هەڤدژیێن بەرفرەه ل دور ڤی بابەتی و كێمیا ڤەكولینێن زانستی ونافخویی ل پارێزگەها دهوكێ.

ئەنجام: ڤەكولینێ دیاركری یە كو ئاستێ (رصاصی) د خوینێ دا (4.4 ± 1.8 µg/dl) و رێژەیا وی لدەف رەگەزێ نێر پتر بوو و جیاوازیا بلند بو ژلایێ واتایی ڤە ($P < 0.001$) تێكرایا دیاركری و یا (DMFS) ل دەف رەگەزێ مێ پتر بوو ژ یێ نێر (12.08 ± 5.52 µg/dl) بەرامبەر (10.37 ± 5.84 µg/dl) لدویف ئێك كو ($P = 0.02$). لێ تێكراییا ساخلەمیا پدیێ (GI) لدەف رەگەزێ نێر پتر بوو ژ یێ مێ (0.94 ± 0.77 µg/dl) بەرامبەر (0.49 ± 0.5 µg/dl) و ($P < 0.001$). وەك هاتیە دیاركرن ئاستێ توخمێ (رصاصی) د خوینێ دای ێ ئەرینی بوو دگەل (GI و DMFS) و پەیوەندیا ب هێزتر بوو دگەل GI (r=0.8) و یێ DMFS (r = 0.5).

دەرئەنجام: ئاستێ جیاواز یێ توخمێ (رصاصی) د خوینێ دا بشێوەكێ جیاواز دێ هێتە گرێدان دگەل ساخلەمیا دەف و ددانا وەكو دیار رێژا (رصاصی) د خوینێ دا پتر گرێدای بلندبوونا (GI) ژ یا (DMFS) و ل دویف پەیوەندیەكا ئەرینی.

الخلاصة

تقدير الرصاص كمؤشر للحالة الصحية للفم لدى طلبة المدارس الثانوية في دهوك–أقليم كوردستان العراق

الخلفية والاهداف: اعتقد منذ فترة طويلة أن الهواء والماء والمكان له تاثير مباشر على صحة الانسان. في السنوات الاخيرة ازداد الاهتمام بفهم الدور الدقيق للرصاص على صحة الفم والأسنان. وبسبب التناقضات الواسعة حول هذا الموضوع وندرة الدراسات المحلية في هذا السياق تم أجراء هذه الدراسة. تهدف الدراسة الى تحري علاقة االرصاص بصحة الفم والاسنان.

المواد والطرق: اعتمدت الدراسة التصميم المقطعي بضم ثمانية مدارس ثانوية في مدينة دهوك بالفترة من ١٥ نيسان الى ١٥ حزيران ٢٠١٣ وقد شملت عينة البحث (٢٨٠) من الطلبة الاصحاء ظاهريا (١٨٨ ذكور، ٩٢ إناث) وبأعمارتراوحت بين (١٨–٢٣) عاما .ان مستوى الرصاص في الدم لجميع الطلاب كان معلوما من خلال دراسة سابقة للدكتور علي حسين احمد . تم تنظيم أستمارة أستبيان للحصول على المعلومات المتعلقة بالعمر، الجنس، الأمراض السابقة والادوية المستخدمة تلا ذلك فحص للفم والاسنان لتحديد مؤشر تسوس وقلع وحشوة الاسطح للأسنان الدائمية (DMFS) ومؤشر صحة اللثة (GI) لكل طالب.

النتائج: ان مستوى الرصاص في الدم كان (4.4 ± 1.8 µg/dl) وكانت القيمة أعلى لدى الذكورمنه في الاناث وكان التباين بمستوى احصائي معنوي ($p < 0.001$). كان معدل مؤشر (DMFS) أعلى لدى الاناث منه في الذكور (5.52 ± 12.08 مقابل5.84 ± 10.37) وبمستوى احصائي معنوي ($p = 0.02$) بينما كان مؤشر دالة صحة اللثة (GI) أعلى لدى الذكور منه في الاناث (0.77 ± 0.94 مقابل 0.5 ± 0.49) وبمستوى احصائي عالي المعنوية ($p <$ 0.001). ان نسبة الرصاص في الدم كانت تتوافق ايجابيا مع مؤشري (DMFS, GI) وكانت العلاقة اقوى مع مؤشر GI (r = ٠.٨) منها مع مؤشر DMFS (r = ٠.٥).

الاستنتاجات: ان المستويات المختلفة للرصاص في الدم تترابط بشكل متغاير مع الحالة الصحية للفم . يرتبط الرصاص في الدم بشكل اساسي بمؤشر (GI) وفقا لعلاقة موجبة.

TRAUMATIC EXPERIENCES AMONG IRAQI INTERNALLY DISPLACED PERSONS AND SYRIAN REFUGEES

PERJAN HASHIM TAHA M.B.Ch.B. MSc.C.A.P. F.I.C.M.S. (psych)*

Submitted 18 October 2015; accepted 31 December 2015

ABSTRACT

Background and objectives: After civil war in Syria and Islamic state invasion of Northern Iraqi areas, high number of Iraqi internally displaced persons and Syrian refugees arrived to Iraqi Kurdistan, including children who constitute more than half of population. The impact of psychological trauma among them is likely high, but little has been reported on traumatic experiences among these two groups in the area they first escaped to, apart from children and adolescents who have been reported in other articles. This article reports the traumatic events that adults were able to describe during a short screening.

Methods A community based cross-sectional survey was conducted at Khanke and Domiz 2 camps in Kurdistan region of Iraq in May and June, 2015. Sample size collection yielded 822 adults of Iraqi internally displaced persons and 820 adults of Syrian refugees and the participants were determined randomly. Harvard Trauma Questionnaire was used to determine exposure to psycho-traumas.

Results Multiple sever traumatic events were reported in both groups. Mild traumatization is common in Syrian refugees and sever one is more in Iraqi internally displaced persons. Violence due to belongingness, separation, emotional violence, threats, and starvation were more experienced by Iraqi displaced people. Physical violence, and beating to head were more common in refugees. Combat situation, murder, and sexual violence were similar in both groups.

Conclusions Internally displaced people and refugees experienced multiple traumatic events with high levels and different types. There are huge needs in mental health among survivors. These findings have important implications for the planning and implementation of mental health promotion and treatment programs for resettled internally displaced persons and refugees and those who work with them.

Duhok Med J 2015; 9 (2): 18-33.

Keywords: Traumatic, Internally displaced, Refugees.

Armed conflicts, wars, and associated displacement affect large numbers of people in the world.[1] Some war survivors are displaced within the borders of their countries as internally displaced persons (IDPs), while others are displaced to other countries as refugees.[2] Internal conflicts causing forced displacement of non-combatant populations are a common global occurrence.[3]

Worldwide, the number of refugees defined narrowly by the refugee convention, as individuals who have been forcibly displaced outside their native countries is estimated to be about 13 million in 2002.[4] The UN high commissioner for refugees (UNHCR) reported in 2014 that the total number of refugees worldwide exceeded 50 million for the first time since World War II. The

* *Specialist Psychiatrist and Lecturer, University of Duhok/College of Medicine, Azadi Teaching Hospital/Psychiatry Department Perjanht74@yahoo.com 00964 750 766 7450*

recent increases were largely due to the Syrian civil war. During the same year, one million refugees were registered by UNHCR, most of them headed to the surrounding countries including Iraqi Kurdistan due to the instability in north eastern Syria caused by Islamic state of Iraq and Syria (ISIS).[5]

Northern Iraq has witnessed a chain of dramatic political and military developments in the last year that have thrown the entire region into a vortex. It is estimated that since the Islamic State (IS; formerly ISIS)'s takeover of Mosul on June 10, 2014, northern Iraq has seen a population displacement. The majority of those recently displaced belong to the main religious and ethnic minorities of the region including Yezidis. On August 3, 2014, IS militants attacked and conquered the town of Sinjar, approximately fifty miles south of the southernmost point controlled by the Kurdistan Regional Government (KRG).[6] Attacks by IS militants designed to kill Yezidi men and kidnap their women and children, some of whom were sold as sex-slaves in the markets in IS controlled cities in Iraq and Syria.[7] Prolonged exposure to the extreme temperatures on the mountain resulted in many deaths from thirst, hunger, and disease, mainly among children and the elderly.[8]

Psychological trauma and posttraumatic stress disorder (PTSD) in displaced population remained understudied in areas of first they escaped to partly due to the difficulty in gathering clinically informative data during times of humanitarian crises. Little has been reported on traumatic experiences on such group apart from children and adolescents who have been reported in other articles.[9, 10] KRG together with some non-governmental organizations (NGOs) are taking the responsibility for the health needs of IDPs and refugees including mental issues.

The purpose of this study is to investigate the traumatic events experienced by the adult populations among the Iraqi IDPs and Syrian refugees settled in refugee camps in Iraqi Kurdistan.

METHODS

Study setting and design

A community based cross-sectional survey with 822 adults of Iraqi IDPs and 820 adults of Syrian refugees was conducted in May and June, 2015 at Khanke and Domiz 2 camps in Kurdistan region of Iraq. Khanke camp is 20 km west to Duhok city, situated in Khanke town (with a population of 23 000). About 60 000 IDPs are currently accommodated in the camp, mostly from Sinjar. Domiz 2 camp is located 20 Km southwest of Duhok 4 km south Domiz town containing 20 000 refugees from Syria.

Data were collected by face to face interviews and the socio-demographic characters were assessed using a semi-structured questionnaire. The quantities and qualities of trauma and torture were assessment by Harvard Trauma Questionnaire (HTQ). Interviews were carried out by 6 psychosocial workers trained on the study tools in 5 days full time course.

Target population and sample size determination

According to statistics gained from the DOH, about 800,000 Yezidi IDPs (more than 50% being children and adolescents) are living in the camps and unfinished buildings and schools inside and around Duhok city. IDPs in Khanke camp and Syrian refugees in Domiz 2 camp were chosen to participate in this study.

This study was conducted from 15th of April, 2015 until 15th of June, 2015. For each camp, the minimum required sample is 800 using the following formula:

Initial sample size (n): The equation for calculating sample size is as follows

$$n = \frac{Z2\ p(1-p)}{e2}$$

According to this formula: (z) is the critical standard score, for 1 tailed hypothesis test, it's the value for which the cumulative probability is 1-alpha (alpha is significance level). (p) is population proportion. (e) is margin of error which is the maximum difference between the observed sample mean and the true value of population mean.[11,12] This equation is estimated 10% non- response rate. A registry of tents and the eligible adults living in each tent were asked to be provided from the camp administration and they were enlisted in excel file.

Initially, a simple random sampling technique was utilized to draw the minimum number tents per camp to be visited. After selection of tents, one eligible adult was selected again from each tent using simple random sampling method.

Study instruments

A questionnaire was designed to measure the socio-demographic characteristics of IDPs and refugees capable of identifying the gender, age, marital status, religion, nationality, educational level, work status, original residence, duration of being in the camp, number of family members, and past psychiatric history of client and of family members. To measure traumatic experiences Harvard Trauma Questionnaire was used; a checklist is written by the Harvard Program in refugee trauma, it's similar in design to the Hopkins Symptom Checklist-25 (HSCL-25).[13]

It inquires about a variety of trauma events, as well as the emotional symptoms considered to be uniquely associated with trauma. Currently, there are six versions of this questionnaire. Part I contain 17 traumatic life events and has been expanded in later versions to contain between 46 and 82 events. Part II and Part III are open-ended questions about injury, and Part IV consists of 30 trauma symptom items. Part V is determining the torture history.

In this study we included only trauma events that IDPs and refugees were likely to have experienced and respondents were to indicate 'yes' or 'no' depending on experience during the conflict.

Validity of the research tools was done after getting agreement from the scientific and ethical committees by presenting the instruments to three specialist psychiatrists to review them and getting feedbacks then reliability also done by interviewing 100 persons from both camps and then re-

interview them by other interviewers after 4 days. The interviewers used Kurdish version for those who speak Kurdish and Arabic version for those speaking Arabic language. While Arabic translation was derived from the Iraqi-Arabic version of HTQ, the kurdish one was obtained by Duhok University linguistics from college of arts/ Kurdish and English departments who translated and retranslated the instrument.

Ethical considerations

Approval was taken from the scientific and ethical committees of Faculty of Medical Sciences/ University of Duhok and the Directorate of Health in Duhok (DOH). Informed written consents were obtained from each participant and information leaflets provided and explained by the interviewers.

Data entry and analysis

Data were entered into excel sheets. Descriptive statistics were used in summarizing the data like frequencies, proportions, tables,..etc. All data were analyzed using the Statistical Package for Social Science (SPSS) version 19 software package. Significance of association between various factors was assessed using the Chi square test, and differences were assessed by paired t test. Level of statistical significance was set at < 0.05 and highly significant was at < 0.001.

RESULTS

The mean age of participants in IDP group is 33.8 years (SD= 12.7, median= 31, range=77, minimum value=18, and maximum value= 95) and in that of refugees group is 33.6 years old (SD= 10.8, median= 31, range= 60, minimum value=18, and maximum value= 78). Table 1 shows that more participants from both groups are young ages (70.1%) and (74.9%) in IDPs and refugees respectively, then the middle age groups and lastly elderly people are few constituting only (2.6%) and (0.7%) of participants. There were more males in IDP sample (56.4%) and more females in Syrian sample (61.7%). Most of Syrian refugees were married (91.6%) but the singles were more in the IDP sample than in refugees 161 (20.1% vs 53 (6.5). Mean age of singles in the IDP group was 21.5 (SD= 4.1, median= 20, range= 22, minimum value=18, and maximum value= 40) and the mean age of singles in the refugees group was 24 (SD= 6.6, median= 23, range= 24, minimum value=18, and maximum value= 42). The IDPs were mostly of Yezidi religion (98.8%) while the Syrian refugees were mostly Muslims (99.6%). Most of participants in both groups have primary school education; very few have academic degrees and higher education and most of participants are unemployed. Few participants or members of their families have positive past psychiatric history.

Table 1: The socio-demographic characteristics of the participants (N=822 IDPs and 820 refugees)

Character	IDPs N %	Refugees N %
Age		
Young (18-40 yr.)	**564 (70.1%)**	**609 (74.9%)**
Middle age (40-64yr.)	**220 (27.3%)**	**198 (24.4%)**
Elderly (>65yr.)	**21 (2.6%)**	**6 (0.7%)**
Gender		
Female	**354 (43.1%)**	**506 (61.7%)**
Male	**464 (56.4%)**	**313 (38.2%)**
Marital status		
Single	**161 (20.1%)**	**53 (6.5%)**
Married	**622 (77.6%)**	**743 (91.6%)**
Divorced	**3 (0.4%)**	**5 (0.6%)**
Widowed	**16 (2%)**	**10 (1.2%)**
Religion		
Muslim	**5 (0.6%)**	**817 (99.6%)**
Yezidi	**812 (98.8%)**	**3 (0.4%)**
Christian	**3 (0.4%)**	**0 (0%)**
Education		
Primary school	**272 (59.4%)**	**308 (51%)**
Secondary school	**162 (33.4%)**	**233 (38.6%)**
Academic degree	**18 (3.9%)**	**59 (9.8%)**
Higher education	**6 (1.3%)**	**4 (0.7%)**
Work status		
Unemployed	**694 (86.2%)**	**728 (89%)**
Employed	**111 (13.8%)**	**90 (11%)**
Past psychiatric history of participant		
Positive	**32 (3.9%)**	**14 (1.7%)**
Negative	**788 (96.1%)**	**804 (98.3%)**
Past psychiatric history of family member		
Positive	**53 (6.3%)**	**18 (2.2%)**
Negative	**763 (93.5%)**	**801 (97.8%)**

Information on sample exposure to traumatic events clarify that a majority of participants (69.2% - 94.4%) from both groups the Iraqi IDPs and Syrian refugees together reported experiencing the following traumas: forced to leave hometown and settle in other locality, expelled to flee city or country based on ancestral origin, religion, or sect, forced evacuation, confiscation, looting or destruction of personal property, lack of shelter, and forced to hide.

Detailed information about traumatic experiences among the participants is shown in table 2. While confiscation, looting and destruction of personal property was the most common trauma experienced by IDPs reported by (96.5%) of them, Syrian refugees reported forced to leave hometown and settle in other country as the most common trauma experience in (93.4%) of them.

Table 2: Traumatic events experienced or witnessed among IDPs and refugees as assessed by HTQ. (N=822 IDPs and 820 refugees)

Traumatic event	IDPs N (%)	Refugees N (%)	P value
Traumas more common in Iraqi IDPs			
Confiscation, looting or destruction of personal property	793 (96.5%)	587 (71.6%)	<0.001
Expelled to flee city or country based on origin, religion, or sect	771 (94%) 739	(90.1%) 0.003	ancestral
Forced evacuation	771 (93.8%)	699 (85.2%)	<0.001
Lack of shelter	747 (91.1%)	456 (55.7%)	<0.001
Forced to hide	700 (85.4%)	435 (53.1%)	<0.001
Lack of food or water	640 (78%)	383 (46.7%)	<0.001
Oppressed because of ethnicity, or religion	519 (63.3%)	137 (16.7%)	nationality, <0.001
Forced to change religion	338 (41.4%)	4 (0.5%)	<0.001
Disappearance, hostage or kidnapping relative or friend	318 (38.9%)	99 (12.1%)	of <0.001
Murder or death of relative or friend due to violence	219 (26.8%)	271 (33%)	0.006
Witness rotting corpses	128 (15.7%)	77 (9.4%)	<0.001
Murder or death of family member due to violence	114 (13.9%)	81 (9.9%)	0.01
Disappearance, hostage or kidnapping family member	110 (13.4%)	45 (5.5%)	of <0.001
Witness video films on violence to known persons or places	50 (6.1%)	8 (1%)	<0.001
Forced separation from family	29 (3.5%)	10 (1.2%)	0.002
Kidnapped	26 (3.2%)	10 (1.2%)	0.007
Requested money instead of receiving person	24 (2.9%)	5 (0.6%)	kidnapped <0.001
Traumas more common in Syrian refugees			
Witness shelling, burning, or razing of residential areas	103 (12.7%)	202 (24.6%)	<0.001
Witness destructing religious shrine	124 (15.3%)	154 (18.8%)	0.006
Witness murder	38 (4.6%)	141 (17.2%)	<0.001
Witness beating	29 (3.5%)	134 (16.3%)	<0.001
Present while searched home	18 (2.2%)	125 (15.2%)	<0.001
Serious physical injury of family member, friend or relative due to combat	64 (7.8%)	110 (13.4%)	<0.001
Witness torture	23 (2.8%)	100 (12.2%)	<0.001
Imprisonment	24 (2.9%)	55 (6.7%)	<0.001
Other traumas			
Forced to leave hometown and settle in other country	782 (95.4%)	766 (93.4%)	0.08
Combat situation	391 (47.7%)	365 (44.5%)	0.18
Searched	152 (18.6%)	148 (18%)	0.7
Torture physical or psychological	91 (11.1%)	93 (11.4%)	0.8
Ill health without medical care	45 (5.5%)	60 (7.3%)	0.13
Witness mass execution of civilians	34 (4.2%)	45 (5.5%)	0.2
Physically harmed	26 (3.2%)	36 (4.4%)	0.19
Serious physical injury	19 (2.3%)	19 (2.3%)	0.9
Forced labor	13 (1.6%)	12 (1.5%)	0.83
Rape	9 (1.1%)	11 (1.3%)	0.7
Other types of sexual abuse	9 (1.1%)	7 (0.9%)	0.6
Forced to physical harm someone	3 (0.4%)	6 (0.7%)	0.3
Witness chemical attacks	3 (0.4%)	9 (1.1)%	0.08
Forced to betray someone	3 (0.4%)	7 (0.9%)	0.2

Regarding differences between traumatic events experienced in Iraqi IDPs and Syrian refugees it seems that IDPs, with a statistically high significant values (P<0.001), experienced more traumatic events than Syrian refugees in the following domains subsequently: oppressed because of ethnicity, nationality, or religion (63.3% vs 16.7%), forced to change religion (41.4% vs 0.5%), lack of shelter (91.1% vs 55.7%), forced to hide (85.4% vs 53.1%) and many other types of traumas as shown in table 2. In contrast to IDPs, the Syrian refugees experienced other types of traumas more than IDPs, with high significant values, subsequently: present while searched home (15.2% vs 2.2%), witnessed beating (16.3% vs 3.5%), witnessed murder (17.2% vs 4.6%), and witnessed torture (12.2% vs 2.8%), imprisonment (6.7% vs 2.9%) and many other types of traumas clearly shown in table 2.

There were no differences between both groups in exposure to some traumatic events like: forced to leave hometown and settle in other country (95.4% and 93.4%), Combat situation (47.7% and 44.5%), physical or psychological torture (11.1% and 11.4%), witnessed mass execution of civilians (4.2% and 5.55) and rape (1.1% and 1.3%) and sexual violence.

Table 3 shows quantity of traumatic experiences among participants graded mildly traumatized when a person have reported only 1-10 traumatic events, moderately traumatized when the person experienced 11-20 traumatic events and severely traumatized when the person reported more than 20 traumatic events. The table shows that mild traumatization is more present in the refugee people (78.3%) and the moderate and severely traumatized persons are more present in the Iraqi IDP people (34.8%) and (1.1%) respectively.

Table 3: Cumulative trauma events recorded among IDPs and refugees as assessed by HTQ. (N=822 IDPs and 820 refugees)

Severity	N of traumas/ person	IDPs N %	Refugees N %
Mildly traumatized	0-10	526 (64.1%)	640 (78.3%)
Moderately traumatized	11-20	286 (34.8%)	170 (20.8%)
Severely traumatized	21-40	9 (1.1%)	7 (0.9%)

Beating to head was more common among Syrian refugees (8.7%) comparing to the Iraqi IDPs (2.6%) as shown on table 4. Suffocation, strangulation, being near drowning also was present in both groups similarly but with low percentages. Starvation was highly prevalent in both groups but more common among Iraqi IDPs (92.2%). Becoming near death due to starvation was experienced again by Iraqi IDPs (62.7%) much more than Syrian refugees (4.3%).

Table 4: Types of head injury and starvation experienced by IDPs and refugees (N=822 IDPs and 820 refugees)

Item	IDPs N %	Refugees N %	P value
Beating to head	21 (2.6 %)	71 (8.7%)	<0.001
Suffocation or strangulation	6 (0.7%)	6 (0.7%)	1
Near drowning	3 (0.4%)	8 (1%)	0.1
Others	7 (0.9%)	3 (0.4%)	0.2
Starvation	756 (92.2%)	372 (45.6%)	<0.001
Near death due to starvation	515 (62.7%)	35 (4.3%)	<0.001

Thirty four types of torture were present in both groups as shown in table 5. Refugees reported more torture types than Iraqi IDPs in the following domains: chained or tied (5% vs 1.9%), punched kicked or slapped (4.4% vs 1.3%), forced to stand on foot for long time (4.3% vs 1.1%) and many other torture kinds.

Table 5 Torture history among IDPs and refugees as assessed by HTQ. (N=822 IDPs and 820 refugees)

Torture types	IDPs N (%)	Refugees N (%)	P value
Forced to confess a crime	8 (1%)	25 (3%)	0.003
Exposed to humiliation	13 (1.6%)	25 (3%)	0.04
Blindfolded	10 (1.2%)	32 (3.9%)	0.001
Forced to stand on foot for long time	9 (1.1%)	35 (4.3%)	<0.001
Chained or tied	16 (1.9%)	41 (5%)	0.001
Placed in a small cage or container	3 (0.4%)	22 (2.7%)	<0.001
Placed in an isolation cell with no toilet	5 (0.6%)	21 (2.6%)	0.004
Deprived from food and water	13 (1.6%)	24 (2.9%)	0.11
Deprived of sleep	6 (0.1%)	24 (2.9%)	0.002
Exposed to continuous loud noise	2 (0.2%)	10 (1.2%)	0.041
Exposed to strong heat, burning	3 (0.4%)	10 (1.2%)	0.09
Exposed to cold or rain	4 (0.5%)	14 (1.7%)	0.036
Exposed to a dirty unhealthy condition	2 (0.2%)	10 (1.2%)	0.041
Prevented from going to the W.C	4 (0.5%)	12 (1.5%)	0.08
Prevented from ablution and prayer	4 (0.5%)	15 (1.8%)	0.024
Forced to perform hard labor	5 (0.6%)	7 (0.9%)	0.513
Suspended from the feet or hands	1 (0.1%)	12 (1.5%)	0.006
Sexually abused or Raped	2 (0.2%)	2 (0.2%)	0.607
Punched, kicked, or slapped	11 (1.3%)	36 (4.4%)	0.001
Beaten of soles of the feet with cable or rod)	7 (0.9%	20 (2.4%)	0.025
Burned by cigarettes, electrical heater,..	1 (0.1%)	10 (1.2%)	0.009
Shocked by electric instrument	3 (0.4%)	10 (1.2%)	0.55
Extraction fingernail or toenail	1 (0.1%)	1 (0.1%)	0.368
Amputation of body parts	1 (0.1%)	2 (0.2%)	0.312
Exposed to mock execution to create panic	3 (0.4%)	2 (0.2%)	0.333
Forced to undress in front of people	2 (0.2%)	4 (0.5%)	0.264
Forced to do different forms of humiliation)	2 (0.2%	3 (0.4%)	0.333
Head submerged in water near drowning	3 (0.4%)	7 (0.9%)	0.165
Forced to participate in sexual assault	2 (0.2%)	1 (0.1%)	0.312
Exposed to humiliating during eating	5 (0.6%)	12 (1.5%)	0.086
Forced to talk dismissively of leaders	5 (0.6%)	11 (1.3%)	0.1
Being forced to watch the sexual assault of people close to you (mother, wife, sister..etc)	2 (0.2%)	1 (0.1%)	0.189
Made to witness other being tortured	5 (0.6%)	13 (1.6%)	0.061
Forced to watch, listen or read political speeches of former government officials	2 (0.2%)	7 (0.9%)	0.055

DISCUSSION

This study employed HTQ to investigate traumatic events and torture exposure among resettled Iraqi IDPs and Syrian refugees in Iraqi Kurdistan refugee camps. Contrary to the belief that stigma prevents refugees from discussing mental health distress, participants readily described complex conceptualizations of degrees of traumas and mental health distress informed by political context, traumas, symptoms, cultural idioms, and functional impairment.[14]

Taking both groups the Iraqi IDPs and Syrian refugees together and looking to the common types of traumas, forced to leave hometown and settle in other locality (95.4% and 93.4% respectively) (Table 2) seems to be the most common traumatic experience which is greater a lot than the findings of other studies like study on conflict affected population in southern Sudan in which only (12.9%) of population displaced.[15] This give us clue to the dangerousness of situation in the conflict areas both in Syria and Iraq .

Regarding traumatic events experienced by Iraqi IDPs, the most common one was the confiscation, looting and destruction of personal property (96.5%) as shown in table 2. This was similar to what is documented in other studies like in IDPs of Kaduna, Northwestern Nigeria (96.1%) but, it was more than what is reported among IDPs in Northern Uganda in which the most common traumatic event was lack of food and water.[16,17] This is because IS took people's homes and used them for military purposes. The second most common traumatic event among IDPs was forced to leave hometown (95.4%) which is because the sample we took is a camp sample so they are mostly those who are obligated to leave their hometown to escape from the escalating violence. This is just similar to what IDPs in Kaduna reported (95.7%).[16] The third common trauma was expelled to flee city or country based on origin and religion (94%) this is because most of IDPs are Yezidi religion in which IS are fighting them as they are their goal because they are not Muslims. The next common traumatic events were forced evacuation and lack of shelter (93.8% and 91.1%) which were more than what is reported among other IDP groups in the world like in Northern Uganda (77.3%), and in southern Sudan (13.1%).[17,15,18] Lack of food and water was present in (78%) in Iraqi IDPs which again was similar to the findings of Bayard Roberts in his study on IDPs of Northern Uganda (89.9%) and is higher than what is reported by Taiwo L in his study in Kaduna IDPs (38.8%).[17,16] This can be due to the fact that most IDPs stayed in mountains after their escaping from IS military forces and stayed days on the way walking until they reached safe places.

The most common traumatic event among Syrian refugees was forced to leave hometown, flee country based on origin, religion or sect and forced evacuation (93.4%, 90.1% and 85.2%) as shown in table 2. The similar findings were obtained in a study on Iraqi refugees in which (81.9%) forced to flee country.[19] Most of them they left their homes and their belonging materials so destruction of personal property found in (71.6%) of

refugees. Lack of shelter and food and water was present in (55.7% and 46.7%) of refugees and this was similar to the findings of Angela N et al on Mandaean adult refugees (48.4%) and is lesser than what is reported by Ree S et al article about traumas among west Papuan refugees resettled in Australia (88%) and among refugees in Uganda (83%).[20,21]

Some specific traumatic experiences were quite different between IDPs and refugees as the difference was highly significant statistically. While most Iraqi IDPs experienced forced to change religion and oppressed because of ethnicity, nationality or religion (41.4% and 63.3%) shown in table 2, Syrian refugees reported only (0.5% and 16.7%). This was because most IDPs are of Yezidian religion which were ordered by IS to change their religion to Muslim at time of their invasion. These problems were not big among Syrian refugees. Iraqi refugees resettled in Australia most commonly reported being oppressed because of ethnicity, religion, or sect (69.9%).[19]

Because the IS attacks on north Iraq areas were sudden in contrast to the Syrian civil war which was insidious so most Iraqi IDPs remain without shelter and housing for days until they reached camps. This made Iraqi IDPs to experience lack of shelter and housing more than Syrian refugees (91.1% vs 55.7%). These rates were a lot higher than other studies done on Mandaean adult refugees in Australia (30.6%).[22]

Kidnapping and forced to hide were triple common in Iraqi IDPs (3.2% and 3.5%) than in Syrian refugees (1.2%) and the disappearance, hostage or kidnapping of family member, relative or friend more commonly happened in IDPs (13.4% and 38.9%) than in refugees (5.3% and 12.1%). Similar rates of Kidnapping found in IDPs of Northern Uganda (43%).[17] Lower rate of Kidnapping or loss found in Angela N *et al* study on Mandaean refugees (11.7%).[22] Requested money instead of receiving kidnapped person was again most common in IDPs (2.9%) than in refugees (0.6%). Witnessed video films on violence to known individuals or places were more reported in Iraqi IDPs (6.1%) in contrast to Syrian refugees (1%). This is happened because IS usually video film their terrorist acts and violent events and distribute to media for the purpose of frightening more people.

Comparing to Iraqi IDPs, Syrian refugees experienced some types of traumatic events much more. The following percentages are seen among refugee population versus IDP population regarding traumas like imprisonment (6.7% vs 2.9%), witnessed beating (16.3% vs 3.5%), witnessed murder (17.2% vs 4.6%), witnessed torture (12.2% vs 2.8%) and present while searched home (15.2% vs 2.2%). Comparing to other studies imprisonment was more found among IDPs in Southern Sudan (13.7%), among IDPs of Northern Uganda (24.5%), among Mandaean refugees (21.3%).[15,17,22] Witnessed murder again was lesser than what is found in IDPs of Northern Uganda (64.3%) and Mnadaean refugees (28.2%).[17,22]

All of this may be because IS uses mass killing in areas they invade so there are no

or few people are remaining to witness their violent acts. This is again clear in our findings where the murder or death of family member was more in IDPs comparing to refugees (13.9% vs 9.9%). But these percentages were quite lesser than what is found in a study among Tuareg refugees of a camp in Burkina Faso in whom (83%) of the surveyed subjects have one or more family members killed.[23]

There are many traumatic events that have similar rates in both groups, like combat situation (47.7%) and (44.5%) in IDPs and refugees respectively which indicate that both groups were went at similar war conditions and they were similar to what is reported in IDPs of Southern Sudan (51.5%) and were more than in Northern Uganda IDPs who reported only (27.3%) and in Mandaean refugees (19.3%).[17,22] Ill heath without access to medical care has similarly low evidence in both groups (5.5%) and (7.3%) in Iraqi IDPs and Syrian refugees respectively which may be because Kurdish Directorate of Health (DOH) sent medical care (mobile teams) to most areas of IDPs and refugees in a short period of time preventing people from suffering health problems as much as they can. This finding was lesser than the sufferings in Southern Sudan IDPs who reported (24.5%), in Mandaean refugees in Australia (31.4%), in Northern Uganda IDPs (65%) and west Papuan refugees (86%).[15,22,17,20]

In contrary to the fact that Iraqi IDPs were exposed to rape, sexual harassment, and abuse, only (1.1%) of them reported these types of traumas and was the same level documented in Syrian refugees. It was similar to the rate found among IDPs in Kaduna, Northwestern Nigeria (1.7%), and in Australia Mandaean refugees (2.8%), and was different from the findings of Barth SK et al which clarify that (41%) of Iraqi women and (4%) of men veterans who served during operations of freedom reported sexual traumas.[16,24,22] It's again lesser to what is reported among IDPs of Northern Uganda (14.1%) and in IDPs of Southern Sudan (6.7%) were exposed to rape or sexual abuse.[17,15] This lower reporting of sexual traumas in our study can be because of the fact that most of raped girls and women were in the hand of IS at time of conducting our study on one hand and because of stigma of talking about the sexual issues in the Yezidian conservative society on the other hand.

Cumulative trauma events among Iraqi IDPs and Syrian refugees which are shown in table 3 demonstrate that both IDPs and refugees reported multiple and sever traumas. While mildly traumatized individuals are present more in the refugee group, the moderate and sever traumatization are more in the IDPs group. These findings are consistent to Schweitzer RD *et al* findings among Burmese refugees in Australia.[25]

Traumas to head like beating the head were more common in Syrian refugees than in Iraqi IDPs (8.7% vs 2.6%) as shown in table 4. Both data were lower than what is reported by Keatley E et al (69%) and are higher than what is documented in the long-term Afghan refugees in Pakistan (1.8%).[26,27]

Starvation and being near death by starvation were more common in Iraqi

IDPs (92.2% and 62.7%) than in Syrian refugees (45.6% and 4.3%) as shown in table 4. This finding was lower than the rate of Cambodian refugees who resettled in United States and experienced near death due to starvation (99%).[28]

Different types of torture were experienced by both Iraqi IDPs and Syrian refugees. (Table 5) Those commonly reported by refugees were chained or tied, punched, kicked or slapped , forced to stand on foot for long time, blindfolded, and others. Similar findings were reported in resettled Karen refugees.[29]

The present study has several limitations. Many Iraqi IDPs and Syrian refugees are living outside camps in rent houses, and unfinished building, that is why the camp population may be quietly not representative of all IDPs and refugees in the region. There is no much published information available concerning mental health of Yezidian community who are the main IDPs group in our study. Regarding refugees most of the males were working during the day time, which is the time of recruiting interviews, so although random sampling was used but females may be over representing in this sample

Findings from this study have important clinical implications for those working with survivors of trauma and torture. Although the interviewers were originally psychosocial counselors and they were able to select cases of highly traumatization and refer them to the suitable mental health services in and out of camps, still there is urgent need for further research investigating the treatments beneficiary for those high percentages of traumatized victims in the IDP and refugee camps.

ACKNOWLEDGEMENT

This study was partly supported by AISPO organization (Italian Association for Solidarity among people; is an Italian non-profit organization created by Italean hospital San Raffaele) for their taking the initiative of supporting the interviewers financially. We acknowledge also the due of Duhok DOH for the help and statistical analysis.

REFERENCES

1. Steel Z, Chey T, Silove D, Marnane C, Bryant RA, van Ommeren M. Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta- analysis. JAMA. 2009;302:537–49.
2. Porter M, Haslam N. Predisplacement and postdisplacement factors associated with mental health of refugees and internally displaced persons: a meta-analysis. JAMA. 2005;294:602–12.
3. Neuner F, Elbert T. The mental health disaster in conflict settings: Can scientific research help?. BMC Public Health. 2007; 7:275.
4. Fitzpatrick J. Human rights protection for refugees, asylum seekers and internally displaced persons: a guide to international mechanisms and procedures. 1st ed., Transnational Publishers, Inc;2002.
5. Harriet S. Global refugee figure passes 50m for first time since Second World

War. The Guardian. 2014. Available from: http://www.theguardian.com/world/2014/jun/20/global-refugee-figure-passes-50-million-unhcr-report
6. Idan B. The Yezidis: Traumatic Memory and Betrayal. Teaviv Notes. 2014; 8(17):1-6. Available from: http://dayan.org/sites/default/files/TLVNOTES_Idan_Barir_Yezidis_10092014.pdf
7. Ford S. Rape and Sexual Slavery inside an ISIS Prison. The Daily Beast. 2014. Available from: http://www.thedailybeast.com/articles/2014/08/28/rape-and-sexual-slavery-inside-an-isis-prison.html
8. Jonathan K. Iraq Crisis: 'It Is Death Valley. Up to 70 Per Cent of Them Are Dead'. The Telegraph. 2014. Available from: http://www.telegraph.co.uk/news/worldnews/middleeast/iraq/11024037/Iraq-crisis-It-is-death-valley.-Up-to-70-per-cent-of-them-are-dead.html
9. Ahmad A. Crisis intervention program for children and adolescents (CIPCA) to prevent posttraumatic psychopathology, preliminary report. Duhok Med J 2014;8(2):1-11.
10. Ahmad A. War-displaced children in Iraqi Kurdistan. IACAPAP Bulletin. 2015; 42:13-15.
11. www.sattrek.com
12. www.surveysystem.com
13. Mollica RF, Caspi-Yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard Trauma Questionnaire. Validating a cross-cultural instrument for measuring torture, trauma, and posttraumatic stress disorder in Indochinese refugees. J Nerv Ment Dis. 1992 ;180(2):111-6.
14. Shannon PJ, Wieling E, McCleary JS, Becher E. Exploring the mental health effects of political trauma with newly arrived refugees. Qualitative Health Res. 2015; 25(4):443-57.
15. Bayard R, Eliaba YD, Olivia L, Egbert S. The influence of demographic characteristics, living conditions, and trauma exposure on the overall health of a conflict-affected population in Southern Sudan. BMC Public Health. 2010; 10: 518.
16. Taiwo LS, Abdulaziz M, Samuel A, Joseph I, William N. E, Oluwatosin A. Psycho-Trauma, Psychosocial Adjustment, and Symptomatic Post-Traumatic Stress Disorder among Internally Displaced Persons in Kaduna, Northwestern Nigeria. Front Psychiatry. 2014; 5: 127.
17. Bayard R, Kaducu FO, John B, Thomas O, Egbert S. Factors associated with post-traumatic stress disorder and depression amongst internally displaced persons in northern Uganda. BMC Psychiatry. 2008; 8: 38.
18. Bayard R, Eliaba YD, Olivia L, Egbert S. Post-conflict mental health needs: a cross-sectional survey of trauma, depression and associated factors in Juba, Southern Sudan. BMC Psychiatry. 2009; 9: 7.
19. Shameran SY, Jonathan MM, Elise B, Maral M, Yaser M, Hanan D et al. Psychological trauma and help

seeking behaviour amongst resettled Iraqi refugees in attending English tuition classes in Australia. Int J Ment Health Syst. 2015; 9: 5.

20. Rees S, Silove DM, Tay K, Kareth M. Human rights trauma and the mental health of West Papuan refugees resettled in Australia. Med J Aust. 2013;199(4):280-3.
21. Peltzer K. Trauma and mental health problems of Sudanese refugees in Uganda. Cent Afr J Med.1999; 45(5):110-4.
22. Angela , Belinda J, Fiona M, Zachary S, Derrick S, Richard AB. Posttraumatic stress disorder and prolonged grief in refugees exposed to trauma and loss. BMC Psychiatry. 2014; 14: 106.
23. Carta M,Wallet O, Moro MF, Moro D, Preti A, Mereu A et al. Trauma- and Stressor Related Disorders in the Tuareg Refugees of a Camp in Burkina Faso. Clin Pract Epidemiol Ment Health. 2013; 9: 189–195.
24. Barth S, Kimerling RE, Pavao J, McCutcheon SJ, Batten SV, Dursa E. et al.Military Sexual Trauma Among Recent Veterans: Correlates of Sexual Assault and Sexual Harassment. Am J Prev Med. 2015: 15318-9.
25. Schweitzer RD, Brough M, Vromans L, Asic-Kobe M.
26. Mental health of newly arrived Burmese refugees in Australia: contributions of pre-migration and post-migration experience. Aust N Z J Psychiatry. 2011; 45(4):299-307.
27. Keatley E, Ashman T, Im B, Rasmussen A. Self-reported head injury among refugee survivors of torture. J Head Trauma Rehabil. 2013; 28(6): 8-13.
28. Sugerman DE, Hyder AA, Nasir K. Child and young adult injuries among long-term Afghan refugees. Int J Inj Contr Saf Promot. 2005; 12(3):177-82.
29. Marshall GN, Schell TL, Elliott MN, Berthold SM, Chun CA. Mental health of Cambodian refugees 2 decades after resettlement in the United States. JAMA. 2005; 294(5):571-9.
30. Tonya LC, Patricia JS, Gregory AV, James PL, Ehtaw D. War trauma and torture experiences reported during public health screening of newly resettled Karen refugees: a qualitative study. BMC Int Health Hum Rights. 2015; 15: 8.

پوختە

سەرهاتییێت رودانێت پەستا دەرونی لدەف ئاوارێن عێراقێ و پەنابەرێن سوری

پێشەکی و ئارمانج: پشتی رویدانا شەرێ نافخویی ل وەلاتێ سوریا و داگیرکرنا رێکخراوا (داعش) ێبۆ باکورا عێراقێ و پەنابەرێن سوری گەهشتنە هەرێما کوردستانا عێراقێ . کارتێکرنا پەستا دەرونی ل ئاوارا و پەنابەرا گەلەکە . بەلێ پا کێم یا سەر ڤان پەستێن دەرونی هاتینە تومارکرن. ئارمانج ژ ڤێ ڤەکولینێ دیارکرنا سەرهاتییێت پەستا دەرونی لدەف ئاوارا و پەنابەرا ددەمەکێ کێم دا.

رێکێن ڤەکولینێ: ئەڤ ڤەکولینا دەرونی هاتنە کرن لکەمپا خانکێ و دومیز ٢ لدەڤەرا هەرێما کوردستانی لهەردوو هەیڤێن ئایار و حوزەیران ل سالا ٢٠١٥. (٨٢٢) ئاوارێن عێراقێ و (٨٢٠) پەنابەرێن سوری هاتنە دەست نیشان کرن بۆ ڤێ ڤەکولینێ پیڤەرێ هارڤارد بۆ پیڤانا پەستێن دەرونی هاتە بکارئینان .

ئەنجام: گەلەك پەستێن دەرونی یێ بهێز هاتنە تومارکرن لدەف ئاوارێن عێراقێ و پەنابەرێن سوری. پەنابەرێن سوری توشی پەستێن دەرونی بوون لسەر ئاستەکێ سڤك بەلێ پا ئاوارێن عێراقی ئاسێ پەستا دەرونی یا توند بو . پەستێن ئاوارا یێن مشە: توند و تیژی ژبەر بنەمایا، و ژێك ڤەبوون، و توندو تیژیا هەستی، و گەف، و برسیبون. و لدەف پەنابەرێن سوری: توند و تیژیا جستەیی و لێدانا سەری. هەروەسا هەڤرکی و کوشتن و توندو تیژیا سکسی یا هەڤپشك بۆ ل هەردوو گروپا.

دەرئەنجام: ئاوارا و پەنابەرا گەلەك سەرهاتییێن تروما و پەستێن دەرونی هەنە لئاستێن بلند و جوراوجور . گەلەك پێتڤییێت ساخلەمیا دەرونی لدەف وان هەنە . ئەڤ ڤەکولینە و ئەنجامێت وێ پلانێت چارەسەرکرنێ و پروگرامێت ساخلەمیا دەرونی ددەنە بەرچاڤ .

الخلاصة

خبرات الحوادث الصدمية لدى النازحين العراقيين و اللاجئين السوريين

خلفية وأهداف البحث: بعد الحرب الأهلية في سوريا و إحتلال تنظيم داعش لمناطق شمال العراق، وصلت أعداد كبيرة من النازحين العراقيين واللاجئين السوريين الى كردستان العراق. يعتبر تأثير الصدمة النفسية كبيرا على النازحين واللاجئين، ولكن القليل من الحوادث الصدمية تم توثيقه لدى هؤلاء الناس في المنطقة التي هربوا اليها أولا. تهدف هذه الدراسة إلى معرفة الحوادث الصدمية لدى النازحين واللاجئين خلال فترة قصيرة.

طرق البحث: تمت الدراسة كمسح ميداني في مخيم خانكى و دوميز ٢ في كردستان العراق في شهر مايس و تموز عام ٢٠١٥. عينة البحث شملت ٨٢٢ بالغا من النازحين العراقيين و ٨٢٠ من اللاجئين السوريين تم إختيارهم عشوائيا. تم إستعمال مقياس هارفارد لقياس الصدمات النفسية التي تعرضوا لها.

النتائج: وجدت صدمات شديدة و متعددة لدى النازحين العراقيين و اللاجئين السوريين. الصدمات النفسية الخفيفة كانت شائعة في اللاجئين السوريين أما الشديدة فهي أكثر في النازحين العراقيين. أكثر الصدمات التي تعرض اليها النازحين العراقيين هي: العنف بسبب الخلفية و الإنفصال و العنف العاطفي والتهديدات والمجاعة. أما في اللاجئين السوريين فهي العنف الجسدي وضربات الرأس. بالنسبة للصدمات المتعلقة بحالة الحرب والقتال والعنف الجنسي فكانت متشابهة لدى المجموعتين.

الإستنتاج: نستنتج من البحث أن النازحين العراقيين و اللاجئين السوريين قد تعرضوا إلى حوادث صدمية متعددة بمستويات عالية و أنواع مختلفة. هناك إحتياجات نفسية مهمة لدى الباقين. هذه النتائج لديها فوائد عديدة في تخطيط و تنفيذ برامج الصحة النفسية و العلاج النفسي لمجاميع النازحين العراقيين و اللاجئين السوريين و الأشخاص العاملين في هذا المجال.

IMPACT OF DIABETES MELLITUS ON PULMONARY FUNCTIONS TEST

Qassim H. Abdullah, MBChB, MSc, PhD*
Ihsan H. M. Ali, BVM&S, M.Sc**
Hazhmat. A. Ali, BVM&S, MSc (UK)**

Submitted 10 September 2015; accepted 8 November 2015

ABSTRACT

Background and Objectives: Diabetes mellitus (DM) is an endocrine-metabolic disorder resulting from insulin insufficiency or dysfunction characterized by hyperglycemia associated with a series of macro and micro vascular complications. The aim of this study is to evaluate the impact of DM on lung functions and its association with inflammatory markers mainly serum C- reactive protein.

Methods: This study involved 58 patients with DM and 30 apparently healthy subjects as controls. In addition to other laboratory assessments, pulmonary functions were carried out through measurement of FVC, FEV1 and FEV1/FVC ratio, using a computerized spirometer (SpiroLap III).

Results: Among diabetic patients 72.41% of them showed restrictive lung disease, and lung volumes (particularly in type I) represented by the means of FVC (2.43L) and FEV1 (2.32L) were significantly lower (p=0.03 & p=0.02 respectively) than those of controls (FVC=2.83L & FEV1=2.73L). No significant difference in FEV1/FVC ratio was found between them. In addition, restrictive lung disease in patients with positive diabetic complications was significantly higher (51.72% Vs 20.68%, p= 0.005) than those with negative complications. Restrictive lung disease was significantly higher in patients with poor glycemic control compared to those with fair and good control.

Conclusion: Respiratory system of diabetic patients may undergo a dysfunction during the course of the disease represented by subclinical restrictive tendency and its severity become more intense particularly in diabetics with poor glycemic control which provide a clue to the idea that the Respiratory system, especially the lungs and respiratory muscles can be the target organs for diabetic complications.

Keyword:

Duhok Med J 2015; 9 (2): 34-43.

Keywords: Diabetes mellitus, diabetic complications, pulmonary functions test.

Diabetes Mellitus (DM) is a mixture of metabolic and endocrine disorders and it is one of the major worldwide health problems nowadays characterized mainly by hyperglycemia associated with a dysregulation in carbohydrate, fat and protein metabolism that results from insufficient insulin secretion or function.[1] There are two main types of Diabetes Mellitus; type 1 diabetes mellitus and type 2 diabetes mellitus. The first form is immune mediated disorder occurs as a result of autoimmune damage of β-cells in Langerhan's islets leading to a severe deficiency of insulin.[2] Type 2 affects approximately 90% of diabetic populations usually after the fourth decade of age characterized by insulin resistance.

* *Professor, Head of the Dept. of Physiology, College of Medicine, University of Duhok.*
** *Assistant Lecturer, Dept. of Physiology, College of Medicine, University of Duhok.*
Correspondent author: Ihsan H.M. Ali, email: ihsan.phys@gmail.com

Although genetics plays a major role in the incidence of DM, environmental factors have influences as well, such as obesity, unhealthy diet, longevity…etc.[3,4] Diabetes has been associated with a series of complications. Microvascular complications including diabetic retinopathy, nephropathy and neuropathy; whereas macrovascular complications such as coronary artery disease and peripheral vascular disease.[5]

Lung diseases can be classified into two major categories; obstructive diseases that result from obstruction of the airway passage such as chronic obstructive pulmonary disease, whereas restrictive diseases involve fibrosis of interstitial lung tissue.[6] Evaluation of pulmonary functions are performed using spirometry to differentiate between obstructive and restrictive diseases depending on FEV1/FVC ratio.[7] A variety of research have been conducted in the context of diabetes complications but very few studies were performed examining the effects of diabetes on lung functions by estimating lung vital capacities in diabetic patients compared with non diabetic controls. These studies concluded that both type 1 and type 2 diabetics develop a decline in lung functions particularly[5] years after the onset of the disease[8,9] although there is controversy in other studies.[10] We hypothesized that, in addition to the ordinary complications that are developed as a result of diabetes, abnormalities in lung functions may be noticed as well, and accordingly this study was designed to evaluate pulmonary functions in diabetes mellitus to examine the above hypothesis.

SUBJECTS AND STUDY DESIGN:

This study was conducted in Duhok Diabetic Centre (D.D.C.) from March 2013 to June 2013.

Two groups were included in this study. The first group involved 58 randomly selected diabetic patients which is further subdivided into two subgroups. The first subgroup composed of 45 patients (16 Males and 29 females) with type 2 diabetes mellitus with their mean age ± SE of (44.6±1.07 years). The second subgroup consisted of 13 patients (8 Males and 5 females) with type 1 diabetes mellitus (28.6±1.9 years).

The second group comprised of 30 apparently healthy subjects (19 male and 11 female, average age of 38.9±1.49 years). All members of this group underwent clinical and laboratory assessments by the researchers to confirm that they are free of diabetes or inflammatory conditions. The acquired data at study entry involved age, gender, height, weight, blood pressure, and patient's history including type and duration of diabetes mellitus, diabetic complications, respiratory problems, smoking habit as well as medications intake. Diabetes was defined by self-report of diabetes diagnosis or use of diabetes drug or if fasting plasma glucose >126mg/dl.[11]

Patients were classified according to HbA1c % into three groups (good control < 6.5 %, fair control ≥ 6.5% - < 7.5%, poor control ≥7.5%).[12] Diabetic patients of both

types were selected carefully using the previously mentioned diagnostic criteria. Then 10ml of blood sample was taken from both patients and controls, one part was sent for complete blood count and HbA1c %, another part was distributed into two tubes (EDTA containing tube to obtain plasma and plane tube to obtain serum). Centrifugation was done for each sample then plasma and serum were distributed into labeled epindorff tubes and frozen at -28Co till time of analysis.

Pulmonary functions tests (FVC, FEV1 and FVC/FEV1 ratio) and pulse rate were carried out using an instrument Spirolap III colour (a computerized Spirometer, 00155 ROME-Italy). Patients were asked to take a rest for at least 15 minutes, then they were made to undergo pulmonary function test for three times at every 15 minutes interval. Mean of three measurements was taken into consideration. Quantitative determination of high sensitivity C-reactive protein in human serum was done using hs-CRP ELISA Kit(from Monobind Inc./USA manufacture, www.monobind.com)

Other biochemical tests like Fasting blood sugar were also measured in this study using chemical autoanalyzer. HbA1c percentage was estimated using commercial kit (StanbioGlycohemoglobin Pre-Fil procedure No. P350). All statistical analysis was computer assisted using SPSS version 18 (Statistical Package for Social Sciences). All the outcome quantitative variables were described by mean and SE (standard error), and the independent samples t- test was used to test statistical significance of difference in mean between two groups, while more than two groups one way ANOVA was used. The difference in proportion of population between two groups and more than two groups was assessed by chi-square test. P value less than the 0.05 level of significance was considered statistically significant.[13]

RESULTS:

Results showed highly significant increases in the mean HbA1c%, total W.B.C count, F.B.S hs-CRP in diabetic patients compared with control group, associated with significant decrease in Hb level in diabetic patients (table 1).

Table 1: Comparison of blood hemoglobin, glucose, Total WBC count and C-reactive protein between diabetic and control groups.

Parameters	Diabetics Mean ± SE	Control Mean ± SE	p value
Hb g/dl	13.61 ± 0.22	14.42 ± 0.33	p = 0.04
FBS mg/dl	177 ± 9.22	98.9 ± 1.39	p = 0.001
HbA1c %	8.5 ± 0.3	4.94 ± 0.03	p = 0.001
Total WBC cell/ml3	8.15 ± 0.24	6.83 ± 0.31	p = 0.001
hs-CRP mg/dl	9.22 ± 0.23	3.26 ± 0.6	p = 0.001

As it is shown in table 2, the mean level of both forced vital capacity (FVC) (2.43 Vs 2.83) and forced expiratory volume during the first second (FEV1) (2.32 Vs 2.73) showed significant decreases in patient group compared to control (p=0.03 and p=0.02 respectively). On the other hand,

FEV1/FVC % and peak expiratory flow showed no significant alterations.

Table 2: Comparison of Pulmonary function Parameters between diabetic and control groups

Pulmonary functions Parameters	Diabetics Mean ± SE	Control Mean ± SE	p value
FVC (Liter)	2.43 ± 0.09	2.83 ± 0.19	p = 0.03
FEV1 (Liter)	2.32 ± 0.09	2.73 ± 0.16	p = 0.02
FEV1 / FVC %	85.9 ± 0.73	87.3 ± 0.93	p = 0.3 (NS)
PEF (Liter)	4.23 ± 0.18	4.58 ± 0.33	p = 0.3 (NS)

According to the results of pulmonary function test (PFT), 14 (24.13%) of patients revealed normal PFT, 2 (3.45%) showed obstructive lung disease, but the majority of patients 42 (72.41%) showed PFT consistent with restrictive lung disease (Table 3). Moreover, restrictive lung disease was significantly higher in diabetic patients with positive history of diabetic complications compared to those with negative complications (30 (51.72%) Vs 12 (20.68%), p= 0.005) (Table 4). Moreover, the patients with poor glycemic control showed a significant higher restrictive lung disease compared to those with fair & good control (51.72% Vs 12.06% & 8.62% respectively, p= 0.001) (Table 5). According to the type of diabetes, restrictive lung disease were significantly higher in type I diabetes than type II (100% Vs 63.04%, p= 0.039) (Table 6).

Table 3: Categories of patients according to results of pulmonary function test (PFT).

Diabetics group No. = 58	No. of patients	% of patients
Normal PFT	14	24.13 %
Obstructive	2	3.45 %
Restrictive	42	72.41 %

Table 4: Comparison of pulmonary functions results according to the history of diabetic complications.

Diabetes complications	Normal PFT	Obstructive	Restrictive
Positive complications	No. = 10 17.24 %	No. = 1 1.72 %	No. = 30 51.72 %
Negative complications	No. = 4 6.89 %	No. = 1 1.72 %	No. = 12 20.68 %
p value	0.1 (NS)	1 (NS)	0.005

Table 5: Comparison of pulmonary function tests according to glycemic control state.

Glycemic control (No. = 58)	Normal PFT	Obstructive	Restrictive
Good control	No. = 5 8.62 %	Zero 0 %	No. = 5 8.62 %
Fair control	No. = 2 3.44 %	No. = 1 1.72 %	No. = 7 12.06 %
Poor control	No. = 7 12.06 %	No. = 1 1.72 %	No. = 30 51.72 %
p value	0.2 (NS)	1 (NS)	0.001

Table 6: Comparison of pulmonary function test according to the type of diabetes.

Diabetes type (No. = 58)	Normal PFT	Obstructive	Restrictive
Type I No. = 13	Zero 0 %	Zero 0 %	No. = 13 100 %
Type II No. = 45	No. = 14 30.43 %	No. = 2 4.35 %	No. = 29 63.04 %
p value			0.039

DISCUSSION:

Current results showed a highly significant elevation in the inflammatory markers (hs-CRP and the total WBC count) in diabetic patients compared with control (p= 0.001). Such findings indicate that inflammation is enhanced in diabetes mellitus i.e. there is existence of systemic inflammation during the pathogenesis of diabetes which is triggered by hyperglycemia and this statement is strongly approved in previous studies.[11,12,13] In addition, there is an association between glycemic status and systemic inflammation in diabetic patients.[14.15] Previous literature indicated that hyperglycemia can be regarded as an inducer of the inflammatory response in lungs during diabetes.[16] Histological examination of biopsies taken from streptozotocin induced diabetes rats showed alterations in the structure of inter alveolar septum, Clara cells and alveolar walls which revealed signs of inflammation in the basal laminae of alveoli and alveolar epithelia.[17] Other studies showed an increase in intravascular macrophages suggesting the presence of inflammation.[18,19]

Regarding pulmonary performance in diabetes, this study demonstrated a significant decrease in both FVC and FEV1, although the FEV1/FVC ratio was elevated and statistically not significant. Furthermore, majority of our diabetic patients revealed abnormal lung function test of restrictive type. Although there is controversy regarding the impact of diabetes on lung functions,[20] previous studies support these findings regarding a remarkable reduction in pulmonary function parameters particularly FEV1 and FVC in diabetic subjects.[21,22,23,24,25] In the current study, the restrictive lung disease was significantly higher in diabetic patients especially with those of poor glycemic control. The possible mechanism could be due to up regulation of systemic inflammation that may lead to pulmonary inflammation26, in addition to non enzymatic glycosylation resulting in destruction of connective tissue of the lung.[23,27] In-vitro exposure of endothelial cells to high levels of glucose enhances inflammatory process by stimulating mitochondria to produce high levels of reactive oxygen species (ROS) which subsequently enhances inflammation.[28,29]

In addition to the influences of diabetes on pulmonary functions, the data of this study confirmed that the diabetic patients who have positive complications are at high risk for developing pulmonary dysfunction particularly restrictive lung diseases. These data illustrate that pulmonary dysfunction in general may be considered one of the complications of diabetes.[30,31,32,33] Moreover, restrictive lung disease was significantly higher in type 1 diabetics

compared with type 2 (p=0.03); although, it has been found in both types. Accordingly, it can be concluded that patients with type I diabetes are more susceptible to restrictive disease than type 2.

In summary, it can be concluded that pulmonary dysfunction in general and restrictive lung diseases in particular may be considered another complication of diabetes specifically in type 1 diabetics which emphasize the idea that lungs being a target organ in diabetes. Therefore, it is suggested that diabetics and people who are at risk of developing diabetes should be subjected to pulmonary functions test as a screening test.

REFERENCES:

1. Shah A, Kanaya AM. Diabetes and associated complications in the South Asian population. Curr Cardiol Rep. 2014 ;16(5):476. doi: 10.1007/s11886-014-0476-5.
2. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.
3. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract. 2002; 55(1):65-85.
4. Ko GT, Chan JC, Yeung VT, Chow CC, Tsang LW, Li JK et al. Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. Diabetes Care. 1998; 21(8):1221-5.
5. Colman PG1, Thomas DW, Zimmet PZ, Welborn TA, Garcia-Webb P, Moore MP. New classification and criteria for diagnosis of diabetes mellitus. The Australasian Working Party on Diagnostic Criteria for Diabetes Mellitus. N Z Med J. 1999. 23;112 (1086):139-41.
6. George S. Eisenbarth. Type I Diabetes Mellitus. N Engl J Med. 1986; 314:1360-68.
7. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care. 1996; 19(3):257-67.
8. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2008; 31.
9. Pradhan D, Manson E, Rifai N, Buring E, Ridker M. C-Reactive protein, Interleukin 6 and Risk of Developing Type 2 Diabetes Mellitus. Journal of American Medical Association. 2001;286: 227-34.
10. National Diabetes Data Group. Classification and diagnosis of Diabetes Mellitus and other Categories of Glucose Intolerance. Journal of Diabetes. 1979; 28: 1039-57.
11. King A, Buchanan T, Mainous A, Pearson W. C reactive protein and glycemic control in adults with diabetes. Diabetes Care. 2003; 26(5): 1535-9.
12. Souza J, Oliveira R, Blotta M, Coelho O. Serum Levels of Interleukin-6 (IL-6), Interleukin-18 (IL-18) and C-Reactive Protein (CRP) in Patients

with Type-2 Diabetes and Acute Coronary Syndrome without ST-Segment Elevation. Arq Bras Cardiol. 2008; 90(2) : 86-90.
13. Tong P, Chan J. White Blood Cell Count Is Associated With Macro- and Microvascular Complications in Chinese Patients with Type 2 Diabetes. Diabetes Care. 2004; 27:216–22.
14. Preciado-Puga MC, Malacara JM, Fajardo-Araujo ME, Wröbel K, Wröbel K, Kornhauser-Araujo C et al. Markers of the Progression of Complications in Patients with Type 2 Diabetes: A One-year Longitudinal Study. Exp Clin Endocrinol Diabetes. 2014; 122(08): 484-90.
15. Kalninova J, Jakus V, Glejtkova M, Kuracka L, Sandorova E. Impact of glycemic control on advanced glycation and inflammation in overweight and obese patients with type 2 diabetes mellitus. Bratisl Lek Listy. 2014;115(8):457-68.
16. Strojek K, Ziora D, Sroczynski JW, Oklek K. Pulmonary complications of type 1 diabetic patients.Diabetologia 1992;35:1173-6.
17. Sandler M, Stewart R. Pulmonary function in young insulin-dependent diabetic subjects. Chest. 1986; 90: 5.
18. Francisco V, Jorge H, Eduardo M, Angel G, Lopez L, Javier S, et at. Diabetes induces pulmonary artery endothelial dysfunction by NADPH oxidase induction. Am J Physiol Lung Cell Mol Physiol. 2008; 295: L727-L32.
19. Luiz J, Nélson K, Marilene P, Alexandre D, Norma P. Experimental diabetes mellitus: oxidative stress and changes in lung structure. J Bras Pneumol. 2009; 35(8):788-91.
20. Haffner SM: Insulin resistance, inflammation and the prediabetic state. AmJ Cardiol. 2003; 18:18-26.
21. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L: Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal study. J Intern Med. 2003; 253:574–81.
22. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et at. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000; 404: 787–90.
23. Shravya G, Sharan M, Hari B, Suresh M, Preetham J K, Mallikarjuna N. Deterioration of Pulmonary Functions in Type 2 Diabetes Mellitus. Journal of Pharmacy and Biological Sciences. (May-June 2012); 2278-3008 Vol. 1, Iss. 1: 39-43.
24. Kanya DH , Nataraj S M , Devaraj H S. Correlation of duration of diabetes and pulmonary function tests in type 2 diabetes mellitus patients. J Biol Med Res. 2011; 2(4): 1168 -70.
25. Irfan M, Haque A, Awan H, Hussain S. Pulmonary functions patient with diabetes mellitus. Lung India. 2011; 28: 89-92.
26. Kaparianos A, Argyropoulou E, Sampsonas F, Karkoulias K, Tsiamita M, Spiropoulos K. Chronic complications in diabetes mellitus. Chronic Respiratory Disease. 2008; 5: 101–108.
27. Shah SH, Sonawani P, Nahar P, Vaidya S, Salvi S. Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic control and duration of the disease. Lung India. 2013; 30: 108-12.

28. Augusto L, Ross L, David S, Debbie D, Scott W. Lung function in type 2 diabetes: the Normative Aging Study. Respiratory Medicine. (2005); 99: 1583–90.
29. Amal A , Gehan H , Mohamed A, Alaa R. Pulmonary function changes in diabetic lung. Egyptian Journal of Chest Diseases and Tuberculosis. (2013); 62: 513–7.
30. Benbassat CA, Stern E, Kramer M, Lebzelter J, Blum I, Fink G. Pulmonary Function in Patients with Diabetes Mellitus. Am J Med Sci. 2001; 322(3):127–32.
31. Kaminsky DA. Spirometry and Diabetes; implications of reduced lung functions. Diabetes care. 2004; 27(3):837-8.
32. Gita S, Mohammad Kh, Nader R, Rokhsareh A, Mojtaba M. Alteration of pulmonary function in diabetic nephropathy. Journal of Diabetes & Metabolic Disorders. 2013; 12: 15.
33. Michael G. Lung Dysfunction in Diabetes. Diabetes Care. June 2003; 26(6):1915-8.

پوختە

کاریگەریا بلندبونا شەکرێ لسەر کارێن سیها

پێشەکی و ئارمانج: بلندبونا شەکرێ نەخوشیەکا ترسناکە ژئەگەرێ بلندبونا ئاستێ ئەنسولینی و هەروەسا نە کارکرنا وێ ب شیوەکێ دورست پەیدا دبیت. هەبونا ڤێ نەخوشیێ بو ماوەیەکێ درێژ دبیتە ئەگەرێ پەیدابونا ژمارەکا زور یا سەربارکا.

رێکێن ڤەکولینێ: ئەڤ ڤەکولینە هاتە ئەنجامدان ل لسەر ٥٨ نساخێن شەکرێ و ٣٠ کەسێن نورمال وەک گروپا کونترول. سەرەرای ئەنجامدانا تاقیکرنێن پێدڤی, ئەمجامدانا تاقیکرنا کارێن سیها بو وان هاتە کرن برێگا ئامیرێ سپایرومیتری.

ئەنجام: ئەنجامین ڤەکولینێ دیارکرن کو ٦٨,٨٪ ژ نەخوشێن شەکرێ تەنگەنەفەس بو چێدبیت و ب بورینا دەمی ئەڤ چەندە دژوارتر لێ دئێت. بهایێ FVC د گروپێ شەکرێ و کونترولی دا (٢,٤٣ و ٢,٨٣ لتر) لدیف ئێك دگەل ژێکجوداهیا (p=0.03) و بهایێ FEV1 دگروپێ شەکرێ و کونترولی دا (٢,٣٢ و ٢,٧٥ لتر) لدیف ئێك دگەل ژێکجوداهیا (p=0.02)، بەلێ چ ژێکجوداهیا بەرچاڤ د FEV1/FVC دا نە هاتە دیتن. هەروەسا ئەو نساخین سەربارك پتر هەین, تەنگەنەفەس لدەف وان برێژەیەکا دژوارتر (٥١,٧٢٪) بەراوەر دگەل بێن سەربارك نەی (٢٠,٦٨٪) ب ژێکجوداهیا (p=0.05). دیسان ژێکجوداهیەکا بەرچاڤ هەیە دناڤبەرا هەردوو گروپا دا د بهایێ خروکێن سپی دا و C-reactive protein.

دەرئەنجام: سیهێن نەساخێن شەکرێ جورەکێ تەنگەنەفەسێ هەیە و ئەف چەندە ب رێکا کلینیکی نا ئێتە دیارکرن. هەروەسا ب بورینا دەمی ئەڤ چەندە دژوارتر لێ دئێت لەوما ئەم دکارین بێژین کو سیهـ دبیت بهێتە هەژمارتن وەک قوربانیەکێ نەساخیەما شەکرێ ب بورینا دەمی.

الخلاصة

تأثير داء السكري على وظائف الرئة

الخلفية: داء السكري هو خلل افرازي ايضي ناتج عن قصور او غياب لوظيفة الانسولين والذي يتميَز بارتفاع فوق الطبيعي لمستوى سكر الدم والمؤدي لسلسلة من المضاعفات للاوعية الدموية الكبيرة والدقيقة. هدفنا هو تقييم اداء وظائف الجهاز التنفسي في مرضى السكري و بيان العلاقة بينهما.

طرق العمل

تضمنت هذه الدراسة ٥٨ مريضا بداء السكري و ٣٠ شخص اصحاء من حيث المظهر ككونترول. نُفّذتْ الوظائف الرئوية من خلال قياس FVC، FEV 1 و نسبة FVC / FEV 1، بإستعمال السبايروميتر الكمبيوتري (SpiroLap III).

النتائج:

اوضحت نتائج الدراسة ان ٦٨.٨% من مرضى السكري يعانون من الامراض االتنفسية المحددة بحيث وجدت فروق معنوية في حجوم الرئتين. حيث كانت قيم FVC في مجموعتي داء السكري والضابطة (٢.٤٣ و ٢.٨٣لتر) على التوالي وبفارق معنوي (p= 0.03) وقيم FEV1 في مجموعتي داء السكري والضابطة (٢.٣٢ و ٢.٧٥لتر) على التوالي وبفارق معنوي (p= 0.02) بينما لم تظهر فروق معنوية في النسبة بين FEV1 / FVC بين المجموعتين.

كذلك كان نسبة مرضى السكري من الذين لديهم مضاعفات المرض هم اكثر اصابة بالامراض االتنفسية المحددة بنسبة (٥١.٧٢%) مقارنة بالاخرين الذين ليس لديهم مضاعفات (٢٠.٦٨%) وبفارق معنوي (p= 0.05). بينما وجدت نسبة الامراض االتنفسية المحددة اكثر حدوثا عند مرضى السكري غير المسيطرين على مستوى سكر الدم مقارنة مع الذين لديهم سيطرة متوسطة وجيدة. كذلك وجود فروق معنوية بين المجموعتين في قيم عدد كريات الدم البيضاء ومؤشر الالتهاب (C–reactive protein) ولصالح مجموعة مرضى السكري.

الاستنتاج:

احجام رئتَي مرضى السكري قد تعاني اختلالاً وظيفيا اثناء مرض السكري وهذا الاختلال يتمثل في االانخفاض التدريجي لقوة العضلات التنفسية وكفاءة الرئتين تحت السريري والغير ملاحظ وشدَّتِها تكون أكثرَ حدّة خصوصاً في المرضى الذين عندهم قلة السيطرة على مستوى سكرِ الدم , مما يقودنا الى فكرة ان الرئتين يمكن ان تكونا هدفا لمضاعفات السكري

CAROTID ARTERY ATHEROSCLEROTIC DISEASE IN SYMPTOMATIC PATIENTS: DOPPLER STUDY

JIHAN H.TAHA, MBSHB, DMRD*
MAYSALOON S. SAEED, FIBMS**

Submitted 1 August 2015; accepted 30 December 2015

ABSTRACT

Background and Objectives : Stroke is one of the leading causes of death, which is known to be due to unstable plaques in the carotid vessels or stenosis of the carotid arteries , to detect carotid atherosclerosis in symptomatic patients with risk factors noninvasively using carotid Doppler ultrasonography .

Patients and Methods: A total of 66 patients, including 40 males and 26 females, aged between 37 and 89 years were assessed by carotid ultrasound, using grey scale, color, duplex and power Doppler. The stenosis, if present, was graded and characterized in detail in each of the enrolled patients.

Results: Grade 1 stenosis was the most common type followed by grade 2; while type 2 plaques were the most frequent , followed by type 4 .

Conclusions: Carotid Doppler is a valuable and non-invasive method for detecting carotid arterial stenosis, by providing valuable information about the plaques, their morphology, as well as the degree of stenosis.

Duhok Med J 2015; 9 (2): 44-51.

Keywords: carotid artery stenosis, stroke, plaque, Ultrasound.

Ischemia as a consequence of flow limited stenosis is a known predisposing factor for stroke[1]. It is known to be due to unstable plaques in the carotid vessels or stenosis caused by extensive atherosclerotis changes[2], so early detection of these changes will reduce morbidity and mortality[3]. Grey scale Ultrasound (US) is useful in evaluation of the increased intima – media thickness and in helping detect plaques morphology[4,5]. The intima–media thickness, increases with age, with a mean of (0.4–1.02)[6]. Color Doppler US, on the other hand, is useful in evaluating the pattern of blood flow, while pulsed wave US is useful in evaluating the flow and velocity indices, and degree of stenosis. Furthermore, power Doppler US is useful in detecting the remaining flow after severe stenosis.

The frequently used method for plaque characterization as suggested by Zwiebel (2005)[6] subdivides it into the following grades or types:

Grade (type 1) is uniformly echolucent, grade (type 2) is predominantly echolucent, grade (type 3) is predominantly echogenic due to calcification, grade (type 4) is uniformly echogenic also due to calcification, while grade (type 5) is unclassified due to poor vascularization.

To assess the degree of stenosis, certain

* *Department of Radiology , Azadi teaching hospital , Duhok*
** *Lecturer of Radiology , Departement of Surgery ,College of Medicine ,University of Duhok*
Correspondace to Dr maysaloon S Saeed, e.mail maysaloonshaman@gmail.com

criteria are used including: the diameter of the vessel lumen, plaque characterization, peak systolic velocities (PSV), end diastolic velocities (EDV) values, to divide the stenosis into: mild, moderate and severe.

Patients and methods: The current study is a descriptive cross sectional study, performed from June 1014 to February 2015, at the radiology department of Azadi Teaching Hospital. Sixty six patients with an age range of 37 to 89 years with symptoms of ischemic stroke were enrolled. Data were compared by the use of Chi- square test and Fisher's Exact test and a (p-value) of < 0.05 was considered significant.

A special questioner form was prepared including: age, sex, signs and symptoms, past history of ischemic changes, surgical and medical history. All enrollees are examined by using grey scale, color, pulse and power Doppler (Siemens, Acuson X300). PSV and EDV were measured by a high frequency waves (5–13MHZ), examining the common carotid artery (CCA), external carotid artery (ECA) and internal carotid artery (ICA), assessing the intima–media thickness, vascular diameter, grades of plaques characterization, percentage of the degree of stenosis. Power Doppler was used for the detection of residual string flow in severe stenotic cases.

RESULTS:

A total of 66 patients seen of whom 46 had stroke, while 20 had transient Ischemic attacks (TIA). Our main focus was on patients with Stroke. The latter group had a mean age of 65.7 years +6.1, and included 26 males. Hypertension was the most common risk factor (84 .7%), followed by diabetes mellitus (45.6 %)

Intima–media thickness (IMT): Twenty seven of the patients with stroke (58.7%) showed increase IMT which ranged 1-2 mm, IMT of less than 1 mm was seen in 18 patient.

Number of Plaques: No plaques were observed in 7 patients, whereas they had been seen in 39 patients. The bulb area was the most common site for plaque location accounting for 79.5% (31 patients), while the ICA plaques (proximal or mid segments) accounted for 20.5% (8 patients) (Table 1).

Table (1): Number and multiplicity of plaques

No. of plagues in a patient	No. of stroke patients	% of patients
None	7	15.2
1	23	50
2 or more	16	34.8
Total	46	100

Grading of Stenosis: Seven patients had no carotid artery stenosis accounted for 15.2% of stroke patients, five were females and two were males. The IMT ranged from 0.8mm–1.4mm. Gray scale US showed no plaques in these patients.

Nine patients showed bilateral stenosis, six were males and three were females. Bilateral infarction was seen in five of these patients, two males and three females. Six patients had grade I stenosis bilaterally, another three showed variable degrees of stenosis between the right and left ICA (Table 2,3).

Table (2): Age group and gender versus number of patients with unilateral stenosis

Age	Grade I		Grade II		Grade III		Grade IV		Grade V		Total
	M	F	M	F	M	F	M	F	M	F	
40-49	3										3 (10%)
50-59	1	1	1								3 (10%)
60-69	5	4				1			2		12 (40%)
70-79	4	3	2					1			10 (33.3%)
80-89		2									2 (6.7%)
Total	13	10	3			1		1	2		30 (100%)

Table (3): Age group and gender versus number patients with bilateral stenosis

Age	M	Grade of stenosis		F	Grade of stenosis		Total
		Right	Left		Right	Left	
40-49							
50-59							
60-69	1	I	I	1 1	I III	I I	3(33.3%)
70-79	3 1	I V	I II	1	I	I	5(55.6%)
80-89	1	I	II				1(11.1%)
Total	6			3			9(100%)

Grade I Stensosis (Less than 50 %)

This was seen in 23 patients with unilateral stenosis, six patients with bilateral stenosis in both sides and two patients with bilateral stenosis in one side only (in one of them in the contra lateral side of infarction).

These patients showed the PSV at the stenotic area of up to 110cm/s, EDV of up to 23.9cm/s as upper values and the ratio of the ICA /CCA PSV was up to 1.9 as an upper limit.

The most common type of plaque in patients with grade one stenosis was type II (risky) accounting for 23 of plaques (59%) from total of 39 plaques that caused grade I stenosis.

Type IV and type V (calcified) were seen in 2 plaques together accounting for 5 % (Table 2-4).

Spectral broadening was seen at 25 % stenosis and above.

Grade II Stenosis (50-69%)

Total of 5 patients, 3 patients with unilateral stenosis and 2 patients with bilateral stenosis (in one of them in the contra lateral side of infarction).

The PSV was seen up to 180 cm/s, EDV up to 60 cm/s and the ICA/CCA PSV ratio up to 3.8 as upper limits.

The most common type of plaques were type I and type II plaques seen in 9 plagues (60 %) from total of 15 plaques that caused

grade II stenosis, one plaque of type V was also detected (6.6%) (Table 2 ,3, 4).
Color Doppler imaging showed narrowing of the stream of the blood flow with a filling defect and high velocity jet at the site of stenosis. The black spectral window was filled (broadened) due to the turbulent flow and variable velocities.

Grade III Stenosis (70% to near occlusion)
This was seen in two patients, one of them with unilateral stenosis and the other one with bilateral stenosis in the ipsilateral side of infarction. In both patients type II plaque was found (100%).
The PSV was noticed up to 247cm/c, EDV of up to100 cm/c and the ratio of more than 4 as upper limits. Color Doppler imaging showed more narrowing of the steam of flow. Spectral wave form showed aliasing. Spectral broadening was very clear with filling of the whole spectral window.

Grade IV Stenosis (Near Occlusion)
This was seen in one patient with unilateral stenosis (ipsilateral side of infarction). In this patient, type1 plaque (echolucent and risky) was found which was difficult to detect on gray scale (Table 2-4). Color Doppler imaging showed a very narrow stream of flow (string sign), and power Doppler helped more in the diagnosis. The PSV was 35cm/s

Grade V Stenosis (Total Occlusion)
This was seen in three patients, two with unilateral and one with bilateral stenosis in the ipsilateral side of infarction in all (table 2-4).
In these patients the lumens of the whole ICAs were filled with internal echoes, without detected flow on color, power Doppler imaging so the pulsed wave, even with low flow settings, there were reverse of flow on color Doppler imaging at the site of stenosis without detected flow beyond the obstruction.

Table (4): Type of plaque versus degree of stenosis

Percentage stenosis	Type of plaque										Total
	I		II		III		IV		V		
	No.	%	No.	%	No	%	No.	%	No.	%	
<50	2	5.1	23	59	12	30.7	1	2.5	1	2.5	39
50-69	5	33.3	4	26.6	2	13.3	3	20	1	6.6	15
70 or more			2	100							2
Near occlusion	1	100									1
Total Occlusion	3	100									3

Plaque Surface Type: Irregular plaques were observed in 22 patients (56.4%), smooth plaques in 11 (28.2%) and ulcerated plaques in 6 patients accounted for (15.4%).
Eighteen out of 20 TIA patients (90%) showed carotid artery stenosis. Thus the

sensitivity of carotid Doppler in stroke and TIA were 84.7% and 90% respectively.

Discussion: Thirty nine out of 46 stroke patients showed evidence of carotid artery stenosis while 7 patients showed none, thus the sensitivity of carotid Doppler was 84.7 %which is nearly similar to that found by Rajesh and Tiwari (2013) which was 84% in stroke patients.[7]

In our study the mean IMT for stroke patients was 1.1 mm which was lower than that found by Rajesh and Tiwari (2013), which was 1.73 mm, but higher than that found by Sahoo et al (2009) which was 0.78 mm.[7,8]

In our study 39 patients (84.7%) had plaques, which is similar to that reported by Rajesh and Tiwari (2013) at 84 % , but is higher than that reported by Al-Najim et al (2007) which was 63 % and much higher than reported by sahoo et al (2009) at 30% .[7-9]

Sixteen patients had multiple plaques , the CCA bulb was the most common type of plaque formation (79.5%), while ICA formed 20.5%.

Irregular plaques were the most common type seen (56.4%) while smooth and ulcerated plaques were seen in 28.2% and 15.4% respectively, these were similar to earlier studies[7,10].

Most of the plaques (65%) caused grade 1 stenosis , this contradicts that reported by Rajesh and Tiwari (2013) where 43% of plaques caused grade 2 , and of that of Al-Najim et al (2007) where 50% had grade 3 and 4, this may be explained by the facts that it is not necessary to find higher grades of stenosis as a primary cause of stroke, since the nature of the plaque itself (ulceration and heterogeneity of plaque) play as an important cause of stroke development, and secondly coexistence of atherosclerosis in the intra cranial cerebral arteries cannot be excluded.

Stenosis of 70% and more (grade 3 and more) was observed in 10% of stroke patients, which is consistent with previous reports[7].

CONCLUSION:

Doppler ultrasound of carotid arteries is valuable as a non-invasive, safe procedure which provides valuable information about the morphological and functional or hemodynamic status of the carotid vessels and may help determine the treatment protocol. Moreover, power doppler was quite valuable in detection of total occlusion of the carotid artery.

REFERENCES:

1- Sims, M. R. and Muyderman, H. Mitochondria oxidative metabolism and cell death in stroke. Biochimica et Biophysica Acta .Molecular Basis of Disease. 2010; Elsevier; 1802: 80-91

2- Brant , W. E. and Dougherty, R. S. Vascular Ultrasound. In: W. E. Brant, C.A. Helms (eds.). Fundamentals of Diagnostic Radiology, 4th ed., Vol.3, Philadelphia; Lippincott Williams and Wilkins . 2012 ; p. 954-87

3- Bluth , E. I., Carroll, B. A. The extra cranial cerebral vessels, In: C. M. Romack, S.R. Wilson, W.J. Charboneau, and D. Levin (eds.). Diagnostic Ultrasound, Vol. 1, 4th ed., 2011; Elsevier Mosby: p. 948-94.

4- Polak J F. Intima-media thickness: A tool for atherosclerosis imaging and

event prediction. The American Journal of Cardiology.2002; 14:244-69

5- Sitzer M., Muller W , Sielber M. and Hort, W. Plaque ulceration and lumen thrombus are the main source of cerebral micro emboli in high – grade internal carotid artery stenosis. Am heart Assoc. 1995 ; 8: 456-61

6- Zwiebel , W. J. Ultrasound assessment of carotid plaque. In: W. J. Zwiebel (ed.). Introduction to Vascular ultrasound, 5th ed., New York; Elsevier Saunders.2005; p. 155-69

7- Rajesh , M., Tiwari, R. Carotid Doppler Evaluation of Transient Ischemic Attack and Stroke Patients and it`s correlation with the CT scan head: A prospective study. In: IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) . 2013 ; 7: 20 – 25

8- Sahoo , R., Krishna, V. M., Subrahmaniyan, D.K.S., Dutta, T. K., Elangovan, S. Common Carotid Intima –media thickness in acute ischemic stroke: A case Control Study. Neurology India. 2009 ;57: 627-30

9- James C, Gotta M . Carotid Stenosis . N Engl. J Med.2013 ;369 : 1143-1150

10- Schminke D., Motsch M. Three Dimensional ultrasound observation of carotid artery plaque ulceration. Stroke .1997 ;28: 243-47

پوختە

ڤەکولینەك ل دور بکارئینانا ئامیرێ سونارا (دوبلەر)ی ل دەڤ نەخوشێن کو تەنگ بوون و گرتنا خوین بەرێن سەری یێن مەزن هەی

پێشەکی: تەنگ بوون یان گرتنا خوین بەرێز سەری یێن مەزن ژ ئەگەرا کومبوونا کەرستێن چەوری کو پاشی دبنە ئەگەرا چێبوونا چەوریە پلێتا و دئەنجامدا خوین ب کێمی دگەهیتە مێشکی و لبەر ڤێ چەندێ خوین مەینیا مێشکی پەیدادبیت، ئامیرێ سونارا دوبلەری رۆلەکێ تایبەت هەیە بو پشکنینا رەق بوونا ڤان خوین بەرێن مەنێ.

بو هەلسەنگاندنا نەخوشێن خوین مەینیا مێشکی ب ئامیرێ سونارا دوبلەری بو دیارکرنا پلا تەنگ بوونا خوین بەرێن سەری یێن مەزن و د یارکرنا چەوریە پلێتا و دیارکرنا نەخوشێن مەترسیا توشبوونا ڤێ نەخوشیێ هەی.

نەخوش و رێك: ئەڤ ڤەکولینە هاتەکرن ل خزیرانا ٢٠١٤ تا کو شوباتا ٢٠١٥ پشکنینا نەخوشێن خوین مەینیا مێشکی یا دومدرێژ و دەمکی ب ئامیرێ سونارا (دوبلەری) (Simens, Acuson x 300) هاتەکرن هەژمارا نەخوشان (٦٦) بوون (٤٠ نێر) و (٢٦) مێ.

ئەنجام: نەخوشێن ئەڤێن کو خوین مەینیا مێشکێ دومدرێژ هەی، تەنگ بوونا خوین بەرا ژ جورێ I مشەترین تەنگ بوون، تەنگ بوون ژ جورێ III پتر هاتە دیتن ب رێژێت جوراوجور، مشەترین جورە چەوریە پلێتا دناڤ ڤان نەخوشاندا جورێ II (مەترسیدار) بوو. بلندبوونا فشارا خوینێ و نەخوشیا شەکرێ هاتە دیتن دناڤ نەخوشێن خوین مەینیا مێشکی یا دومدرێژ و دەمکی.

دەرئەنجام: سونارا دوبلەری رۆلەکێ هەرەگرنگ هەیە بو پشکنینا نەخوشێن رەقبوونا خوین بەرێن سەری یێن مەزن.

الخلاصة

دراسة عن استخدام السونر الملون لدى المرضى الذين يعانون من تضيق وانسداد الشريان السباتي

الخلفية والأهداف: أي تضيق أو انسداد في الشرايين السباتية نتيجة تراكم الترسبات الدهنية التي فيما بعد تكون اللوحات , تؤدي الى نقص تدفق الدم للدماغ وبالتالي حدوث الجلطة الدماغية التي ينتج عنها الموت أو الاعاقة أحياناً.
يلعب جهاز أمواج الدوبلر فوق الصوتية دورا مهما في تشخيص مرض تصلب الشريان السباتي.
لتقييم مرضى الجلطة الدماغيةبأمواج الدوبلر فوق الصوتية وتحديد درجة تضيق الشرايين السباتية وتحديد نوع اللوحات وبيان المعرضين لخطر الاصابة بالمرض.
المرضى وطرق البحث: هذه دراسة مقطعية ووصفية تمت في حزيران ٢٠١٤ حتى شباط ٢٠١٥ عن مرضى الجلطة الدماغية الدائمة والعابرة , تضمنت الدراسة ٦٦مريض (٤٠ ذكر- ٢٦ انثى). تم فحص المرضى بأمواج الدوبلر فوق الصوتية باستعمال جهاز(Simens, Acuson X 300) .
النتائج: بالنسبة لمرضى الجلطة الدماغية الدائمة وجد التضيق من الدرجة الاولى والثانية اكثر شيوعا,التضيق من الدرجة الثالثة وأكثر وجد بنسب متفاوتة في مرضى الجلطة الدماغية الدائمة، اللوحات من النوع الثاني (الاكثر خطورة) كانت الأكثر شيوعافي مرضى الجلطة الدماغية الدائمة. في الجلطة الدماغية الدائمة والعابرة تبين أن ارتفاع ضغط الدم و يليه مرض السكر اكثر شيوعا.
الاستنتاجات: لوحظ من الدراسة الحالية أن لأمواج الدوبلر فوق الصوتية دور مهم في تشخيص مرض تصلب الشريان السباتي.

THE PREVALENCE OF THYROID DYSFUNCTION AMONG WOMEN WITH TYPE 2 DIABETES MELLITUS IN DUHOK

SHERWAN F. SALIH M.B.ch.B, FIBMS*

Submitted 15 September 2015; accepted 31 December 2015

ABSTRACT

Background: Diabetes mellitus has become a major health problem worldwide, and is commonly associated with thyroid dysfunction. The aim of the study was to evaluate the prevalence of thyroid dysfunction among type 2 diabetic women.

Methods: A cross sectional study was conducted on 534 women with type 2 diabetes mellitus, in diabetes and endocrinology unit in Azadi Teaching Hospital, Duhok, from 1st February to 30th of July, 2015. All the women were investigated for serum thyroid stimulating hormone, total T4, total T3, free T4, free T3, plasma glucose concentration and whole blood HbA1c percentage. The correlation of the prevalence of thyroid dysfunction with age, HbA1c, duration of diabetes mellitus, blood pressure and body mass index were done.

Results: There was a high prevalence of thyroid dysfunction in women patients with type 2 diabetes mellitus (24.2%). From this thyroid dysfunction, subclinical hypothyroidism (12%) and subclinical hyperthyroidism (9.6%) were most common. The higher incidence of thyroid dysfunction was found in women with age between 51 and 70 years, body mass index more than 30 kg/m2.

Conclusion: We concluded that all women patient with type 2 diabetes mellitus need a routine measurement of the thyroid function tests and more specifically those women with advanced age and high body mass index.

Duhok Med J 2015; 9 (2): 52-59.

Keywords: Type 2 diabetes mellitus, Thyroid dysfunction.

Thyroid diseases and diabetes mellitus are the most common endocrine diseases encountered in clinical practice[1]. The association between diabetes mellitus and thyroid diseases is widely known, and the relationship between both is characterized by complex interaction of interdependence[2]. Normal cell metabolism depends up on the presence of both insulin and thyroid hormones, excess or deficiency in any one of these can results in functional derangement of the other[3]. Deterioration in thyroid function in diabetes mellitus can cause a number of problems at both hypothalamic levels which control the release of thyroid stimulating hormone and at peripheral level which control the conversion of T4 to T3 such as increase incidence of hypoglycemia in hypothyroidism and life threatening ketoacidosis in hyperthyroidism[4]. Screening of thyroid diseases, especially the subclinical dysfunction in patients with diabetes mellitus is justified because most patients can be asymptomatic[5]. The prevalence of thyroid diseases is increases with increasing the age[6]. Hypothyroidism is the most common thyroid diseases in the adult population, which is associated with

**Lecturer, Department of Clinical Biochemistry, College of Medicine, University of Duhok, Duhok, Iraq*
Correspondence author: SHERWAN F. SALIH. Email sherwanaldarwish1972@gmail.com

insufficient thyroid hormones production, causing weight gain, slow heart rate, cold intolerance and depression[7]. By complete contrast, hyperthyroidism is less common, which is associated with excess thyroid hormones production, causing weight loss, rapid heart rate, heat intolerance and irritability[8]. All these need proper evaluation to be considered. As data on the subject is scare particularly in the women of Duhok. Therefore this study is designed to assess the magnitude of the problem of thyroid dysfunction in the women with type 2 diabetes mellitus.

MATERIAL AND METHODS

A cross sectional study was conducted on 534 female patients with type 2 diabetes mellitus who attended the diabetes and endocrinology unit in Azadi Teaching Hospital in Duhok city, for treatment and follow up. The study was carried out from 1st of February to 30th of July, 2015. Informed consent was taken from the respondents after explaining the objective of the study. After an overnight fast, 6ml of the venous blood was drawn from antecubital vein of the patients by using sterile disposable syringe. Two ml of the blood was collected into a sodium fluoride tube for glucose measurement, another 2 ml of the blood was collected into EDTA tube for HbA1c measurement and the last 2 ml of the blood was collected into plain tube for thyroid hormones measurement which include thyroid stimulating hormone, total T4, free T4, total T3 and free T3. The sodium fluoride tubes and plain tubes were centrifuged at 3000 to 4000 rotation per minute with collection of the plasma and serum respectively, which were processed within one hour of collection. Measurement of the whole blood HbA1c was by DCA Vintage analyzer which depends up on HPLC principle, whereas the measurements of both plasma glucose and serum thyroid hormones were by Cobas 6000 which depend up on glucose oxidase method principle and electrochemiluminescence principle.

The diagnosis of diabetes mellitus was based on the criteria by the American Diabetic Association[9], which includes fasting plasma glucose equal or more than 126mg/dl, or random plasma glucose equal or more than 200 mg/dl or taking hypoglycemic drugs and or insulin. The patients were classified as overt hypothyroidism when the thyroid stimulating hormone (TSH) levels were high (TSH > 4.2 mIU/ml) and the free T4 levels were low (FT4 < 6.4 pmol/L). Patients with normal TSH (TSH between 0.4 and 4.2 mIU/ml) and normal FT4 (FT4 between 6.4 and 20.6 pmol/L) levels were considered to be euthyroid. Patients with low TSH (TSH < 0.4 mIU/ml) and the free T4 levels were high (FT4 > 20.6 pmol/l) were classified as clinical hyperthyroidism. Patients with increased TSH above the reference interval (TSH > 4.2 mIU/ml) and thyroid hormone level within the normal reference interval were classified as subclinical hypothyroidism. Patients with decreased TSH below the reference interval (TSH < 0.42 mIU/ml) and thyroid hormone levels within the reference interval were classified as subclinical hyperthyroidism[10]. Blood

pressure was measured in the left arm in the supine position, 3 readings were taken and the mean value of the 3 readings was taken as the final recording. Hypertension was considered to be present if the systolic BP is >140 mmHg or the diastolic BP is >90 mmHg[11]. The waist circumference was measured at the plane between the anterior superior iliac spines and the lower costal margins at the narrow part of the waistline while the patient was standing and during slight expiration. Body mass index was calculated using Quetlets index (BMI equal to weight in kilogram divided by square height in meter). The BMI was defined as follow, normal body weight (< 25 kg/m2), overweight (25 to 29.9 kg/m2) and obese (> 30 kg/m2)[12]. HbA1c less than 7.0% was defined as good control, between 7.0% and 8.0% fair control, while more than 8.0% was considered a poor control[13]. The prevalence of thyroid dysfunction was calculated and associated with age distribution, body mass index, fasting plasma glucose, HbA1c, blood pressure, duration of diabetes mellitus and family history of diabetes mellitus. Statistical analysis was performed using SPSS, version 19 (Statistical Package for the Social Sciences).

RESULTS

The main characteristics of the study patients are described in Table 1. The mean age was 53.77+9.85. It was found that a high percentage of the females (58.3%) with age between 51 to 70 years, 61.8% had body mass index more than 25 kg/m2 and 66.11% had poor glycemic control (HbA1c >8.0%).

Table 1 Patients characteristics

Characteristics	Mean +SD	number (%)	*p*-value
Age (years)	**53.77 ± 9.85**		
31 – 40		**70(13.2)**	**0.06235**
41 – 50		**154(28.5)**	
51 – 60		**182(34.5)**	
61 – 70		**128(23.8)**	
BMI (kg/m^2)	**30.25± 6.40**		
< 25		**204(38.2)**	**0.028707**
25–29.9		**117(21.9)**	
≥ 30		**213(39.9)**	
HbA1c (%)	**8.91±1.85**		
< 7		**64(11.98)**	**0.660029**
7-8		**117(21.91)**	
>8		**353(66.11)**	
BP (mmHg)			
Systolic	**134±21.3**		
Diastolic	**85.7±9.5**		
Yes		**210(39.3)**	**0.889467**
No		**324(60.7)**	

Of the five hundred and thirty four patients, 129 (24.2 %) had thyroid dysfunction, about half of these 64(12%) had subclinical hypothyroidism. Out of 129 patients, 51(9.6%) had subclinical hyperthyroidism, and the remainders 405 (75.8%) were euthyroid (Table 2). Women in 51-70 year age group had a higher incidence of thyroid dysfunction as compared to the other age groups (P=0.007). Women with a BMI of more than 30 kg/m2 had a higher incidence of thyroid dysfunction as compared to those with overweight and normal weight group (p=0.004). Majority 91(70.6%) of women with thyroid dysfunction had poor glycemic control (Table 3).

Table 2 Distribution of thyroid dysfunction in the study patients

Thyroid diseases	number (percent)
Euthyroid	405(75.8%)
Subclinical hypothyroidism	64(12%)
Subclinical hyperthyroidism	51(9.6%)
Overt hypothyroidism	8(1.5%)
Clinical hyperthyroidism	6(1.1%)
All	534(100)

Table 3 Association of thyroid dysfunction with Age, BMI, HbA1c and BP

Variables	thyroid diseases n(%)	p value
Age (years)		
31 – 40	3(2.32)	0.0078
41 – 50	25(19.3)	
51 – 60	49(37.9)	
61 – 70	52(40.48)	
BMI (kg/m^2)		
< 25	54(41.86)	0.0047
25–29.9	23(17.83)	
≥ 30	52(40.31)	
HbA1c (%)		
< 7	12(9.3)	0.30626
7-8	26(20.1)	
>8	91(70.6)	
Hypertension (mmHg)		
Yes	71(55.14)	0.11234
No	58(44.86)	

DISCUSSION

It has been found that thyroid diseases and diabetes mellitus are strongly associated, and this has important clinical implication for treatment required[14]. Diabetes mellitus and thyroid diseases are independent risk factors of cardiovascular diseases[15]. The most striking findings of our study were a high prevalence of thyroid dysfunction (24.2%). This study revealed that 12% of diabetic women had subclinical hypothyroidism, 9.6% had subclinical hyperthyroidism, 1.5% had overt hypothyroidism and 1.1% was clinical hyperthyroidism. It is therefore, such a high prevalence of thyroid dysfunction in the diabetic women is especially noteworthy because several factors are observed to impact negatively on thyroid status[16]. Of these can be age, gender, weight and insufficient intake of dietary iodine. In the present study, out of 129 diabetic patients who had thyroid dysfunction, 101(78.3%) patients were of age between 51 and 70 years. The advanced age is known to increase the prevalence of thyroid dysfunction[6]. Thus; the prevalence of thyroid dysfunction is likely to be high in a population with age of more than 50 years[15]. Moreover, patients included in our study were females, had a high mean of BMI and possibly at low dietary iodine intake. However, dietary and non-dietary factors are known to be associated with thyroid dysfunction. Therefore, the high prevalence of hypothyroidism in population reported here appears to be associated, at least in part, with low intakes of poorly available dietary iodine[17].

It is noteworthy that the majority of diabetic women were Kurd ethnicity and habitants of Duhok governorate in Iraq, an endemic area with iodine deficiency. Although we did not measure the urinary iodine levels, a study done by Rasheed showed that iodine deficiency is still a public health problem in Duhok Governorate[18].

The pathophysiology of thyroid diseases in DM is still unclear, however, as the thyroid diseases and DM have a common autoimmune etiology, the thyroid antibodies has been suggested to be the causative factors (immunological disturbance). Moreover, the cause may be due to complex interaction of common signals pathway of insulin modulation and feedback mechanism of thyroid hormones. However, the finding of a high prevalence of thyroid dysfunction in our study agrees with that reported by others[6].

This study concludes that diabetic women are at increased risk for thyroid dysfunction especially prevalent in old age group needs routine measurement of thyroid hormones.

REFERENCE

1. American Diabetes Association. The expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2002; 25(1): 3-20.
2. Hage M, Zantout MSM, Azar ST: Thyroid disorders and diabetes mellitus. J Thyroid Res. 2011; 439463.
3. Singh G, Gupta V, Sharma AK and Gupta N. Evaluation of thyroid dysfunction among type 2 diabetic

Punjabi population. Advances in Bioresearch 2011; 2(2): 3-9
4. Shah, S.N. Thyroid disease in diabetes mellitus. J Assoc Physicians India. 2007; 32(12): 1057- 1059.
5. Chen G, Juan W, Yinghua L, Huang B, Yao J, Jiang Q : Associations between cardiovascular risk, insulin resistance, β- cell function and thyroid dysfunction: a cross sectional study in She ethnic minority group of Fujian Province in China. Euro J Endocrinol 2010; 163(5): 775–782.
6. Sachin Bhavthankar, Mahesh Madole, Sachin Somwanshi et al. Evaluation of thyroid hormones in patients with type 2 diabetes mellitus. Journal of Medical Education & Research 2013; 3(2):33-39.
7. Mark P. J. Vander pump. The epidemiology of thyroid disease. Br. Med Bull 2011; 99 (1): 39-51.
8. Johnson JL. Diabetes control in thyroid disease. Diabetes Spectrum 2006; 19(3):148-153.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetic care, 2011; 34(1): 62-69.
10. Jain G, MarwahaTS, Khurana A, Dhoat PS. Prevalence of Thyroid disorders in Patients of type 2 Diabetes Mellitus. Int J Med and Dent Sci 2013; 2(2): 153-161
11. Awtry EH, Locscalo J. Coronary heart disease. In: Cecil Essential of Medicine. Capenter C; Griggs RC; and Locscalo J, Eds. 6th ed. Elsevier Saunders Inc. Philadelphia 2004: 87-173
12. Shiwaku K, Anuurad E, Enkhama B, Kitajima K, Yamane Y. Appropriate body mass index for Asian population. 2004: Lancet.27; 363, 1077.
13. Mehrotra R, Kalantar K, Adler S. Assessment of glycemic control in dialysis patients with diabetes: glycosylated hemoglobin or glycated albumin. Clin J Am Soc Nephrol; 2011: 6(7), 1520-22.
14. Palma CC, Pavesi M, Nogueira VG, Clemente EL, Vasconcellos Mde F, Pereira LC et al . Prevalence of thyroid dysfunction in patients with diabetes mellitus. Diabetology & Metabolic Syndrome 2013, 5:58
15. Turhan H, Yasar AS. High prevalence of metabolic syndrome among young women with premature coronary artery diseases. Coron Artery Dis. 2005: 16; 37-40.
16. Strieder TGA, Prummel MF, Tijssen JGP, et al. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease," Clinical Endocrinology 2003: vol. 59, no. 3, pp. 396–401.
17. Azizi F, Mehran L. experiences in the prevention, control and elimination of iodine deficiency disorders: a regional perspective. East Mediter Health J 2004: 10; 761-70.
18. Rasheed BA, Ahmad B. Urinary iodine level of primary school children in Duhok governorate. Hawler Medical University, College of Medicine, Iraq: 2013.

پوختە

بەربەلاڤبونا تئکچونا شولئ پەریزادئ لدەف ژنکئن ئیشا شەکرئ جورئ دووئ هەین لدهوکئ

پیشەکی: ئیشا شە کری یا بوویە ئیك ژ گرنکترین ئاریشین ساخلە میی ل هە موو جیهانیو, و ئە ف ئیشە یە گریدایە ب تیکجونا کاری (پە ریزادی)یە ,ئارمانج ژڤی فە کولینی ئە وا بو هە لسە نگاندنا بە ربەلافبونا تیکجونا کاری پە ریزادیە لدەف ژنکین توشبوی ب نە خوشیا شە کری ژ جوری دوی .

ریکین فەکولینی: فە کولینە ك ب شیوی study cross sectional لسە ر 534 ژنین توشبوی ب جوری دوی ژ ئیشا شە کری هاتینە وەرگرتن, ل هوبا شە کری (غدە الصمائ) ل نە خوشخانا ئازادی یا فیرکرنی د ماوی دنافبەرا ئیکی شواتی هە تا کو ۳۰ ی تە موزی ۲۰۱۵ لفی دە می نمونین خوینا فان هە مو ژنان هاتە وەرگرتن و پشکنینین free T3 TSH , free T4 , total T3, total T4 پشکنانا شە کرا د خوینی دا (ریژا شەکری) و شەکرا کومبفە بوی HbA1cهاتینە ئە نجامدان .

پەیوەندیەك دنافبەرا بەربەلافبونا تیکجونا کاری پە ریزادی دگەل ژیی ژنکان HbA1c, دەمی ئیشا شەکری ,بلندبونا فشارا خوینی, ئاماژی هەفسەنگیا لەشی (bad mass index) و دریژیا دورماندوری نافتەنگی waist circumference

ئەنجام: ریژەکا بلند یا بەربەلافبونا تیکجونا کاری پەریزادی لدەف ژنکین توشبوی ب جوری دوی ژ ئیشا شەکری, هاتە دیتن ٢٤,٢٪ ژیی تیکجونی. کیم کاریا پەریزادی یا بەرزە ١٢٪ و زیدەکاریا پەریزادی یا بەرزە ٩,٦٪ ژ هەمویان مشەتربون .

ریژەکا بلند یا جیبونا تیکجونا کاری پەریزادی لدەف ژنکین ژیی وان دنافبەرا ٥١–٧٠ سالی هاتە دیتن و هەروەسا یین ئاماژی هەقسەنگیا لەشی وان پتر ژ ٣٠ kg/m

دەرئەنجام: هەموو ژنکین توشبوی ب ئیشا شەکری ژ جوری دوی پیتفیە بهینە ژپشکنین کرن بو هورموناتین پەریزادی نەخاسمە یین ب نافسالفە جوین و یین ئاماژی هەفسەنگیا لەشی وان بلند .

الخلاصة

انتشار اختلال وظيفة الغدة الدرقية لدى النساء المصابات بالنوع الثاني من مرض السكري في دهوك

الخلفية والهدف: مرض السكري اصبحت واحدة من اهم المشاكل الصحية حول العالم, وهذا المرض مرتبط بشكل ملحوظ باختلال وظيفة الغدة الدرقية. الهدف من هذه الدراسة هي لتقييم انتشار اختلال وظيفة الغدة الدرقية لدى النساء المصابات بالنوع الثاني من مرض السكري.

طرق البحث: اخذت دراسة مقطعية على ٥٣٤ نساء مصابات بالنوع الثاني من مرض السكري في وحدة السكري والغدد الصماء في مستشفى ازادي التعليمي من الفترة ما بين الاول من شباط الى الثلاثون من تموز ٢٠١٥. تم اخذ عينات الدم من كل النساء واجري لهن فحص TSH, total T4, total T3, free T4, free T3, فحص السكر في الدم وفحص السكر التراكمي (HbA1c). تم ربط العلاقة ما بين انتشار اختلال وظيفة الغدة الدرقية مع العمر, HbA1c, مدة مرض السكري, ارتفاع ضغط الدم, مؤشر كتلة الجسم, محيط الخصر و اختلال الدهون.

النتائج: وجدت نسبة انتشار عالية من اختلال وظيفة الغدة الدرقية لدى النساء المصابات بالنوع الثاني من مرض السكري (٢٤.٢%). من هذا الاختلال, كان قصور الغدة الدرقية دون السريري (١٢%) و فرط نشاط الغدة الدرقية دون السريري (٩.٦%) الاكثر شيوعا. وجد حدوث نسبة عالية من اختلال وظيفة الغدة الدرقية لدى النساء من عمر ٥١ الى ٧٠ سنة او اللاتي مؤشر كتلة الجسم لديهن اكثر من (٣٠kg/m2).

الاستنتاج: بينت الدراسة أن كل النساء المصابات بالنوع الثاني من مرض السكري تحتاجن الى فحص هورمونات الغدة الدرقية خاصة المتقدمات بالعمر واللاتي مؤشر كتلة الجسم لديهن عالي.

COEXPRESSION OF HER2 AND P53 IN GASTRIC AND ESOPHAGEAL ADENOCARCINOMA

GINA GAMES GEORGE*
HAYDER HUSAIN IBRAHIM**
SARDAR HASSAN ARIF***
INTISAR SALIM PITY****

Submitted 1 October 2015; accepted 31 December 2015

ABSTRACT

Background and objectives: Gastric and esophageal adenocarcinoma remains deadly diseases with an on rise incidence. The recently discovered cancer-related molecular markers, such as HER2 and p53, help facilitate response to preoperative therapy and improve overall survival. This study was aimed to detect the immunoexpression of HER2 and p53 in gastric and esophageal adenocarcinoma and to determine the association of these two markers with clinicopathological parameters.

Method: The study was conducted in the Central Laboratory and Directorate of Health, Duhok-Iraq during a period from May 2009 to September 2014 on 101 gastric and esophageal adenocarcinoma cases. Using monoclonal antibodies against HER2 receptors and p53 nuclear protein, slides were stained with the fully automated immunostaining instrument, Ventana Benchmark.

Results: Total positive HER2 immunoexpression was demonstrated in 33.7% of cases with a significantly higher dense HER2 (3+) expression in esophageal adenocarcinoma compared with its gastric counterpart. p53 nuclear staining was observed in 62.4% of cases; it was significantly higher in gastric cancer than esophageal adenocarcinoma. HER2 was limited to the intestinal type whereas p53 was found to be expressed in both intestinal and diffuse types. No significant coexpression was demonstrated between HER2 and p53 in any of gastric or esophageal adenocarcinoma.

Conclusions: HER2 expression was limited to the intestinal type gastric adenocarcinoma. No significant coexpression of HER2 and p53 was demonstrated in both of gastric and esophageal adenocarcinoma.

Duhok Med J 2015; 9 (2): 60-73.

Keywords: HER2, p53, gastroesophageal adenocarcinoma.

Gastric and esophageal (gastroesophageal) adenocarcinomas form a substantial number of cancer cases with a dramatic rising incidence over the past 20 years, particularly among young adults[1-7]. The overall 5-year survival rates are up to 27% with no significant change over the past 40 years despite advances in surgical treatment and chemotherapy[2,4,5,6,8]. Discovery of new molecular markers and novel pharmacogenetic traits helped improve patients care, fostered hope and applied new directions of cure[9-12]. Markers

* *Lecturer in Pathology, Department of Pathology, College of Medicine, University of Duhok, Iraq.*
** *Assistant professor in Surgery, Department of Surgery, College of Medicine, University of Duhok, Duhok, Iraq.*
*** *Lecturer in Surgery, Department of Surgery College of Medicine, University of Duhok, Duhok, Iraq.*
**** *Professor in Histopathology, Department of Pathology, College of Medicine, University of Duhok, Duhok, Iraq.*
Correspondence: Professor Intisar Salim Pity, Pathology department,
E.mail: intisarsalimpity@gmail.com Mobile:07504788000

of interest include those contributed in growth regulation like human epidermal growth factor receptor-2 (HER2) and those involved in apoptosis and cell cycle control, like p53[8-12]. Given the advantages of both HER2 and p53 as responders for target therapy and predictors for better outcome in breast cancer, such properties facilitated numerous studies that are intriguing in identifying those markers in gastric adenocarcinoma. On the other hand although overexpression of HER2 and p53 in gastroesophageal adenocarcinomas may increase their dismal outcome with a resistance to the conventional chemotherapy, many ongoing studies conducted in this field are intriguing in that patients get benefit from specific therapy targeting these molecular markers, both for prognostic and therapeutic purposes[9,12].

The current study may provide an insight on the immunohistochemical expression of HER2 and p53 immunomarkers in gastric and esophageal adenocarcinoma in Kurdistan-Iraq. To the best of our knowledge, no previous study was conducted in the same field to evaluate the coexpression of HER2 and p53 in adenocarcinoma of stomach and esophagus in this particular area of Iraq.

MATERIALS AND METHODS

The study was conducted in the Central Laboratory/Directorate of Health, Duhok-Iraq. Specimens were retrieved from histopathologic laboratories in Duhok Region during the period from May 2009 to September 2014. Paraffin embedded, pretreatment (endoscopic biopsy or gastrectomy) specimens were available for 101 patients with newly diagnosed gastric (n=63) and esophageal (n=38) adenocarcinoma. Information pertaining to the patient's age at presentation, gender and type of operation were obtained from patient's request forms.

Four micron-thick tissue sections were taken from the tumor, processed and embedded in paraffin wax, then stained again with Hematoxylin and Eosin (H&E) stains to confirm the diagnosis of adenocarcinoma and for grading purposes. Tumors were classified into 2 types, intestinal and diffuse (signet ring). The intestinal-type adenocarcinomas were further graded, according to the modified WHO classification system, into low grades (well and moderately differentiated) and high grades (poor and undifferentiated). Pathological staging, applied only on gastrectomy specimens (n= 43), was done according to the pathologic TNM tired staging system from I-IV based on the microscopic examination of the primary tumor within organ wall, all available lymph nodes, omentum and any associated structure if available[13].

The immunohistochemical technique applied was streptavidin-biotin system, using monoclonal antibodies manufactured by Ventana Corporation (Ventana, Rocklin, Calif), the chromogen used was 3-3'-diaminobenzidine tetrahydrochloride (DAB) and a standard DAB detection kit (Ventana) was used according to instructions supplied by the manufacturer's (Ventana) and as described previously by Pity et al and Pity and Baizeed[14,15]. Representative tissue sections from the

tumor (without necrosis and little mesenchymal tissue) were selected from the paraffin blocks. Three µm tissue sections were cut with a manual microtome and mounted on poly-l-lysine-coated slides. Sections were placed in oven at 56-60 Cº overnight, then stained with a fully automated immunostaining instrument; Ventana Benchmark (Ventana Medical System Inc., Cell Margue, Ventana, Rocklin, Calif.) where deparaffinzation, dehydration, antigen retrieval in addition to the application of primary and secondary antibodies were achieved. The primary antibodies used included monoclonal antibodies for HER2 (REF-790-2991, Ventana, USA) and for p53 (REF-760-2542, Ventana, USA). Positive controls (strongly positive breast carcinoma for both HER2 and p53) and negative controls (using the same procedure without primary antibodies) were used with each run. Sections were counterstained with Mayer's hematoxylin, dehydrated through graded alcohols to xylen and then mounted with DPX solution and coverslipped.

Positive p53 protein expression was defined as clear nuclear immunostaining in more than 10% of tumor cells16. HER2 staining was evaluated as described by Hofmann et al who addressed 4-graded scales [grade 0 referring to tumors without detectable staining or membrane staining of less than 10%, grade 1+ pertaining to weak staining of greater than 10% of tumor cells, grade 2+ which is defined as weak to moderate staining of the entire cell membrane (thin ring) in more than 10% of tumor cells and grade 3+ reflecting moderate to strong staining of the entire cell membrane (thick ring) in more than 10% of tumor cells]17 . Both (0 and 1+) grade scales are considered negative while grade 2+ and 3+ indicate staining[18].

Statistically, the collected data were organized and tabulated, and descriptive statistics were used to summarize demographic variables. Chi square and Fisher exact tests were used for testing associations between categorical tumor parameters, and differences at the level of $p \leq 0.05$ were considered as statistically significant.

RESULTS

Patient's ages ranged between 28-90 years (mean: 61.7 years). Sixty six patients were males and 35 were females. Gastric specimens (n= 63) included 43 (68.3%) gastrectomy specimens and 20 (31.7%) endoscopic biopsies. All esophageal specimens (n=38) were endoscopic biopsies from the lower esophagus. Histologically, 49 (77.8%) gastric cases were intestinal type and the remaining 14 (22.2%) cases were diffuse type adenocarcinoma whereas all esophageal cancers were intestinal type adenocarcinoma. Thus the total (gastric and esophageal) intestinal type adenocarcinoma formed 87 cases; of these, 41 (47.1%) cases were low-grades and 46 (52.9%) were high-grades. Of the 43 gastrectomy specimens, the tumor (T) status comprised 2 (4.7%) T1, 10 (23.2%) T2, 26 (60.5%) T3 and 5 (11.6%) T4. The lymph node (N) status formed 11 (25.6%) N0, 21 (48.8%) N1, 8 (18.6%) N2 and 3 (7%) N3.

HER2 and p53 Expression

Positive HER2 membranous expression (scores +2 and +3) was demonstrated in 34 (33.7%) cases while p53 nuclear staining was observed in 63 (62.4%) cases. No significant association of any marker was observed with age and gender. The highest frequency of positive {20.8% of HER2 and 36.6% p53} cases was observed among 60-69 year age group (Figure 1), and there was trend toward male gender (Figure 2).

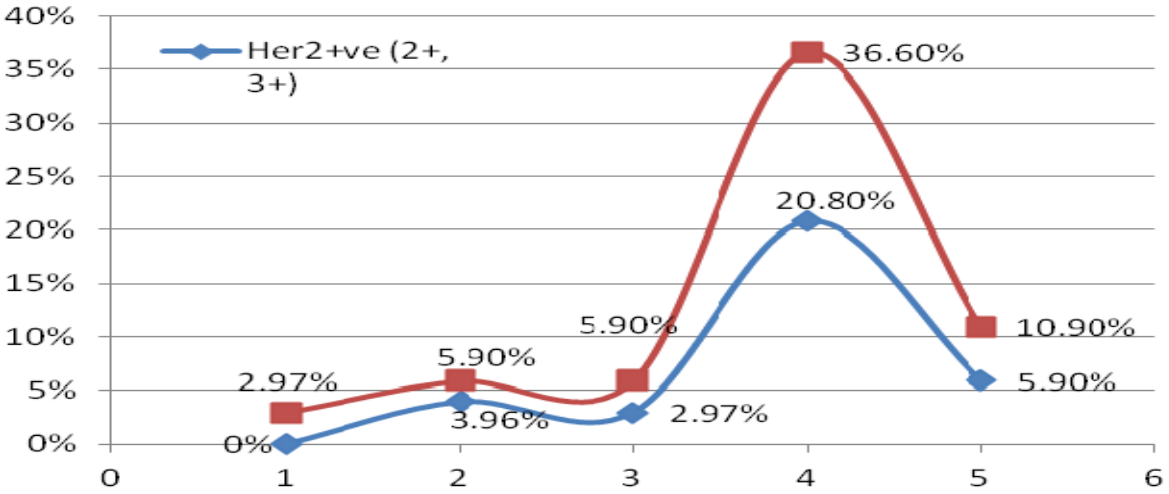


Figure 1. Age distribution for positive HER2 and p53 in gastroesophageal adenocarcinoma cases (Fisher exact test used, p= 0.5 for HER2 and 0.1 for p53).

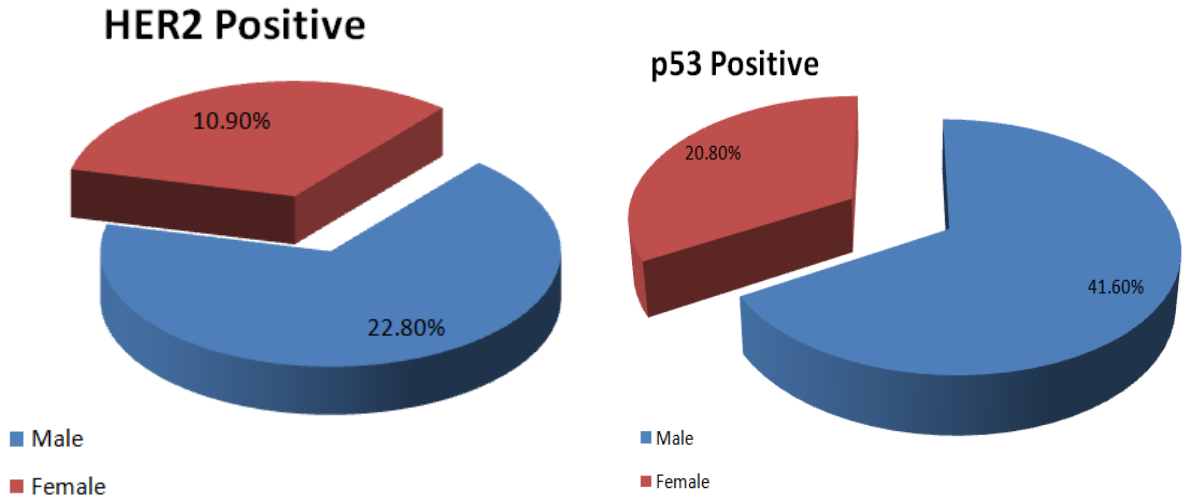


Figure 2. Gender distribution and positive HER2 (p= 0.06) and p53 (p=0.073). X^2 used.

Forty-five gastric and 22 esophageal cancers showed a negative HER2 (0/1+) expression. The remaining positive cases showed a significantly higher dense HER2 (3+) expression among esophageal compared with the gastric cases but lighter density HER2 (2+) was demonstrated only in GC where it was identified in 10.9% of cases (Table 1).

Much higher p53 nuclear expression was demonstrated in gastric 46 (45.6%) compared with the esophageal adenocarcinoma 17 (16.8%), p= 0.06.

Table 1. HER2 scores and site of adenocarcinoma.

	Gastric cancer	Esophageal cancer	Total
HER2			
Negative HER2 (0/+1)	**45 (44.6%)**	**22 (21.8%)**	**67 (66.4%)**
Positive HER2 (+2)	**11 (10.9%)**	**0 (0%)**	**11 (10.9)**
Positive HER2 (+3)	**7 (6.9%)**	**16 (15.8%)**	**23 (22.8%)**
Total*	**63 (62.4%)**	**38 (37.6%)**	**101 (100%)**
P53			
P53 +ve	**46 (45.6%)**	**17 (16.8%)**	**63 (62.4%)**
P53 -ve	**17 (16.9%)**	**21 (20.8%)**	**38 (37.6%)**
Total**	**63 (62.4%)**	**38 (37.6%)**	**101 (100%)**

*: X^2, p= 0.05, **: X^2, p= 0.08

Regarding the histologic type, as shown in figure 3 HER2 immunoexpression was demonstrated only in the intestinal adenocarcinoma. It was completely absent in the diffuse type. In contrast, p53 expression was more obvious in the diffuse (47.5%) than the intestinal type adenocarcinoma (14.9%), but the difference didn't reach the level of significant (p= 0.36).

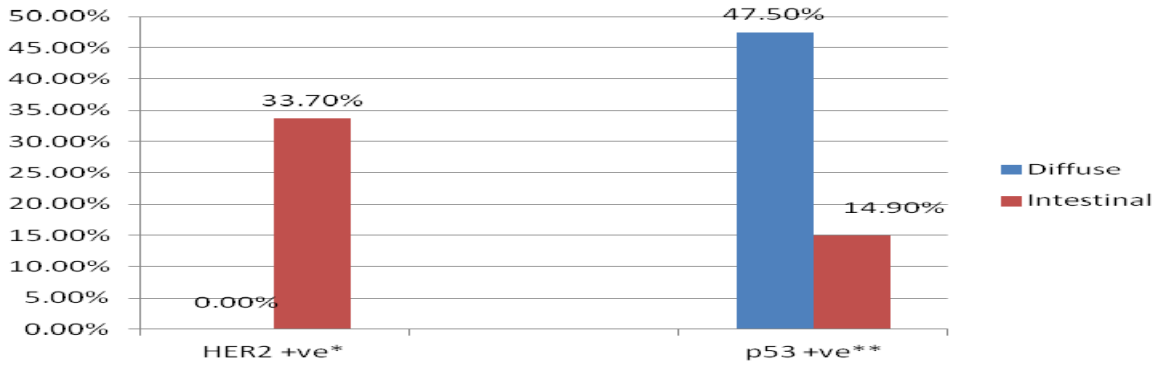
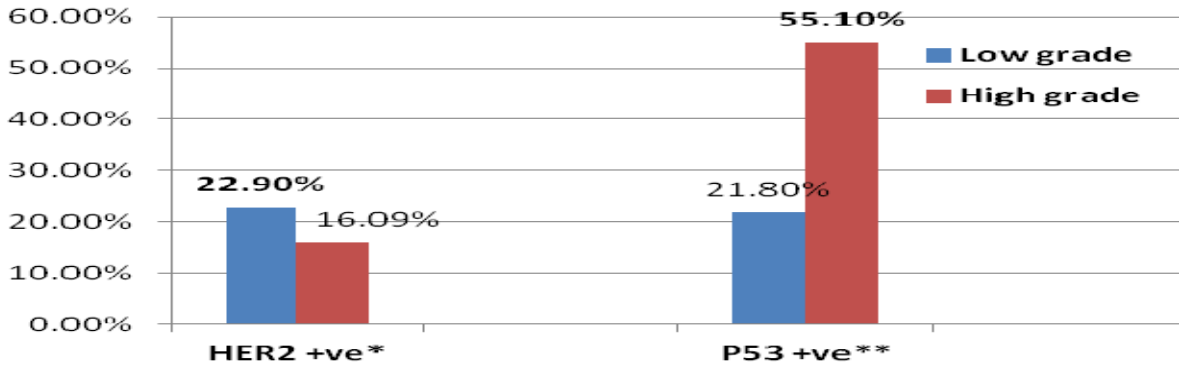


Figure 3. HER2 and p53 immunoexpression and histologic type of adenocarcinoma. (Fisher exact test, p= 0.36).

No statistical significance could be demonstrated between any marker and tumor grade. There was a trend for HER2 toward low grade tumors and p53 toward high grade cancers (Figure 4).



*p= 0.22, **p= 0.09 for p53.

Figure 4. HER2 and p53 immunoexpression and tumor grade.

Considering TNM staging, no significant association was demonstrated between any of HER2 or p53 and T-status despite a trend toward T3 (Figure 5).

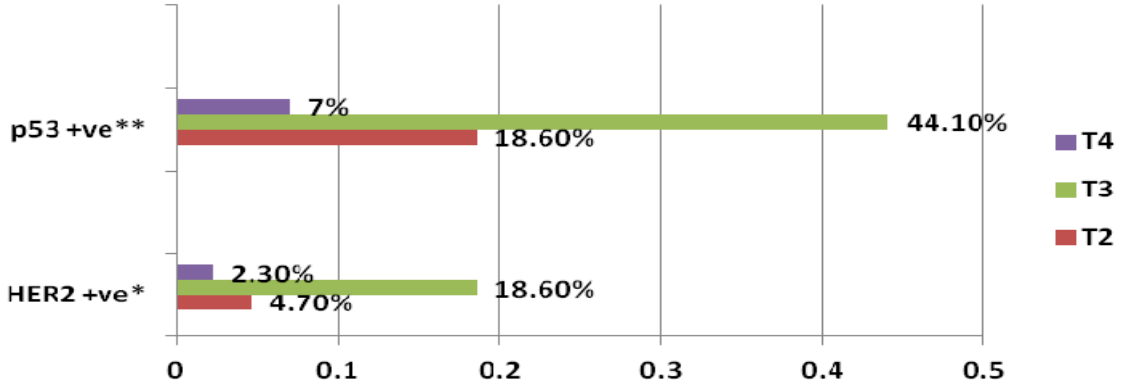


Figure 5. HER2 and p53 expression and T-status.
Fisher exact test used, *: p= 0.93; **: p= 0.14

As shown in figure 6, no statistical differences were observed between any of HER2 or p53 and N-status despite a trend for both markers toward N1.

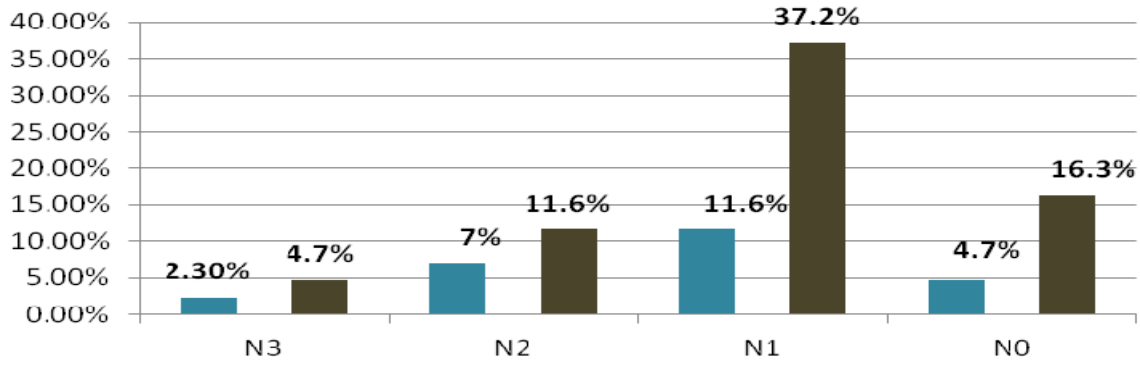


Figure 6. Distribution of gastric cancer cases, according to the the nodal (N) status (n= 43).
Fisher exact test used; *: p= 0.8; **: p= 0.87.

Coexpression of HER2 and p53

Among gastric cancer cases, 19.1% of cases illustrated coexpression of both markers and 53.9% showed negative HER2/positive p53. Lack of both markers was observed in 17.5% of cases, and the remainders (9.5%) showed positive HER2/negative p53. No significant association was found between presence and absence of the 2 markers (Figure 7).

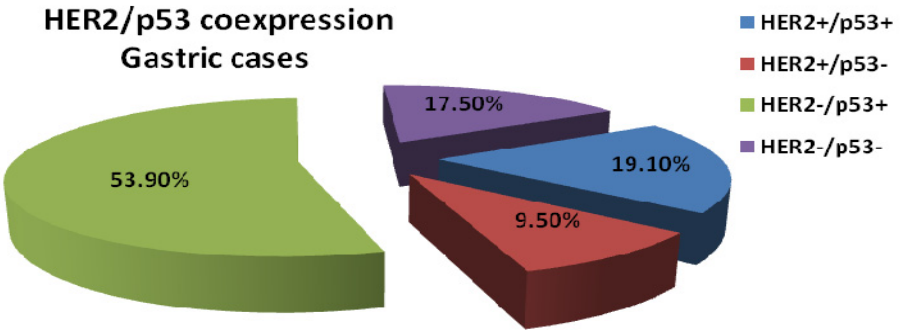


Figure 7. HER2/p53 coexpression in gastric adenocarcinoma, Fisher exact test used, p= 0.67.

On the other hand, all esophageal adenocarcinoma showed either absent HER2, p53 or both markers. No coexpression of both markers was demonstrated among esophageal cases. The difference was statistically significant (Figure 8).

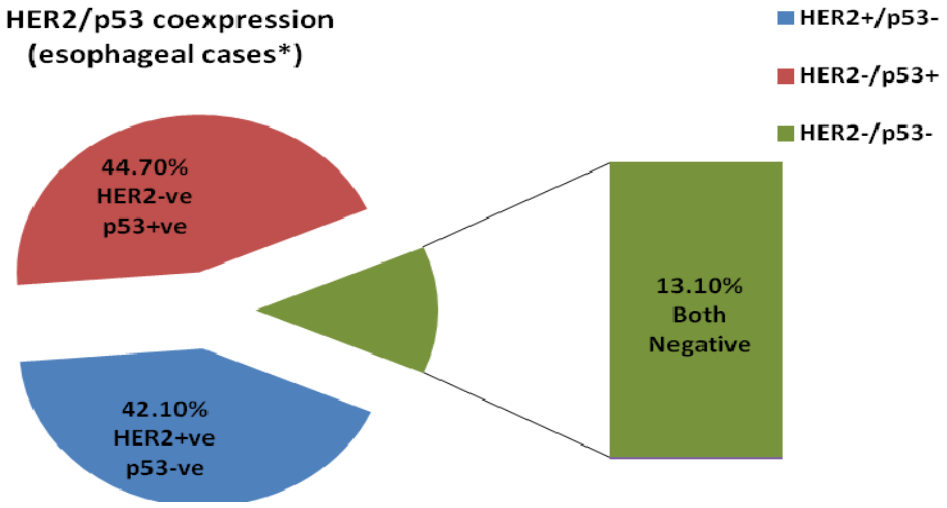


Figure 8. HER2/p53 coexpression in esophageal adenocarcinoma, *Fisher exact test, p= 0.034.

DISCUSSION

Overall, this study demonstrated a relatively high HER2 positivity (33.7%) in gastric and esophageal adenocarcinoma compared with what was previously reported by Kunz et al and Kataoka et al among Americans and Japanese with gastric cancer (8.5% to 10.3%)[19,20]. By a sequence analysis done in 122 centers out of 24 countries with gastric and esophageal cancers, the Trastuzumab anti-HER2 target therapy for Gastric Cancer (ToGA) trial demonstrated 10.4% to 22.1% HER2 positivity[9]. Barros-Silva et al, in their study among Portugal's population, observed a wider HER2 positivity range (5.2%-22.6%) but still lower than the current frequency21. The relatively higher expression of HER2 among our series is probably the result of combining HER2 (2+ and 3+) immunoexpression despite the fact that there is a high concordance between IHC and in situ hybridization for HER2 2+ demonstrated by Hofmann et al and Dowsett et al in their study of HER2 in both gastric and breast cancers[17,22].

It is worth mentioning that HER2-positivity differed by its staining intensity among our series. A strikingly high HER2 (3+) expression was observed among esophageal cancers compared with its gastric counterpart. In contrast, HER2 (2+) was completely absent among esophageal cancer cases. Tanner et al also demonstrated higher HER2 positivity in gastroesophageal junction cancer than GC (24% versus 12%) on their study among Finland population23. However, different results have been observed by many other studies9,16,18. The technique applied for HER2 detection with a further subcategrization of HER2 (2+) into positive or negative according to the in situ hybridization reading may influence the detection rate ranges[17,21,22].

Concerning p53 nuclear immunoexpression, in the course of this experiment we faced an exciting finding

that it was strikingly high in gastric adenocarcinoma compared with its esophageal counterpart (45.6% versus 16.8%). Wide p53 range rates for both gastric and esophageal adenocarcinoma have been documented in the literature (19% to 90%)[27-32]. The conflicting data demonstrated by different studies probably reside in the differences of geographic populations studied with heterogeneous socioeconomic sample sets studied and dietary habits as well as differences in their personal behaviors[2]. However, variation in the methods applied for evaluation of mutated p53 and the anti-p53 antibodies used may also contribute to such wide range rates[31].

In the current study, HER2 positivity was limited to the intestinal adenocarcinoma in both gastric and esophageal tumors; it was completely negative in the diffuse type. Interestingly, this finding is in agreement with numerous prior studies conducted in this field among American and European populations[9,17]. In addition to the fact that mutated HER2 is already low in the diffuse type, lack of HER2 immunoexpression among our diffuse cases is at least partly related to the small sample size of the present study. In contrary to HER2 expression, p53 nuclear expression was found to be expressed in both intestinal and diffuse adenocarcinoma with no significant difference between the two. This finding is comparable to what was observed by Pinto *et al* among Portugal's population[30]. However, contradictory findings were observed by Zheng et al and Lee et al among Japanese and Koreans where nuclear p53 overexpression was much more frequent in intestinal than the diffuse type adenocarcinoma[24,34].

As far as the grade is concerned, we failed to demonstrate any significant association between any of HER2 and p53 positivity and grading despite a trend toward low grade tumor for HER2 and toward high grade for p53. Divergent results have been demonstrated by many other studies conducted among different geographic populations 24-26 although similar results have been reported in a study done by Gleeson *et al* on gastroesophageal adenocarcinoma[35].

The already high T3 and N1 frequencies among our series may explain the predominance of HER2 and p53 positivity among both categories. However, the differences didn't reach the level of significance. Similarly, Kataoka et al denied any correlation between pathological stage and HER2 overexpression[20].

Moreover, despite a trend toward elderly and male gender neither HER2 nor p53 immunoexpression was significantly associated with any of age groups or gender in the current study. Honda et al, in their study among Japanese, have observed a significantly lower p53-immunoreactivity among young patients 36. However, our finding is in sharp contrast to the negative correlation between HER2 with both age and gender that was previously reported by Chen et al among Chinese population and the remarkable predominance of mutated p53 among the Romanian male gender[16,37].

Another important finding in this study is that no significant difference or association between both markers was demonstrated. Cases lacking HER2 with or without p53 among GC cases were more frequent than those expressing both markers together and all esophageal cancers were negative for at least one marker if not both. Such observation is in sharp contrast to what was previously described by Kataoka et al who suggested a possible role of p53 perturbation in the development of HER2-positive gastric cancer[20].

Moreover, the information obtained in this experiment provided a clinicopathological analysis of only 63 patients with GC and 38 patients with esophageal cancer, which is relatively small sample size. As well, we did not perform an in situ hybridization recommended to determine the real HER2 status particularly in equivocal cases, i.e. IHC (2+). These might subject our data to selection bias. More ad hoc-designed studies are needed to clarify these aspects and to ascertain whether HER2 and p53 immunoexpression really reflects their gene mutations and whether alterations of the genes themselves or their pathways have an intercommunicating role in gastric and esophageal adenocarcinoma.

REFERENCES

1. Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA 2010; 303:1723-8.
2. American Cancer Society. Cancer Facts and Figures. Atlanta, Ga: American Cancer Society 2012. http://www.cancer.org/acs/groups.
3. Balbuena L, Casson AG. Physical activity, obesity and risk for esophageal adenocarcinoma. Future Oncol 2009; 5(7):1051-63.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1):11-20.
5. Norsett KG, Lagreida A, Midelfart H, Yadetie F, Erlandsen SE, Falkmer S, et al . Gene expression based classification of gastric carcinoma. Cancer Lett 2004; 227–37.
6. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol; 2006;24(14):2137-50
7. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat ncol 2007; 17:2- 9.
8. Ruschoff J, Hanna W, Bilous M, Hofmann M, Osamura . HER2 testing in gastric cancer: a practical approach. Mod Pathol 2012 ; 25:637-50.
9. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized

controlled trial. Lancet 2010; 376: 687–97.
10. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: Classification, histology and application of molecular pathology. J Gastrointest Oncol 2012; 3(3): 251–61
11. Gibson MK, Abraham SC, Wu T-H, Burtness B, Heitmiller RF, Heath E, et al. Epidermal Growth Factor Receptor, p53 Mutation, and Pathological Response Predict Survival in Patients with Locally Advanced Esophageal Cancer Treated with Preoperative Chemoradiotherapy. Clin Cancer Res 2003 ; 9, 6461-8.
12. Joerger AC, Ang HC, Fersht AR . Structural basis for understanding oncogenic p53 mutations and designing rescue drugs. Proc Natl Acad Sci USA 2006; 103: 15056–61
13. Edge SBB DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors . AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010
14. Pity IS, Arif SH, Hadji DA. Angiogenesis, p53 and Bcl2 in Colorectal Carcinoma. IJOART 2013 ; 2(3):1-6.
15. Pity IS, Baizeed AM . Identification of Helicobacter Pylori in Gastric Biopsies of Patients with Chronic Gastritis, Histopathological, Immunohistochemical Study. Duhok Med J 2011 ; 5(1):69-77
16. Daniela Lazar, Sorina Taban, I. Sporea, Alis Dema, Mariora Cornianu, Elena Lazar, et al. The immunohistochemical expression of the p53-protein in gastric carcinomas. Correlation with clinicopathological factors and survival of patients. RM Morphol Embryol 2010; 51(2):249–57.
17. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, et al Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathol 2008; 52(7): 797–805
18. Park DI, Yun JW, Park JH. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 2006 ; 51(8):1371-9
19. Kunz PL, Mojtahed A, Fisher GA, Ford JM, Chang DT, Balise RR, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. Appl Immunohistochem Mol Morphol 2012 ; 8(1):13–24
20. Kataoka Y, Okabe H, Yoshizawa A, Minamiguchi S, Yoshimura K, Haga H, et al. HER2 expression and its clinicopathological features in resectable gastric cancer. Gastric Canc 2012 ; 8(1):84–93
21. Barros-Silva, JD, Leitao, D, Afonso, L, Vieira, J, Dinis- Riberio, M, Fragoso, M, et al . Association of ERBB2 gene status with histopathological parameters and disease- specific survival in gastric carcinoma patients. Br J Cancer 2009 10;100:487-93.
22. Dowsett M, Bartlett J, Ellis IO, Salter J, Hills M, Mallon E, et al. Correlation between immunohistochemistry (Hercep Test) and fluorescence in situ hybridization (FISH) for HER-2 in 426 breast carcinomas from 37

centres. Journal of Pathology 2003 ; 199(4)418–423
23. Tanner M, Hollmen M, Junttila TT. Amplification of HER-2 in gastric carcinoma: association with topoisomerase IIa gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005 ;16:273-8.
24. Tafe LJ, Janjigian YY, Zaidinski M, Hedvat CV, Hameed MR, Tang LH, Hicks JB, Shah MA, Barbashina V. Human epidermal growth factor receptor 2 testing in gastroesophageal cancer: correlation between immunohistochemistry and fluorescence in situ hybridization. Arch Pathol Lab Med 2011 ; 8(11):1460–5.
25. Yu GZ, Chen Y, Wang JJ. Overexpression of Grb2/HER2 signaling in Chinese gastric cancer: their relationship with clinicopathological parameters and prognostic significance. J Cancer Res Clin Oncol 2009 ; 8(10):1331–9.
26. Zhan GH. Multicenter study on HER-2/neu gene amplification and protein expression in patients with gastric cancer. Chin J Dig 2006 ; 8(10):657–60.
27. Kim R , Clarke MR, Melhem MF. Expression of p53, PCNA, and C-erbB-2 in Barrett's metaplasia and adenocarcinoma. Dig Dis Sci 1997 ;42:2453–62
28. Wang Jy, Lin Sr, Hsieh Js, Hsu Ch, Huang Ys, Huang Tj. Mutations of p53 gene in gastric carcinoma in Taiwan, Anticancer Res 2001 ; 21(1B):513–20.
29. Casson AG, Evans SC, Gillis A, Porter GA, Veugelers P, Darnton SJ, et al. Clinical implications of p53 tumor suppressor gene mutation and protein expression in esophageal adenocarcinomas: results of a ten-year prospective study. J Thorac Cardiovasc Surg 2003 ; 125: 1121-31
30. Pinto-De-Sousa J, Silva F, David L, Leitato D, Deixas M, Pimenta A, et al .Clinicopathological significance and survival influence of p53 protein expression in gastric carcinoma. Histopathol 2004 ; 44(4):323–31.
31. Ismail Hm, Moneer M, El-Baradie M, Khordhid O, Touny A. Clinicopathologic and prognostic significance of overexpression of her-2/Neu and p53 oncoproteins in gastric carcinoma using tissue microarray. J Egypt Natl Cancer Inst 2007 ; 19(2):147–57.
32. Ji F, JIN X, Jiao Ch, Xu Qw, Wang Zw, Chen Yl . Fat 10 level in human gastric cancer and its relation with mutant p53 level, lymph node metastasis and TNM staging. World J Gastroenterol 2009 ; 15(18):2228–33
33. Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Miwa S, et al. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: An immunostaining study on the tissue Microarray.J Clin Pathol 2007 ; 60: 273-7.
34. Lee KE, Lee HJ, Kim YH, Yu HJ, Yang HK, Kim WH, et al. Prognostic significance of p53, nm23,PCNA and c-erbB-2 in gastric cancer. Jpn J Clin Oncol 2003 ; 33 (4): 173-9.

35. Gleeson CM, Sloan JM, McManus DT, Maxwell P, Arthur K, McGuigan JA, *et al*. Comparison of p53 and DNA content abnormalities in adenocarcinoma of the oesophagus and gastric cardia. Br J Cancer 1998 ; 77: 277 – 86.
36. Honda T, Tamura G, Endoh Y, Nishizuka S, Kawata S, Motoyama T, et al. Expression of tumor suppressor and tumorrelated proteins in differentiated carcinoma, undifferentiated carcinoma with tubular component and pure undifferentiated carcinoma of the stomach. Jpn J Clin Oncol 2005; 35(10): 580–6
37. Chen B, Luo RC, Cui F, Qian XY . Association of HER-2/Neu expression with prognosis of gastric cancer. Nan Fang Yi Ke Da Xue Xue Bao 2006 ; 26(3):344-7.

پوختە

لێنێرینا HER2 وp53 ل پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ

پێشەکی و ئارمانج: پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ دمینیت ئێك ژ نەخوشیێن کوژەك دگەل زێدەبوونا رێژا توشبوونێ. نیشاندەرێن گرێدای پەنجەشێرێڤە ئەوێن نوی هاتینە دیارکرن وەکی HER2 وp53 دهاریکارن بو بلەزکرنا بەرسڤدانێ بو چارەسەریا بەری نشتەرگەریێ و ب گشتی ژیانێ باشتر لێدکەن. ئارمانجا ڤێ ڤەکولینێ دیارکرنا خونیشاندانا پارێزکرنێ یا HER2 وp53 ل پەنجەشێرا گلاندی یا گەدێ و بوریکا خوارنێ و دەستنیشانکرنا هەڤبەندییێ دناڤبەرا هەردووا دگەل پیڤەرێن کلینیکی و تاقیگەهی.

رێکێن ڤەکولینێ: ئەڤ ڤەکولینە هاتە ئەنجامدان ل تاقیگەها مەلبەندییا رێڤەبەریا ساخلەمیا دهوکێ – عیراق دناڤبەرا گولانا ٢٠٠٩ێ و ئیلونا ٢٠١٤ لسەر ١٠١ حالەتێن پەنجەشێرا گلاندییا گەدێ و بوریکا خوارنێ بکارئینانا دژەلەشێن ئێك جور دژی وەرگرێن HER2 و پروتینێ ناوەکێ یێ p53 سلاید هاتنە رەنگکرن ب ئامیرێ فول ئوتوماتیکێ رەنگکرنێ (Ventana Benchmark).

ئەنجام: سەرجەمێ خونیشاندانا پوزەتیڤ یا HER2 ب پیڤانا (+٢/ +٣) هاتە دیارکرن ل ٣٢,٧٪ ژحالەتان و بشێوەکێ بەرچاڤ +٣ پتر بوو ل پەنجەشێرا بوریکا خوارنێ ببەراوردی دگەل پەنجەشێرا گەدێ، و بەروڤاژی +٢ هەر هیچ دیارنەبوو ل پەنجەشێرا بوریکا خوارنێ. رەنگدانەڤەیا p53 هاتە دیتن ل ٦٢,٤٪ ژ حالەتان و بشێوەکێ بەرچاڤ پتر بوو ل پەنجەشێرا گەدێ ژ پەنجەشێرا بوریکا خوارنێ.

دەرئەنجام: HER2 ب تنێ ل جورێ رویڤیکی هاتە دیتن لێ p53 لهەردوو جورێن رویڤیکی و بەربەلاڤ هاتە دیتن. چ خونیشاندانێن بهەڤا بێن HER2 وp53 نەهاتنە دیتن لهەردوو پەنجەشێرێن گەدێ و بوریکا خوارنێ.

الخلاصة

معاينة HER2 و p53 في السرطان الغدي للمعدة والمرئ

الخلفية وأهداف البحث: تبقى السرطانات الغدية للمعدة والمرئ أمراض مميتة مع ارتفاع نسبة الإصابة بها، أما العلامات الجينية المتعلقة بالأورام أو المكتشفة حديثاً مثل HER2 و p53 تساعد على تسهيل كل من الاستجابة للعلاج قبل الجراحة وتحسين البقاء على قيد الحياة بشكل عام.

تم تصميم هذه الدراسة لتقييم التعبير المناعي لكل من HER2 و p53 في السرطانات الغدية للمعدة والمرئ ولإيجاد الارتباط بين HER2 و p53 مع الأنماط السريرية.

طرق البحث: أجريت الدراسة في المختبر المركزي للمديرية العامة لصحة محافظة دهوك، وتم البحث على عينات نسيجية (منظارية أو مستئصلة جراحياً) مأخوذة من مائة وواحد شخصاً مصاباً بسرطان الغدي للمعدة والمرئ، كما تم صبغ الشرائح بجهاز الصبغ الكيميائي المناعي الآلي (Ventana Benchmark) باستخدام أجسام مضادة أحادية السلالة لمستقبلات الـHER2 و p53.

النتائج: أظهرت النتائج الإيجابية للمعاينة الكيميائية المناعية لـ(HER2+2/+3) بنسبة ٢٣.٧% لدى المرضى المصابين بسرطان الغدي للمعدة والمرئ مع ارتفاع ملحوظ لـ(HEFR2+3) لدى المصابين بأورام المرئ مقارنة بنظائرها في المعدة، والعكس صحيح بالنسبة للمعاينة المناعية (p53) في ٦٢.٤% من الحالات، مع ارتفاع ملحوظ في الأورام الغدية للمعدة مقارنة بالمرئ. وفيما يتعلق بالنوع النسيجي فقد كان HER2 مقتصراً على النوع المعوي لسرطان المعدة في حين ظهر p53 في كلا النوعين المعوي والمنتشر على الرغم من تغلبه باتجاه النوع المعوي.

الاستنتاج: اقتصرت معاينة الـHER2 على النوع النسيجي المعوي لسرطان الغدي للمعدة، ولم يكن هناك أي ربط بين HER2 و p53 في هذه الأورام ولاسيما أورام المرئ.

BRAF^{V600} GENE MUTATION IN THYROID CANCER IN DUHOK-IRAQ

INTISAR SALIM PITY*
AHMAD MUHAMMAD SALIH**
NARMEEN ADALAT HASSAN***

Submitted 6 April 2015; accepted 31 June 2015

ABSTRACT

Background and objective: This study was done to detect the frequency of BRAFV600 mutation in thyroid cancer in Duhok-Iraq, using real time PCR.

Methods: DNA was extracted from formalin fixed, paraffin embedded tissue sections taken from 54 surgically resected primary thyroid cancers. Using Real-Time PCR, the target (BRAFV600) DNA was amplified with the mutation-specific primers.

Results: BRAFV600 gene mutation was detected in 27.8% of cases. It was significantly high in conventional papillary carcinoma (26.7%) compared with other papillary variants (p= 0.048), and significantly high among cases with extrathyroid extension. Both medullary and one anaplastic carcinomas were BRAFV600 positive. In contrast, all follicular carcinomas and the follicular variant papillary carcinoma were negative for this gene mutation. No association was found between this mutation and any of nodal involvement, gender and age.

Conclusions: Identification of BRAFV600 gene mutation in medullary carcinoma opposes the previous concept that this gene alteration is restricted to papillary carcinoma. Lack of BRAFV600 gene mutation among all follicular variant PTC and follicular cancers including the Hurthel cell tumor, extended the argument that these tumors are closely related. Because this mutation was detected in clinically aggressive cancers like MTC, columnar variant PTC and ATC and was restricted to microcarcinoma with nodal metastasis in addition to its significant association with extrathyroid extension (T4), BRAFV600 molecular testing might emerge as a clinically useful supplement for the histologic assessment as an important predictor of aggressive clinical course.

Duhok Med J 2015; 9 (2): 74-86.

Keywords: Thyroid cancer, BRAFV600, Real Time-PCR.

Thyroid cancer is the most common endocrine malignancy; it forms 1-10% of all cancers in women, 1-3% in men and about 1.4% in children1-4. In Iraq, the prevalence of thyroid cancer is 1.01/100,000. In Kurdistan Region-Iraq, thyroid cancer crude rates reported during 2007, 2008 and 2009 periods ranged from 0.28-0.57/100,0005. While pathological findings remain the "gold standard" for tumor diagnosis, discoveries made in the field of molecular pathology have served to support the great value of the histological evaluation, as well as opened possibilities for new therapies[1,4,6]. Thyroid cancer is particularly interesting for pathologists given that each histological tumor type strongly correlates with its own particular molecular alterations, biological behavior and clinical aggressiveness[6,7].

*Professor in Histopathology, Dept. of Pathology, College of Medicine, University of Duhok Duhok, Iraq.
** Assistant Professor in Microbiology, Department of Microbiology, College of Medicine, University of Duhok Duhok, Iraq.
*** Assistant lecturer in Histology, Dept. of Histology, College of Medicine, University of Duhok Duhok, Iraq
Correspondence to Prof. Intisar Salim Pity, intisarsalimpity@gmail.com Moble: 009647504788000

BRAF gene mutation has recently been the subject of intensive study to investigate its tumorigenic role and clinical implications. Its tumorigenic role in the development of PTC was previously documented in thyroid-targeted BRAF transgenic mice where the rat thyroid cells overexpressed this oncogene, a finding that suggested that BRAF is an initiator in tumorigenesis and is required for tumor progression in PTC[8, 9]. Discovery of BRAF mutation at the hot-spot codon 600 (BRAFV600), has created the opportunity to develop novel clinical strategies for the management of thyroid cancer. The use of this unique molecular alteration in conjunction with the conventional clinicopathological risk factors is found to have both prognostic and therapeutic purposes in thyroid cancer. A substantial body of data indicate that the BRAF mutational status is a significant predictor of poor clinical outcome with a high recurrence rate[7-10]. Hence preoperative analysis of this particular genetic alteration may provide an important value for prognostication, and these patients might benefit from receiving more intensive management and frequent follow-up[9-12].

While BRAFV600 gene mutations have widely been studied in developed countries, very little data are available from the developing countries, and Iraq is one of the countries that lack the data related to these particular molecular alterations of thyroid cancer. Thus the current study, in parallel with others that could be done in the same discipline, might provide an insight on the molecular pathogenesis of thyroid carcinoma in this part of the world.

METHODS

The study was conducted during a period extended from March to December, 2012 in the General Laboratory and Research Center, Duhok-Iraq. A total of 54 surgically resected, primary thyroid cancers were enrolled. Information pertaining to the age at presentation and gender were obtained from the patient's records. No patient had received chemotherapy or radiation therapy prior to surgery. Three mm-thick tissue sections were taken from the tumor, tumor margins, all lymph nodes and any other available tissue. Sections were fixed in 10% formalin overnight, processed and embedded in paraffin wax. Four micron-thick sections were taken and stained again with Hematoxylin and Eosin (H&E) stains to confirm the diagnosis. Cases diagnosed morphologically as medullary carcinoma and anaplastic carcinoma were further subjected to immunohistochemistry (IHC) for the sake of confirmation of diagnosis, and sections from medullary carcinoma were stained by Congo red (histochemistry) to visualize the amyloid material under polarized microscope[13]. Tumor staging was based on the naked eye inspection of the surgical specimen as well as the microscopic examination of the the primary tumor, thyroid capsule, adjacent tissue, all lymph nodes and any associated structure if available, this in addition to the clinical data concerning distant lymph node and organ metastases. Pathological staging was done according to the WHO pathological (pTNM) staging system[13].

Because, in most cases, the exact distant metastasis couldn't be obtained, we depended only on the information related to T (tumor) and N (lymph node) statuses for data analysis. The IHC technique applied for was streptavidin-biotin, using monoclonal antibodies manufactured by Ventana Corporation (Ventana, Rocklin, Calif), 3-3'-diaminobenzidine tetrahydrochloride (DAB) was used as a chromogen, and a standard DAB detection kit (Ventana) was used according to instructions supplied by the manufacturer's (Ventana) and as described previously by Pity et al and Pity and Baizeed[14,15]. DNA extraction and measurement of its concentrations by Nano Drop and the Real-time (RT)-PCR were carried out as described by the manufacturer's, and the ABI-7500 fast real time PCR kits were used for detection of BRAF gene mutation. This kit was a mix (AmoyDx) kit arranged to detect five mutations (V600E, K, D, R and M). Finally, data analysis was conducted using Bioneer data analysis system (software) as described by Logan et al, 2009[16, 17].

RESULTS

Table 1 demonstrates detailed age range and gender of the studied thyroid cancer cases. The mean age was 42.6 years (ranged, 19-72; median, 45.5). Nineteen patients were males (35.1%) and 35 (64.8%) were females (male to female ratio, 0.5: 1). Forty five (83.3%) cases were papillary carcinoma and 6 cases were follicular and anaplastic carcinomas, 3 (5.6%) cases each. Of the remaining 3 cases, 2 (3.7%) were medullary carcinoma and one (1.9%) was Hurthel cell carcinoma which, as shown in the table, was included within the follicular carcinoma group.

BRAFV600 Mutation:

Fifteen (27.8%) cases were positive for BRAFV600 gene mutation, of these 12 (26.7%) were PTC, both MTC and one ATC, (Figure 1). All follicular carcinoma cases were negative for this mutation; the difference was statistically not significant (p= 0.07).

Table 1. Distribution of cancer cases with age and gender.

Cancer		Number (%)	Age (years)		Gender	
			Range	Mean	Male	Female
			Years	Years	Number (%)	Number (%)
Papillary		**45 (83.3%)**	**19-72**	**40.2**	**16 (29.6)**	**29 (53.7)**
			Subtype			
	Conventional	**37 (68.5%)**	**19-72**	**41.3**	**13 (24.1)**	**24 (44.4)**
	Microscopical	**4 (7.4%)**	**25-32**	**29**	**1 (1.9)**	**3 (5.6)**
	Follicular	**2 (3.7%)**	**37-49**	**43**	**1 (1.9)**	**1 (1.9)**
	Columnar	**2 (3.7%)**	**24-35**	**29.5**	**1 (1.9)**	**1 (1.9)**
Follicular*		**4 (7.4%)**	**42-59**	**50.3**	**00**	**4 (7.4%)**
Anaplastic		**3 (5.6%)**	**50-65**	**60**	**1 (1.9)**	**2 (3.7%)**
Medullary		**2 (3.7%)**	**65-70**	**67.5**	**2 (3.7%)**	**00**
Total (%)		**54 (%)**	**37-55**	**42.6**	**19 (35.2%)**	**35 (64.8%)**

* Includes follicular carcinoma cases and the single Hurthel cell carcinoma case.

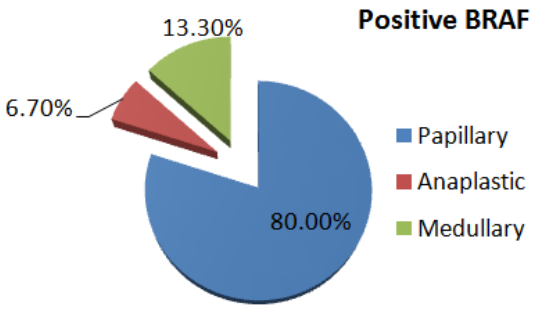
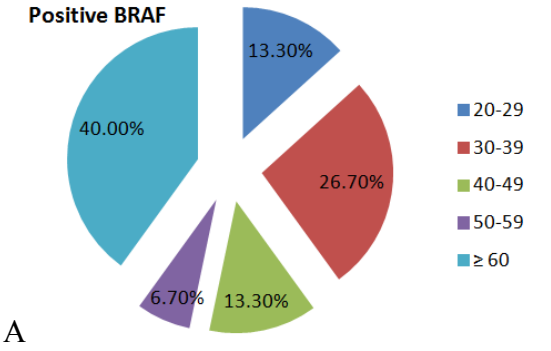


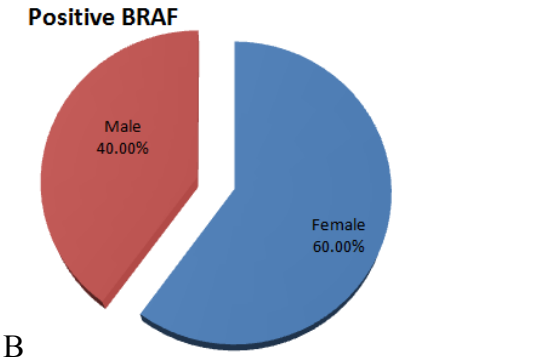
Figure 1. Positive BRAFV600 and type of thyroid carcinoma ($\chi 2$= 6.81, P=0.07).

BRAFV600 Mutation, Age and Gender

As shown in figure 2A, the frequency of BRAFV600 gene mutation was highest among patients 60 years and older. However, the difference didn't reach the level of significance (p= 0.11). As such although this mutation was more frequent among females than males (Figure 2B), the difference was of no significant value (p= 0.64).



A



B

Figure 2A. Positive BRAF mutation and age groups ($\chi 2$= 7.34; P= 0.11).

Figure 2B. Positive BRAF mutation and gender ($\chi 2$= 0.21; P= 0.64).

BRAFV600 Mutation and Papillary Thyroid Carcinoma Variants

Of the 12 positive cases of PTC, the frequency of BRAFV600 mutation was statistically highest among the conventional papillary carcinoma (n= 8; 66.7%; p= 0.048). Both columnar and 2 microscopical variants were positive for BRAFV600 mutation, while both follicular variants were negative (Figure 3).

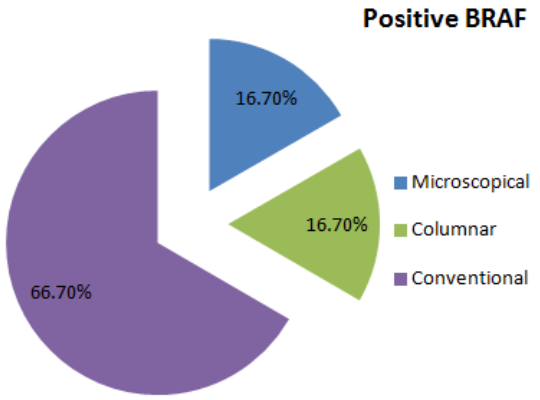


Figure 3. Positive BRAF mutation and papillary carcinoma variants ($\chi 2$= 7.8; P= 0.048).

BRAFV600 Mutation Positive and Tumor (T) status

Of the 12 BRAFV600 positive PTC cases, 2 (microscopical) were at T1, 3 (2 conventional and 1 columnar) were at T2 and 2 (1 conventional and 1 columnar) were at T3. The remaining 5 (41.7%) cases were at T4; all were of conventional PTC (Figure 4). The BRAFV600 positivity was statistically vast among T4 (p= 0.03).

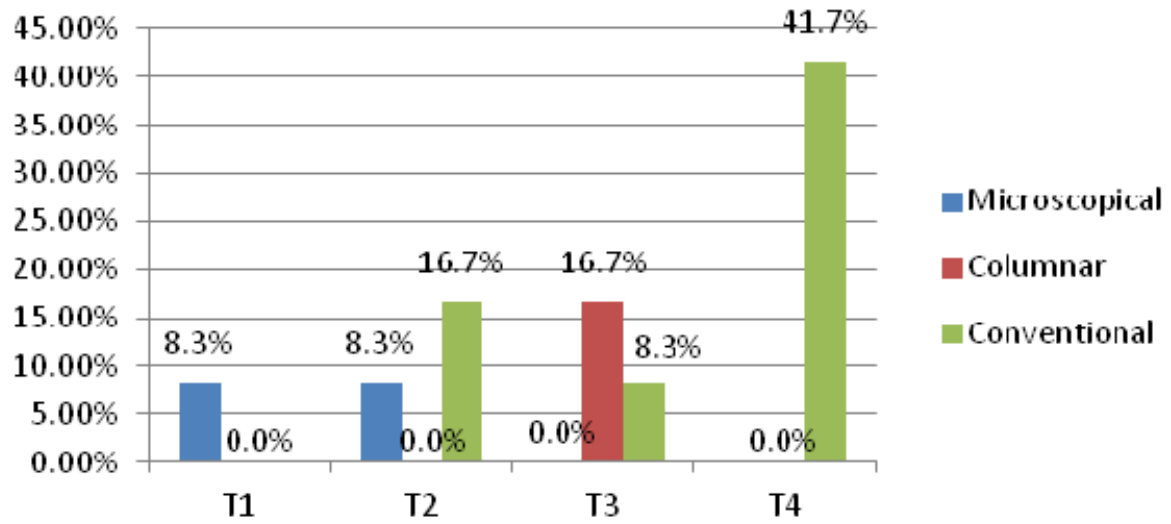


Figure 4. BRAF positive papillary carcinoma variants and tumor (T) status ($\chi 2$= 14; P=0.03).

BRAFV600 Mutation and Nodal (N) status

Six out of 12 positive BRAFV600 gene mutation cases, PTC cases were at N1. They included 2 conventional, 2 microscopical and 2 columnar. The difference was not prominent statistically (P> 0.05).

All positive ATC and MTC cases were at T4N1 status.

BRAFV600 Mutation and Psammoma Bodies

Seven out of 12 BRAFV600 positive PTC cases showed positive psammoma bodies. They included 6 conventional and 1 microscopical. The difference was statistically not significance (P> 0.05).

DISCUSSION

Overall, this study demonstrated a relatively low BRAFV600 gene mutation among thyroid cancer (27.8%). Studies conducted in this field from different ethnic and geographic populations, showed divergent frequency rates ranged from 27-90% (Table 2). Such wide range rates could be actual differences because of the genetic and/or environmental heterogeneity between different populations[8,9,18-21]. Other factors that may influence the prevalence rates include different study samples and variable thyroid cancer histologic subtypes in addition to the impact of the technique employed for DNA identification and variations in the accustomed DNA-reading thresholds ranges, reflected in the different subjective interpretations of positive values[19-23].

In the course of this experiment, we faced an exciting observation which is worth mentioning that is testing both medullary carcinoma cases revealed positive BRAFV600 gene mutation (i.e. 100%). Although this finding might strengthen and extend a previous study done by Goutas et al on 99 Greek patients with PTC and MTC,12 however, it is in sharp contrast to what was observed by Cerrato et al in their meta-analysis study on MTC who denied any role of RAF gene alteration in this aggressive cancer25. As such, information derived from the limited studies done on MTC by Xing and Nikiforova et al,

indicated that BRAFV600 mutation is restricted to the PTC and its subsequent ATC[7,21,22]. More ad hoc-designed molecular studies are required to clarify these aspects and to ascertain whether some sporadic MTC cases could be due to other alterations in Ras-Raf-MAPK/ERK pathways.

An important finding in the current study is that certain histologic differences were apparent between papillary thyroid cancers harboring BRAFV600 gene mutation. The significantly high positivity among the conventional histology is in agreement with several studied conducted in Korea, Greece, US, Italy, and Spain[8,12,23,26,27].

Table (2): Frequency rates of BRAFV600 mutation positive thyroid cancer, literature review.

Series	Sample number	Country	Frequency (%)			
			Total	Papillary	Anaplastic	Medullary
Current Study, 2013	**54**	**Iraq (Duhok)**	**27.8**	**26.7**	**33**	**100**
Jeong et al, 2013	**211**	**Korea**	**-**	**90**	**-**	**-**
Chien and Koeffler, 2012		**Meta-analysis**	**-**	**40**	**25**	**-**
Tang and Lee, 2010	**-**	**Meta-analysis**	**-**	**29-83**	**25**	
Giusti et al, 2010	**-**	**Meta-analysis**		**45**	**20**	
Goutas et al, 2008	**99**	**Greece**	**45.5**	**27.3**	**-**	**68.2**
Kebebew et al, 2007	**111**	**US**	**-**	**34.2**		
Lupi et al, 2007	**500**	**Italy**	**-**	**43.8**	**-**	**-**
Lee et al, 2007	**1168**	**Meta-analysis**	**-**	**49**	**-**	**-**
Riesco-Eizaguirre et al, 2006	**67**	**Spain**	**-**	**41.7**	**-**	**-**
Kondo et al, 2006	**-**	**Meta-analysis**	**29–69**		**10-35**	
Xing, 2005	**1860**	**Meta-analysis**	**44**	**45**	**25**	**0.0**
Kim et al, 2004	**70**	**Korea**	**-**	**83**	**-**	**-**
Nikiforova et al, 2003	**320**	**Italy**		**38**	**10**	**0**
Xu et al, 2003	**599**	**US**	**-**	**38**	**-**	**-**

The association of this particular gene mutation with both cases of columnar variant-papillary carcinoma was particularly striking. Studies conducted in this regard, imply that this histotype may represent an aggressive variant of papillary carcinoma[21,22]. The positivity of BRAFV600 among the more aggressive cancers, like MTC and anaplastic carcinoma, emphasizes the unfavourable behavior of columnar variant of PTC. Chen et al in their analysis of BRAF positive columnar variant papillary carcinoma presumed that this mutaion may influence the behavior of columnar cell carcinomas[28].

Meanwhile, in our series BRAFV600 gene mutation was also positive in two out of four cases of papillary microcarcinoma. Conceivably, this variant has an excellent clinical course[3,6,29]. The scientific and general perceptions of the problem are different. Large meta-analysis studies described papillary microcarcinoma

harboring BRAFV600 mutation associated with increased aggressiveness[7,9,30]. The positive nodal metastasis in both cases of microcarcinoma harboring this gene mutation, further proves the important association of BRAFV600 mutation with the aggressive clinicopathological signs, or it may be an early event in thyroid carcinogenesis that may predispose the tumor cells to acquisition of additional genetic alterations, which, in turn may activate more aggressive pathways[21,22].

On the other hand, BRAFV600 gene mutation was totally absent among the follicular variant PTC. Comparably, an exceedingly low prevalence or absent BRAF gene mutations have been previously demonstrated by studies performed among American, European and Asian populations[9,10,12,22,23, 26,27,31]. It has been postulated that the follicular variant PTC develops through a distinct set of molecular abnormalities and may have unique biological properties, and the finding that RAS gene mutations have been restricted to the follicular variants and virtually absent in conventional papillary carcinoma, indicates that this major variant of papillary carcinoma is different from the conventional PTC and shows molecular alterations that are (at least statistically speaking) intermediate between follicular neoplasm and papillary carcinoma[7,9,20,22,32]. This, together with the difficulty in making a reproducible histologic diagnosis, suggests that at least some encapsulated follicular variants of papillary carcinoma could actually be regarded as follicular carcinomas when invasive, or adenomas when non-invasive[20,33,34]. This, together with the difficulty in making a reproducible histologic diagnosis, suggests that at least some encapsulated follicular variants of papillary carcinoma could actually be regarded as follicular carcinomas when invasive, or adenomas when non-invasive[20,33,34]. In the same line, our findings, concerning lack of BRAFV600 in FTC are in agreement with several studies conducted in different American, European and Asian populations[7,9,10,20, 22,34,35]. This confers another proof for the concept that BRAFV600 alterations have no impact in follicular neoplasms[10,12, 21,22]. As well, they strengthen the concept that follicular variant PTC is closely related to the follicular thyroid carcinoma[20,34,35].

As such, the only Hürthle cell carcinoma case reported in this study was negative for BRAFV600 mutation. The main molecular alterations reported in Hurthel cell carcinoma comprised RAS gene mutations[20,36]. In one study, BRAF mutations were described in Hurthel cell carcinomas but, on subsequent follow up, they were proved to be papillary carcinomas with oncocytic feature[20]. This clarifies that Hurthel cell tumors (at least in part) are related to the follicular neoplasms or perhaps form a distinct entity that might be regulated by different molecular pathways that do or do not involve RAS alteration[6,36].

Although the information obtained in this experiment provided a clinicopathological analysis of only 54 patients with thyroid cancer, we observed an important finding which is worth mentioning, that is the significant increased BRAFV600 mutation

with advanced tumor (T) status, particularly those cases with extrathyroid extension (T4). This finding, which is consistent with previous studies conducted in this regard, might offer insights into the stepwise progression of thyroid cancers harboring this gene mutation[8,21,22,31]. Therefore, BRAFV600 gene mutation is considered challenging for thyroid cancer management, as majority of recurrent BRAFV600 positive thyroid cancers had no avidity for radioiodine (131I)[7,18,23].

Furthermore, although all ATC and MTC cases revealed lymph nodes involvement and both positive microcarcinoma cases had lymph nodal metastasis, we failed to demonstrate any significant association between BRAFV600 positive PTC and nodal status. Conflicting data have been written in prior studies, some demonstrated a slight correlation of BRAF mutation with the advanced TNM stage particularly the extrathyroid extension and distant metastases, but not with nodal status[21,22,31] while Jeong et al in their study on 211 Koreans with PTC described BRAFV600 mutation correlation with extrathyroid invasion, lymph nodal metastasis and tumor multiplicity8. These inconsistent results could be partially due to an insufficient number of patients and/or different combinations of various age groups as well as various subtypes of PTC included in their analyses[12,23,37].

As far as the genotype-phenotype correlation is concerned, discordant and scant data were generated in different published studies. In the current study, we failed to demonstrate any significant association between BRAFV600 gene mutation and age despite a trend toward elderly patients (≥ 60 years). This observation is consistent with a study done by Jeong et al on Koreans[8]. Riesco-Eizaguirre et al in their study among Spanish people and Nikiforova et al in their meta-analysis reported an age older than 45 years at presentation[22,23]. Divergent results were demonstrated by studies done among different geographic populations where they demonstrated a significant correlation between patient's age and BRAFV600 positive histological types[12,20,22,37,38]. Similarly, although the difference was statistically not significant, there was a trend showing a female predominance among our BRAFV600 positive cancers cases. The originally higher proportion of female gender (64.8%) in our series may contribute to this variation. However, this finding is comparable with what was observed by Jeong et al, but diverged with that reported by Nikiforova et al and Xu et al who described BRAFV600 mutations linked to the male gender[8,22,39]. In view of these controversial data, it is difficult to indicate any possible association between BRAF mutation and age or gender. It can infer that both age and gender may represent potential biases and may account for these substantial differences[12,20,22,37,38,39].

Although this finding needs to be confirmed by other studies, identification of BRAFV600 gene mutation in medullary carcinoma is acknowledged as it opposes the previous concept that this gene alteration is restricted to papillary carcinoma. Lack of BRAFV600 gene mutation among all follicular variant PTC

and follicular cancers including the Hurthel cell tumor, extended the argument that these tumors are closely related. Because this mutation was detected in clinically aggressive cancers like MTC, columnar variant PTC and ATC and was restricted to microcarcinoma with nodal metastasis in addition to its significant association with extrathyroid extension (T4), BRAFV600 molecular testing might emerge as a clinically useful supplement for the histologic assessment as an important predictor of aggressive clinical course.

REFERENCES:

1. American Cancer Society. Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society, 2012. http://www.cancer.org/acs/groups.
2. Davies L, Ouellette M, Hunter M, Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? Laryngoscope. 2010;120(12):2446-51.
3. Wartofsky L. Increasing world incidence of thyroid cancer. Increased detection or higher radiation exposure. Hormons. 2010; 9(2):103-8.
4. Iraqi cancer registry. Results of Iraqi cancer registry 1976-2004. World health organization, Ministry of Health (WHO), Baghdad, lraq. 2004.
5. Othman RT, Abdulljabar R, Saeed A, Kittani SS, Sulaiman HM, Mohammed SA, et al. Cancer Incidence Rates in the Kurdistan Region/Iraq from 2007-2009. APJCP. 2011;12:1261-64.
6. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and Genetics of Tumours of Endocrine Organs (The International Agency for Research on Cancer. WHO classifiacation of tumours). 1st ed. Lyon: WHO, 2004.
7. Xing M. Prognostic utility of BRAF mutation in papillary thyroid cancer. Molecular and Cellular Endocrinology. 2010;321(1):86-93.
8. Jeong D, Jeong Y, Park JH, Han SW, Kim SY, Kim YJ, et al. BRAFV600E Mutation Analysis in Papillary Thyroid Carcinomas by Peptide Nucleic Acid Clamp Real-time PCR. Annals of Surgical Oncology. 2013;20(3):759-66.
9. Tang KT, Lee CH. BRAF Mutation in Papillary Thyroid Carcinoma: Pathogenic Role and Clinical Implications. J Chin Med Assoc. 2010;73(3):113-28.
10. Chien W and Koeffler HP. Molecular Biology of Thyroid Cancer. Endocrine Updates. 2012;30:35-43.
11. Davies H, Bignell GR, Cox C, Stephe ns P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949-54.
12. Goutas N, Vlachodimitropoulosi D, Bouka M, Lazaris AC, Nasioulas G, Gazouli M. BRAF and K-RAS Mutation in a Greek Papillary and Medullary Thyroid Carcinoma Cohort. Anticancer research. 2008;28: 305-8.
13. Rosai J. Thyroid gland in: Rosai and Ackerman's Surgical Pathology. 10th ed. St Louis: Mosby. 2010;488-538.
14. Pity IS, Arif SH, Hadji DA. Angiogenesis, p53 and Bcl2 in Colorectal Carcinoma. IJOART. 2013;2(3):1-6.
15. Pity IS, Baizeed AM. Identification of Helicobacter Pylori in Gastric Biopsies of Patients with Chronic Gastritis, Histopathological,

Immunohistochemical Study. Duhok Med J. 2011;5(1):69-77.
16. Logan J, Edwards K, Saunders N. Real-Time PCR: Current Technology and Applications. Caister Academic Press. Health Protection Agency, London. 2009.
17. Greenberg J. BSCS Biology: A Molecular Approach. BSCS Blue Version Revision Team. Glencoe/McGraw-Hill Companies, Inc. 9th Ed. Springer Science + Business Media B.V. 2006.
18. Giusti F, Falchetti A, Franceschelli F, Marini F, Tanini A, Luisa Brandi M. Thyroid cancer: current molecular perspectives. J Oncol. 2010;2010.
19. Lee JY, Shin JH, Han BK, Ko EY, Kang SS, Kim JY, et al. Diffuse sclerosing variant of papillary carcinoma of the thyroid: imaging and cytologic findings. Thyroid. 2007;17(6):567-73.
20. Kondo T, Ezzat S, Asa SL. Pathogenet ic mechanisms in thyroid follicular-cell neoplasia. Nat Rev Cancer. 2006;6:292-306.
21. Xing M. BRAF mutation in thyroid cancer. Endocrine-Related Cancer, 2005;12:245–62.
22. Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo F, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anasplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab. 2003;88:5399-404.
23. Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, Nistal M, Santisteban P. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I-targeting to the membrane. Endocr. Relat. Cancer. 2006;131:257–69.
24. Tallini G. Poorly differentiated thyroid carcinoma. Are we there yet? Endocr Pathol. 2011;22(4):190-4.
25. Cerrato A, De Falco V, Santoro M. Molecular genetics of medullary thyroid carcinoma: the quest for novel therapeutic targets. Journal of Molecular Endocrinology. 2009;43, 143–55.
26. Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh Q. The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg. 2007;246(3):466-71.
27. Kim KH, Kang DW, Kim SH, Seong IO, Kang DY. Mutations of the BRAF gene in papillary thyroid carcinoma in a Korean population. Yonsei Med J. 2004;45(5):818-21.
28. Chen JH, Faquin WC, Lloyd RV, Nos e V. Clinicopathological and molecular characterization of nine cases of columnar cell variant of papillary thyroid carcinoma. Mod Pathol. 2011;24(5):739-49.
29. Lin JD, Kuo SF, Chao TC, Hsueh C. Incidental and nonincidental papillary thyroid microcarcinoma. Ann Surg Oncol. 2008; 15:2287-92.
30. Roti E, Uberti EC, Bondanelli M, Braverman LE. Thyroid papillary microcarcinoma. A Descriptive and Meta-Analysis Study. Eur J Endocrinol. 2008;159(6):659-73.
31. Lupi C, Giannini R, Ugolini C, Proietti A, Berti P, Minuto M, et al. Association of BRAF V600E mutation with poor clinicopathologic outcomes in 500 consecutive cases of papillary

thyroid carcinoma. J Clin Endocrinol Metab. 2007; 92:4085-90.

32. Flanagan MB, Li-Volsi VA, Baloch ZB: Long term follow-up of patients with follicular variant of papillary thyroid carcinoma (FVPTC). Lab Invest. 2009;89(1):247-11.
33. Adeniran AJ, Zhu Z, Gandhi M, Stew ard DL, Fidler JP, Giordano TJ, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006;30:216-22.
34. Giordano TJ, Kuick R, Thomas DG, Misek DE, Vinco M, Sanders D, et al. Molecular classification of papillary thyroid carcinoma: distinct BRAF, RAS, and RET/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. Oncogene. 2005;24:6646-6656.
35. Castro I, Soares P, Máximo V, Silva P , Magalhães J, Abrosimov A, et al. BRAF mutations are associated with some histological types of papillary thyroid carcinoma. J Pathol. 2004;202:247-51.
36. Asa SL. My approach to oncocytic tumours of the thyroid. *J Clin Path*.2004;57(3):225-32.
37. Kuo SF, Chao TC, Hsueh C, Chuang WY, Yang CH, Lin JD. Prognosis and risk stratification in young papillary thyroid carcinoma patients. Endocr J. 2008;55(2):269-75.
38. Collini P, Mattavelli F, Pellegrinelli A, Barisella M, Ferrari A, Massimino M. Papillary carcinoma of the thyroid gland of childhood and adolescence: Morphologic subtypes, biologic behavior and prognosis: a clinicopathologic study of 42 sporadic cases treated at a single institution during a 30-year period. Am J Surg Pathol. 2006;30:1420-6.
39. Xu X, Quiros RM, Gattuso P, Ain KB, Prinz RA. High prevalence of BRAF gene mutation in papillary thyroid carcinomas and thyroid tumor cell lines. Cancer Res. 2003;63(15):4561-7.

پوختە

یوختەدیارکرنا کوهورینا جینی BRAFل نە خوشین شیر بە نجا پایرویدی ب ریکا RT-PCR وبە یوە ندیا وان دکە ل جورین هیستوبەلوجی

پێشەکی و ئارمانج: بو دیارکرنا گوهرینێن جینی و BRAFv600 و نەخوشیا شێربەنجا پایرویدی دا بریکا بکارئینانا RT-PCR و پەیوەندیا وان دگەل جورێن نەخوشیێ .

ریکێن فە کولینی: دئەقێ ڤەکولینێ دا ٥٤ سامپل ژنەخوشێن پەنجەشێرا پایرویدی هاتنە بکارئینان و DNA ژەمی سامپلێن دناف شمایی دا هاتنە دەرئینان و رێکا RT-PCR هاتە بکارئینان ژ بو دیارکرنا گوهرینێن BRAF .

ئەنجام: تەکنیکا RT-PCR دیار کر کو ٢٧,٨٪ ژ هەمی بەنجەشیرا پایرویدی گوهرینێن BRAF هەبوون . پەنجەشیرا Convantional Papillary Carcinoma ژ هەمیا پتر بو. بەروڤاژی پەنجەشێرا Follicular and Follicular variant papillary ئەف جورە گوهرینە نەبوون درێژا گوهرینێBRAF دناف کال و مێیادا پتربوو.

دەر ئە نجام: دەستنیشانکرنا گوهرینا BRAF یا گرنکە دشێربەنجا پایرویدا یا Medullary بەروڤاژی وێ چەندێ کو ئەف گوهرینە د شێربەنجا پایرویدا یا ژ جورێ Papillary بتنێ هەیە. نەبونا گوهرینا BRAF دشێربەنجا Hurthal and Folliuular variant Papillary دیاردکەت کو ئەف جورە پێگۆە گرێداینە چونکو ئەف جورە گوهرینە ل BRAF هاتینە دیتنە دیتن دناف شێربەنجا پایرویدی یا دزەکی دا ، لەورا پشکنینێن مولیکیولی بێن گرنگن بوو دیارکرنا ڤان جورە نەخوشیان دا.

الخلاصة

الكشف عن طفرة الـBRAF في حالات سرطان الغدة الدرقية بطريقة الـ Real Time PCR وعلاقتها بالتغيرات النسيجية

الخلفية وأهداف البحث: هذه الدراسة تمت للكشف عن تكرار الطفرات الجينية لجين ال BRAFv600 فى اورام الغدة الدرقية باستعمال طريقة RT–PCR في مدينة دهوك العراق.

طرق البحث: تم استخلاص ال DNA في العينات المثبتة بالفورمالين والمحفوظة بالشمع المأخوذة من ٥٤ عينة مستأصلة جراحيا والمشخصة مبدئيا بأنها سرطان الغدة الدرقية ثم باستعمال RT–PCR ثم الكشف عن الطفرات المتوقعة فى جين الـBRAF وبأستخدام بادئات مخصصة للعملية.

النتائج: تم الكشف عن طفرة BRAFv600 في ٢٧,٨% من الحالات, حيث كانت النسبة عالية بصورة معنوية بالمقارنة مع الحالات الحليمية الاخرىBRAF وكانت عالية ايضا فى حالات سرطان الدرقية الممتد خارج الغدة . كلتا حالات اللبية وحالة أنابلاستيك كانت تحمل الطفرة فى جينBRAF .على العكس من ذلك حالات الاورام الحويصلية والمتغيرات الحويصلية الحليمية لم تلاحظ فيها الطفرات فى جينBRAFv600 .فى مايخص العمروالجنس لم تكن هناك فروقات معنوية تذكر.

الاستنتاج: ما توصل اليه البحث ان تحديد الطفرة فى جين الـBRAF لدى حالات سرطان الدرقية اللبى يجب الاخذ به وذلك يتعارض مع المفهوم السابق والذى يؤكد بأن التغيرات الجينية كانت محددة بسرطان الدرقية الحليمى وفقدان الطفرة الجينية لBRAFv600 بين جميع حالات سرطان الدرقية الحويصلى وخلايا BRAF ومتغيرات سرطان الدرقية الحليمى تظهر هذه الحالات بانها جميعا من الاورام المتقاربة . بسبب الكشف المسبق عن هذه الطفرات فى حالات الاورام العدائية وارتباطها معنويا بحالات اورام الدرقية الممتد خارج الغدة الدرقية .الفحص الجزيئى لجين BRAFv600 يصبح من الفحوصات السريرية الضرورية للمساعدة فى التشخيص النسيجى للحالات المرضية الشديدة العدائية.

RISK FACTORS FOR RADIOLOGIC CERVICAL SPONDYLOSIS IN DUHOK: A CASE CONTROL STUDY

MERDAN KHALEEL MOHAMED MB Ch. B, DIM, M Sc.*
QAYSER S. HABEEB MB Ch. B, M Sc., DM**
MOHAMMED T. RASOOL FRCP.G, FRCP, DRMR***

Submitted 20 October 2015; accepted 31 December2015

ABSTRACT

Background and Objective: Cervical spondylosis is a broad term usually used to denote a chronic degenerative condition generally ascribed to progress in age and other possible risk factors. The disease is common and may lead to possible neurological deficits. There is thus a clear need for identifying its probable risk factors in order to better understand their control and prevention.

Patients and methods: A case control study conducted at Duhok's Center for Rheumatic Diseases during the period1st April - 30th September, 2014. Depending on the presence of symptoms and radiologic findings, 129 patients were selected and registered as 'cases' and another 129 patients without radiological abnormalities were collected and registered as 'controls'. For each participant age, gender, marital status, weight, height, smoking status, family history, drug use and number of pillows were recorded. In addition, for men, the history of wearing Kurdish turban (Shashek) was recorded. The increased risk was estimated by calculating the odds ratio and 95% CI.

Results: Overall, age was found the most significant risk factor in both genders (OR13.55). For women, the highest odds ratio related to chronic drug use (OR 4.01) followed by BMI (OR 3.44) and sedentary work (OR 2.64). For men, the highest odds ratio related to Shashek use (OR 16.8) followed by sedentary work (OR 5.6) and smoking (OR 4.18). Physical activity of ≥ 150 min/week gave a statistically significant negative association in both men and women (OR of 0.34 and 0.18 respectively with a p value <0.05).

Conclusions: Radiological cervical spondylosis is positively associated with aging and sedentary work in both genders. Significant positive associations were found with chronic drug use and high BMI in women compared to significantly high association with the Kurdish male turban (Shashek) and smoking in men.

Duhok Med J 2015; 9 (2): 87-96.

Keywords: BMI, cervical spondylosis, Duhok, physical activity, risk factors, shashek, smoking

Cervical spondylosis (CS) is a broad term usually used to denote a chronic degenerative condition generally ascribed to progress in age. This condition affects the vertebral body, the intervertebral disc and the facets as well as other soft tissues supporting these joints.[1] It presents itself in several clinical syndromes, sometimes clearly separated and distinct, others quite overlapping. These are: a) neck pain usually associated with pain in the shoulder, b) radiculopathy and c) myelopathic symptoms[2]. Most research papers stressed on advancing age

* *Assistant Lecturer, Department of Medicine / College of Medicine/University of Duhok*
** *Professor, Department of Family and Community Medicine / College of Medicine/University of Duhok*
*** *Assistant Professor, Department of Medicine / College of Medicine/University of Duhok*
Correspondence to Merdan Khaleel Mohamed E-mail: merdanhida@yahoo.com

as the risk factor which is most important as a cause for CS3. Besides, there are other possible risk factors such as overweight 4,5 and smoking[6]. There is also a presumed role for heredity, especially in regard to cervical spondylotic myelopathy[7,8] and carrying loads on the head[9,10,11]. Neck pain is so common as to be considered a public health problem[12]. In the United States at least one person of every hundred who visits a primary care center does so because of neck pain and nearly 70% of the population have suffered or will suffer this symptom, one time in their life[13]. Due to paucity of local studies in this context, this study has been conducted to assess some potential risk factors for radiologic cervical spondylosis among residents of Duhok.

PATIENTS AND METHODS

The study was conducted at Duhok Center for Rheumatic Diseases (DCRDs) during the period from the 1st of April to the 30th of September 2014. The DCRDs is a specialized, governmental, tertiary health-care center to which patients are referred from all primary and secondary heath centers of Duhok for rheumatologists consultation. Included subjects were symptomatic adults aged ≥ 20 years of both genders, suspected of having cervical spondylosis, who were referred to DCRDs, during the study period, for rheumatologist's consultation. Exclusion criteria included rheumatoid arthritis, multiple sclerosis, trauma to the neck or head, syringomyelia, severe osteoporosis, tumor of the neural elements, meninges or vertebrae (primary or secondary), amyotrophic lateral sclerosis, spinal cord infarction, sub acute combined degeneration of the spinal cord, normal pressure hydrocephalus.

A consecutive sampling procedure was used to enroll 129 patients with x-ray findings consistent with cervical spondylosis as "cases" and 129 x-ray negative persons were selected as "controls" and registered similarly. The final study sample size amounted to 258 adults including 61 men and 197 women, all muslim and kurdish. A specially designed questionnaire was prepared to document the required data. It included demographics, presenting symptoms, potential risk factors and radiographic findings. Data were analyzed using SPSS (version 22nd / 2013).

RESULTS:

The sample consisted of 258 adults whose ages ranged from 20 years to 60+ years, of whom 61 were men and 197 were women. The age group 30-49 years included 50% of all the participants .Most subjects were married (85.5%), others were still single, widowed or divorced. There was no statistically significant difference between men and women regarding age and marital status. The other findings are presented in the following tables.

Table 1. Cases and Controls by Gender

		Cases		Controls		Total	P*
		No.	Percent	No.	Percent	No.	
Gender	Men	32	52.5%	29	47.5%	61	0.660
	Women	97	49.2%	100	50.8%	197	

* Chi-square test

Table 2. Cases and Controls by Age

			Cases (n=129)		Controls (n=129)		Total (n=258)	Odds Ratio (95% CI)*	P*
			No. (%)		No. (%)		No.		
Male	Age	20-39 years	2	(6.3)	23	(79.3)	25	57.5 (10.61-311.6)	<0.001
		≥ 40 years	30	(93.7)	6	(20.7)	36		
Female	Age	20-39 years	18	(18.6)	69	(69.0)	87	9.77 (5.023-18.99)	<0.001
		≥ 40 years	79	(81.4)	31	(31.0)	110		
Both	Age	20-39 years	20	(15.5)	92	(71.3)	112	13.55 (7.36-24.96)	<0.001
		≥ 40 years	109	(85.5)	37	(28.7)	146		

* Binary logistic regression.

Table 3. Cases and controls by BMI and Gender

			Cases (n=129)		Controls (n=129)		Total (n=258)	Odds Ratio (95% CI)*	P*
			No. (%)		No. (%)		No.		
Male	BMI	<25 kg/m2	8	(25.0)	12	(41.4)	20	2.12 (0.71-6.29)	0.177
		≥ 25kg/m2	24	(75.0)	17	(58.6)	41		
Female	BMI	<25 kg/m2	9	(9.3)	26	(26.0)	35	3.44 (1.52- 7.79)	0.003
		≥ 25kg/m2	88	(90.7)	74	(74.0)	162		
Both	BMI	<25 kg/m2	17	(13.2)	38	(29.5)	55	2.75 (1.46-5.19)	0.002
		≥ 25kg/m2	112	(86.8)	91	(70.5)	203		

* Binary logistic regression.

Table 4. Cases and Controls among Men by Weight and Height

	Total (n= 61)		Cases (n=32)		Controls (n=29)		P*	95% CI	
	Mean ± SD		Mean ± SD		Mean ± SD			Lower	Upper
Weight	77.13	±14.90	78.06	± 14.7	76.10	±15.26	0.612	-5.73	9.65
Height	1.68	± 0.08	1.67	± 0.09	1.70	± 0.08	0.200	-0.07	0.02

* Unpaired t-test.

Table 5. Cases and Controls among Women by Weight and Height

	Total (n= 197)		Cases (n= 97)		Controls (n= 100)		P*	95% CI of difference	
	Mean ± SD		Mean ± SD		Mean ± SD			Lower	Upper
Weight	74.29 ±	15.84	78.25	± 14.88	70.45	±15.87	<0.001	3.47	12.12
Height	1.56	± 0.06	1.55	± 0.05	1.57	±0.07	0.014	-0.04	-0.01

* Unpaired t-test.

Table 6. Cases and Controls by Risk Factors among Men

Risk Factor		Cases No. (%)	Controls No. (%)	Total No.	Odds Ratio (95% CI)*	P*
Family History	Yes	5 (15.6)	6 (20.7)	11	0.71 (0.19-2.63)	0.608
	No	27 (84.4)	23 (79.3)	50		
Chronic Drug Use	Yes	7 (21.9)	2 (6.9)	9	3.78 (0.72-19.94)	0.117
	No	25 (78.1)	27 (93.1)	52		
Shashek Wear	Yes	12 (37.5)	1 (3.4)	13	16.80 (2.02-139.85)	0.009
	No	20 (62.5)	28 (96.6)	48		
Physical Activity	< 150 min/wk	19 (59.4)	6 (20.7)	25	0.18 (0.06-0.56)	0.003
	≥ 150 min/wk	13 (40.6)	23 (79.3)	36		
Smoking	Smoker	23 (71.9)	11 (37.9)	20	4.18 (1.43-12.26)	0.009
	Nonsmoker	9 (28.1)	18 (62.1)	27		
No. of Pillows	One	28 (87.5)	25 (86.2)	53	0.89 (0.20-3.95)	0.881
	Two	4 (12.5)	4 (13.8)	8		
Sedentary Work	Yes	19 (59.4)	6 (20.7)	25	5.60 (1.79-17.56)	0.003
	No	13 (40.6)	23 (79.3)	36		
Total		32 (100)	29 (100)	61		

*Binary logistic regression.

Table 7. Cases and Controls by Risk Factors among Women

Risk Factor		Cases No. (%)	Controls No. (%)	Total No.	Odds Ratio (95% CI)*	P*
Family History	Yes	38 (39.2)	33 (33.0)	71	1.31 (0.73-2.34)	0.367
	No	59 (60.8)	67 (67.0)	126		
Chronic Drug Use	Yes	47 (48.5)	19 (19.0)	66	4.01 (2.12-7.59)	<0.001
	No	50 (51.5)	81 (81.0)	131		
Physical Activity	< 150 min/wk	35 (36.1)	16 (16.0)	51	0.34 (0.17-0.66)	0.002
	≥ 150 min/wk	62 (63.9)	84 (84.0)	146		
Smoking	Smoker	9 (9.3)	5 (5.0)	6	1.94 (0.63-6.02)	0.250
	Nonsmoker	88 (90.7)	95 (95.0)	183		
No. of Pillows	One	88 (90.7)	87 (87.0)	170	0.68 (0.28-1.68)	0.409
	Two	9 (9.3)	13 (13.0)	22		
Sedentary Work	Yes	34 (35.1)	17 (17.0)	51	2.64 (1.35-5.14)	0.004
	No	63 (64.9)	83 (83.0)	146		
Total		97 (100)	100 (100)	197		

* Binary logistic regression.

DISCUSSION:

The findings revealed consistency of advancing age as a risk factor for CS, similar to the results of most available reports[3,2]. Singh et al. (2014) conducted a hospital-based case-control study on 200 hospital attendants in Lucknow, India. They found that age, occupation, female gender and short stature, were significant risk factors[14]. This strong CS-age relationship reflects the age-related intervertebral disk degeneration found by a number of investigators[15].

As to the BMI, the results showed an overall, statistically significant association with CS (p= 0.002). Differentially the association was significant in women (OR 3.44 and p= 0.003) but non-significant in men (p= 0.177). The difference of the effect of high BMI between men and women in the current study is a question to be studied by a more extensive research work in the future as the present literature points to a relationship between body fat and IVD degeneration without gender discrimination4,. The underlying cause of this apparent discrepancy between the two genders may be the small percentage of overweight subjects among men or probably because men are more active physically than women according to WHO[16] and physical activity proved in this study to be associated with a negative odds ratio.

According to the available literature, the investigator could not find studies that investigated the height in relation to CS, except the aforementioned study of Singh et al which found short stature as a risk for CS[16] The present study revealed a negative association between CS and height in women (p= 0.014 with a CI − 0.04 to− 0.01) but not in men (p= 0.20). This, again, is not readily amenable to explanation but it can be related to the fact that women in our sample were significantly shorter than men. Another possibility may be the confounder effect of the BMI difference between the two genders in our population that has been demonstrated.

Despite the fact that more women than men reported 'symptoms', direct association between the 'disease' and female gender has not been demonstrated in our study like in other studies e.g. Singh et al[14]. Contrary to that, differential gender analysis of age-associated risk revealed that men's OR exceeded markedly that of women. There could be more than one explanation to this finding and apparent difference between these two studies. The first one is the difference between both communities, the Indian and the Kurdish. While the present day Duhok's women lead, in general, a home-bound, relatively easy life with electricity-powered laundry machines, dish washers, sweepers, tap water, etc, the Indian women in general, one expects, lead a harder life, probably bearing heavy loads on their heads like Pakstani and Bangladishi women[17].

Chronic drug use showed a significant association with CS in women (OR 4 and p < 0.001) compared to the same parameter in men. This may be a reflection of the longer duration of symptoms in women: the longer the history, the more likelihood of drug use.

Despite reports in favor of strong genetic effect in neck pain and cervical

spondylosis[18], this study failed to show statistically significant association with the family history of patients. This may reflect underdiagnosis in the relatives of the patients, forgetfulness of the patients in the tense, crowded situation of outpatient (recall bias), or real absence of wide spread familial aggregation as Yoo and Origitano stated[19]. Anyhow the available literature which stresses the role of heredity in cervical spondylosis depends largely on studies of identical twins[20]. There is a logic objection on interpretations from twin studies, that is, the twins in most situations share the same environment[21].

Smoking displayed a statistically significant association with spondylosis only in men. This can be ascribed to a small percentage of smokers among women of the study sample. This, in turn, can be real or caused by a sort of denial caused by the socio cultural embarrassment of the stigma which is linked with smoking of women in a conservative Duhoki community, making women unwilling or reluctant to admit smoking. Takatalo et al (2013) found similar results in Finnish males connecting smoking to lumbar disk degeneration[22].

A novel factor which has been examined for the first time in the present study is the traditional Kurdish male head turban called "shashek". The shashek use proved to have a statistically significant association with cervical spondylosis (OR 16.8 and p= 0.009). This can be compared to the effect of bearing loads on head studied by other researchers[10,9] ,or a confounding effect of age as more aged men wear shashek.

As to physical activity, those who exercised at a rate ≥ 150 min/week were less prone to CS (OR 0.18 and p= 0.003) than others who exercise < 150 min/week. According to the WHO, about 3.2 million deaths per year globally are attributable to insufficient physical activity which is the fourth cause of mortality globally[16].

Study limitations included the following: Fist, the study sample was totally hospital based as it was wholly recruited from a tertiary health care center. Thus the gathered data may not have reflected the experience among the whole population. The other point is the difficulty of assessing occupational exposure accurately, as assessment relied on self-reporting of exposures not objective measures. In addition, the majority of subjects were women, whose majority were housewives.

In conclusion, radiological CS is positively associated with aging and physical inactivity in both genders. Female gender exhibited positive association with BMI and chronic drug use contrasting negative association with height. Kurdish turban and smoking showed a statistically significant association with radiological CS in men. Adoption of public educational programs to help control and prevention of the documented risk factors is suggested.

REFERENCES

1. Kelly JC, Groarke PJ, Butler JS, Poynton AR, O'Byrne JM. The Natural History and Clinical Syndromes of Degenerative Cervical

Spondylosis. 2011. Adv Orthop. 2012; 2012: 393642.
2. Rana S S. Diagnosis and Management of Cervical Spondylosis. 2013. http://emedicine.medscape.com/article/1144952.
3. Zejda JE, Stasiow B. Cervical spine degenerative changes in coal miners. Int J Occup Med Environ Health. 2003; 16: 49-53.
4. Liuke M, Solovieva S, Lamminen A, Luoma K, Leino-Arjas P, Luukkonen R et al. Disc degeneration of the lumbar spine in relation to overweight. Int J Obes. 2005; 29(8):903-8.
5. Vismara L, Menegoni F, Zaina F, Galli M, Negrini S, Capodaglio P. Effect of obesity and low back pain on spinal mobility: a cross sectional study in women. J Neuroeng Rehabil. 2010; 7:3. http://doi.org/10.1186/1743-0003-7-3
6. Battié MC, Videman T, Gill K, Moneta GB, Nyman R, Kaprio J. et al. Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. Spine. 1991;16(9): 1015-21.
7. Battié, M.C., Videman, T., Kaprio. J., Gibbons, L.E., Gill, K., Manninen, H. et al. The Twin Spine Study: Contributions to a changing view of disc degeneration. Spine J. 2009; 9 (1): 47–59.
8. Wilson, J.; , Patel, A.A.; , Brodt, E.D.; Dettori JR, Brodke, D.S.; ,Fehlings, M.G. Genetics and heritability of cervical spondylotic myelopathy and ossification of posterior longitudinal ligament: results of a systematic review. Spine J. 2013; 38 (22 Suppl 1): 123-46,
9. Echarri, J.J. and, Forriol, F. Influence of the type of load on the cervical spine: a study on Congolese bearers. Spine J. 2005; 5(3):291-6
10. Joosab M, Torode M, Rao PV.Joosab, M.; Torode, M.; Rao, P.V. Preliminary findings on the effect of load-carrying to the structural integrity of the cervical spine. Surg Radiol Anat. 1994; 16(4): 393-8. PMID 7725195
11. Jumah KB1, Nyame PK.. Jumah, K.B. and Nyame, P.K. Relationship between load carrying on the head & cervical spondylosis in Ghanaians. West Afr J Med. 1994;13 (3):181-2. PMID 7841112
12. Mäkelä, M.; Heliövaara, M.; Sievers, K.; Impivaara, O.; Knekt, P.; Aromaa, A. Prevalence, determinants, and consequences of chronic neck pain in Finland. Am J Epidemiol. 1991; 134 (11): 1356-67.
13. Daniels, J.M. and Hoffman, M.R. (eds.), Common Musculoskeletal Problems: A Handbook. 1st ed. New York: Springer-Verlag; 2011.
14. Singh S, Kumar D, Kumar S. Singh, S.; Kumar, D.; Kumar, S. Risk factors in cervical spondylosis. J Clin Orthop Trauma. 2014; 4 (5): 221-6. PMC 4264061.
15. Singh, K.; Masuda, K.; Thonar, E.; An, H.S., and, Cs-Szabo, G. Age-related changes in the extracellular matrix of nucleus pulposus and anulus fibrosus of human intervertebral disc; Spine. 2009; 34(1): 10–6.

16. WHO. Physical activity, key facts. WHO Media Center. 2014; Fact sheet No.385. Available from: http://www.who.int/mediacentre/factsheets/fs385/en/
17. Mahbub MH, Laskar MS, Seikh FA, Altaf MH, Inoue M, Yokoyama K. et al. Prevalence of Cervical Spondylosis and Musculoskeletal Symptoms among Coolies in a City of Bangladesh, J Occup Health. 2006; 48:69-73
18. MacGregor AJ1, Andrew T, Sambrook PN, Spector TD.MacGregor, A.J.; Andrew, T.; Sambrook, P.N.; Spector, T.D. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis Rheum. 2004; 51 (2): 1607.
19. Yoo K1, Origitano TC.Yoo, K. and Origitano, T.C. Familial cervical spondylosis. Case report. J Neurosurg. 1998; 89 (1): 139-41. PMID 9647185.
20. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: do age and gender matter? A population-based study of 34,902 Danish twins 20–71 years of age. BMC Musculoskelet Disord. 2011; 10:39
21. Williams, F.M.K.; Sambrook, P.N. Neck and back pain and intervertebral disc degeneration: Role of occupational factors. Best Pract Res Clin Rheumatol 2011 ;1 (25); 69–79.
22. Takatalo J, Karppinen J, Taimela S, Niinimäki J, Laitinen J, Blanco Sequeiros R. et al. Body mass index is associated with lumbar disc degeneration in young Finnish males: subsample of Northern Finland birth cohort study 1986. BMC Musculoskelet Disord. 2013; 14:87. Available from: http://www.biomedcentral.com/1471-2474/14/87.

پوختە

هۆکارێن مەترسیێ بو ژنافچوونا دومدرێژ یا بربرا ستوی لدهوکی: ڤەکولینەکا بەراوردییا نەخوش وساخلەما

پێشەکی: بڕبڕا ستوی ناڤ و نیشانەکێ درێژە ئاماژە ب بوارێ ژنافچوونا دوم درێژ ب رەنگەکێ گشتی پێشڤەبووی د تەمەنیدا تـوش دبـن زێدەباری هۆکارێن مەترسیا پەیدا دبیت. ئەو نەخۆشی یا بەربەلاڤە و چێدبیت ببتە ئەگەرێ گەلەك تەنگاڤیێن مەزن و تێکچوونا دەمارا و ئەڤجا پێدڤیەکا روون و ئاشکەرا هەیە بو نیاسینا هۆکارێن مەترسیا پەیدا دبیت، دا ب رەنگەکێ باشتر تێبگـەهین کـا چـەوا دێ خـو پارێزین و وێ نەخۆشیێ کونترول کەین. ژبەر وێ چەندێ من ئەڤ ڤەکولینە ئامادەکر بـو گـەریان ل هۆکـارێن مەترسـیا پەیـدا دبیـت لنـك ئاکنجیێن پارێزگەها دهۆکێ.

ڕێکێن ڤەکولینێ: پشت بەستن ل سەر هەبوونا گورانکاریێن تیشکی، نموونەیا ڤەکولینێ هاتە دابەشکرن کو (٢٥٨) هەتا (١٢٩) نەخۆشن و (١٢٩) حالەتێن بهێز ژ بنگـەهێ دهـوك یـێ نەخۆشـێن روماتیزمێ ژ ٤/١ هـەتا ٢٠١٤/٩/٣٠ . ، ئـەڤ پێزانینـە ژ هـەمی پـشکداران هاتنـە وەرگرتن، تەمەن، رەگەز، بوارێ هەڤژینیێ، کێش، درێژی، جگارەکێشان، روژا نەخۆشیێ، بکارئینانا دەرمانا، هژمارا بـالیفکێن نڤستنێ زێدەباری لبەرکرنا شاشکێ لنك زەلامان. بەرنامێ (SPSS) هاتە بکارئینـان د شـرۆڤەکرنا ئامارێدا وئاسـتێ (≤ 0.05) هاتـەوەرگرتن وەك جیاوازیا ئاماریّ یا مەعنەوی هەروەسا ڕێژەیێن (odds ratio and95% CI) هاتە وەرگرتن وەك پێڤەرەك بو مەترسیێ.

ئەنجام: ب رەنگەکێ گشتگر تەمەن مەزنترین هۆکارێ مەترسیا بهێزبـوو لنـك هـەردوو رەگـەزان (OR 13 – 55) سـەبارەت ئافرەتـان هۆکارێن مەترسیێ ب ڤی رەنگینە: بکارئینانا دەرمانان (OR 4.01) تێکرایێ پارستەیا لەشی (OR 3.44). پاشـی کارکرنـا گەلـەك رویـنـشتن (OR 2.64). لێ زەلام ب ڤـی رەنگینـە: لبـەرکرنا شاشـکێ (OR 16.8) کارکرنـا گەلـەك رویـنـشتن (OR 5.6) پاشـی جگارەکێشان (OR 4.18) چالاکیا لەشی ب تێکرایێ (150 min/wk≥) پەیوەندیەکا بەرەڤاژی دیارکر ب ئاستێ ئامـارا مەعنـەوی (P value < 0.05) لنك زەلامان (OR 0.34) و ئافرەتان (OR 0.18).

دەرئەنجام: بڕبڕا ستوی یا جیاواز ب نیشانان گرێدایە ب پەیوەندیەکا پۆزەتیڤ دگەل تەمەنی و کارکرنـا گەلـەك رویـنـشتن لنـك هـەردوو رەگەزان، هەروەسا پەیوەندیەکا پۆزەتیڤ هەیە ب ئاستێ ئامارا مەعنەوی دگەل بکارئینانـا دەرمانـان و تێکرایـێ پارسـتەیا لەشـی لنـك ئافرەتان ب بەراوردکرن ب لبەرکرنا شاشکێ و جگارەکێشانێ لنك زەلامان.

الخلاصة

عوامل الأختطار للفقار العنقي المشخص شعاعيا في دهوك:
دراسة الحالات المراقبة

خلفية واهداف البحث: ان الفقار العنقي هو عنوان عريض يشير الى حالة اضمحلال مزمنة تعزى بشكل عام الى تقدم العمر اضافة الى عوامل اختطار محتملة. ان المرض شائع ويمكن ان يتسبب بمعاناة كبيرة وخلل عصبي وعليه فهناك حاجة واضحة للتعرف على عوامل الاختطار المحتملة. لاجل ذلك اعدت هذه الدراسة لتقصي عوامل الاختطار المحتملة لدى قاطني محافظة دهوك.

الاشخاص والطرق: أجريت الدراسة في مركز دهوك للامراض الروماتزمية للفترة من ٤/١ الى ٩/٣٠ /٢٠١٤.اعتمادا على وجود التغيرات الشعاعية (علامات الفقار) في اشعة العنق تم اختيار (١٢٩) مريض ومن المراجعين الذين لم توجد عندهم تغيرات شعاعية تم جمع (١٢٩) حالة ضابطة. هذا وقد تم اخذ المعلومات التالية من كل المشاركين: العمر، الجنس، الحالة الزوجية، الوزن، الطول، التدخين، التاريخ المرضي، استعمال الادوية، عدد وسائد النوم اضافة الى ارتداء غطاء الراس التقليدي لدى الرجال. تم استعمال برنامج (SPSS) في التحليل الاحصائي واعتمد المستوى (0.05%) كفارق احصائي معنوي كما اعتمدت نسب الـ(odds ratio and 95% CI) كمقياس للاختطار.

النتائج: كان العمر اكثر عوامل الاختطار قوة لدى الجنسين (OR 13.55). بالنسبة للنساء كانت عوامل الاختطار كالاتي: استعمال الادوية (OR 4.01) معدل كتلة الجسم (OR 3.44) ثم العمل كثير الجلوس (OR 2.64) اما الرجال فكانت كالاتي: ارتداء غطاء الراس التقليدي (OR 16.8) العمل كثير الجلوس (OR 5.6) ثم التدخين (OR 4.18). أظهر النشاط البدني بمعدل (١٥٠%دقيقة أسبوعيا) علاقة عكسية بمستوى احصائي معنوي (P value <0.05) لدى كل من الرجال (OR 0.34) والنساء (OR 0.18).

الاستنتاجات: ان الفقار العنقي المتسم بالاعراض يرتبط بعلاقة ايجابية مع العمر والعمل كثير الجلوس لدى كلا الجنسين كما ان هناك علاقة ايجابية بمستوى احصائي معنوي مع استعمال الادوية ومعدل كتلة الجسم لدى النساء مقارنة بارتداء غطاء الراس التقليدي والتدخين لدى الرجال

REFLEX SYMPATHETIC DYSTROPHY: RECOGNITION OF SOME RISK FACTORS

JAGER OMER AHMED, M.B.Ch.B, FICMS*
YOUSIF ALI YASEEN, M.B.Ch.B, FIBMS (PSYCH)**

Submitted 20 October 2015; accepted 31 December 2015

ABSTRACT

Background: Reflex sympathetic dystrophy occurs most often in the extremities after an injury. It causes the limb to undergo chronic pain, swelling, redness, tenderness and stiffness with patchy rarefaction. The diagnosis is mainly clinical and delay in diagnosis ends with poor prognosis. Therefore predicting this problem is important by noticing the risk factors. Aim of this study is to highlight some risk factors for development of this disorder.

Patients and methods: The study included those patients who sustained trauma to their extremities or underwent surgery. Children and those with clear nerve injury were excluded from the study. Those who did not show the clinical features of RSD were included in the group 1 and we considered them as a control group, while those who had RSD features were included in the group 2.

Results: The total number of the patients were 143 case. In Group 1 the male to female ratio was 3:2, the average age was 36 years. 65 of them had trauma to their upper limb and 31 to lower limb. Most of them had no psychological symptoms. In Group 2 the male to female ratio was 1:4 and the average age was 53 years. 27 with upper limb trauma and 20 with lower limb. All the patients of this group had clear psychological disturbance and 45 (95.7%) of them had pre-morbid stressful personality.

Conclusion: age (middle), gender (female) and stressful personality are risk factors to develop RSD if such a person sustained trauma or did a surgical procedure. The extremity involved and the type of injury seems to have no role in development of RSD.

Duhok Med J 2015; 9 (2): 97-108.

Keywords: reflex sympathetic dystrophy, risk factors

Reflex sympathetic dystrophy (RSD) is considered type 1 of complex regional pain syndrome which occurs most often in the extremities after an injury. Despite a multitude of theories, there is no well-defined or complete system for explaining the etiology of this problem. It is associated with dys-regulation of the central nervous system and autonomic nervous system resulting in multiple functional loss, impairment and disability.[1-4]

The patient complains of continuous pain, often described as 'burning' in character and beyond what would be expected for an injury. At first there is local swelling, redness and warmth, as well as tenderness and moderate stiffness of the nearby joints.

* *Lecturer of Orthopedics, Department of Surgery, College of Medicine, University of Duhok, Kurdistan Region, Iraq E-mail: jager.doski@yahoo.co.uk*
** *Lecturer of Psychiatry-Department of Medicine, College of Medicine-University of Duhok, Kurdistan Region, Iraq E-mail: yousif.ali@uod.ac*

As the weeks go by the skin becomes pale and atrophic, movements are increasingly restricted and the patient may develop fixed deformities. Most of the patients may experience anxiety or depression because of the long lasting symptoms. X-ray characteristically shows patchy rarefaction of the bone.[1,2,5]

Unfortunately, there is neither laboratory nor imaging studies that are diagnostic for this syndrome. Thus the diagnosis remains clinical.[2]

The earlier the condition is recognized and treatment begun, the better the prognosis and vice versa (i.e. delay in diagnosis = poor prognosis).[1,2,6-8] Therefore predicting this problem is important by noticing the risk factors in order to diagnose the condition early and minimize its catastrophic sequels.

Aim of this study is to highlight some risk factors for development of RSD specially regarding age, sex, extremity involved, type of trauma and psychological status of the patient.

PATIENTS AND METHODS

This study was done in Duhok city over a period extended from February 2013 to October 2015. The study included those patients who sustained trauma to their extremities which had been treated and followed by the orthopedic surgeon at the orthopedic department of Emergency teaching hospital or private clinic. The total number of the patients was 145 case of upper or lower limb injuries of different types (including ligamental injuries, fractures, subluxations or dislocations of the joints and surgical operations). The exclusion criteria were children and adolescents (age less than 20 years) and those who had clear evidence of nerve injuries (in order to exclude causalgia which is the type 2 of complex regional pain syndrome). Two cases with features of RSD in their upper limb were excluded from the study as they had no history of recent trauma but a history of cerebro-vascular accident (one before 2 months and the other before 6 months from the date of diagnosis of RSD disorder); their RSD features were in the paralyzed side. So the final number was 143 cases.

For diagnosis of RSD the current study depended on the diagnostic criteria adapted by the International Association for Study of Pain with its recent modifications "the Budapest criteria". Table 1,2[9-14]

Those who did not show the clinical features of RSD (up to 3 months from time of trauma or operation) were included in the group 1 and we considered them as a control group, while those who had RSD features were included in the group 2. (examples of cases figure 1 and figure 2)

All the patients were asked about any psychological abnormalities (like anxiety, depression, obsession).

(A)

(B)

Figure 1: A patient with left sided Colles' fracture complicated by reflex sympathetic dystrophy (a: clinically; b: X-ray changes)

(A)

(B)

Figure 2: A patient developed features of reflex sympathetic dystrophy after an ankle twist injury with partial lateral collateral ligamental injury (a: clinically; b: X-ray changes).

Table 1: IASP diagnostic criteria for complex regional pain syndrome (CRPS)*9-11

1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

* If seen without "major nerve damage" diagnose CRPS I; if seen in the presence of "major nerve damage" diagnose CRPS II.

Table 2: Clinical Diagnostic Criteria (the "Budapest Criteria") for CRPS12-14

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
   - Sensory: Reports of hyperesthesia and/or allodynia
   - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - Sensory: Evzaidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - Vasomotor: Evidence of temperature asymmetry (>1 °C) and/or skin color changes and/or asymmetry
   - Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

For research purposes, diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

The data of each patient were reported in a special form that include name, age, sex, occupation, type of injury, date of injury, treatment received, date of diagnosis of RSD from the time of injury and psychological abnormalities in the history. Those patients who had psychological abnormalities specially of group 2 were sent to the psychiatrist for further diagnosis of the psychological abnormality, assessment of pre-morbid personality, and treatment of his (her) psychiatric disorder. The opinion of the psychiatrist was included in the form of the patient.

RESULTS

The total number of the patients included in this study was 143 cases, 65 males and 78 females. Their age ranged from 20-70 years. Ninety two of them sustained trauma to their upper limb and the rest 51 of the patients to their lower limb. The types of trauma were of 4 categories: bone fracture 98 cases, joint dislocation 5 cases, soft tissue contusion and ligamental injuries 12 cases, and post-operative 28 cases. The time of diagnosis of RSD was extended between 6-13 weeks from the time of trauma with an average of 8 weeks. (Table 3,4,5)

Table 3: Gender characteristics of the study sample

Gender	Group 1	Group 2	Total
Male	56 (58.3%)	9 (19.1%)	65
Female	40 (41.7%)	38 (80.9%)	78
	96 (100%)	47 (100%)	143

Table 4: Limb involved characteristics of the study sample

Limb involved	Group 1	Group 2	Total
Upper	65 (67.7%)	27 (57.4%)	92
Lower	31 (32.3%)	20 (42.6%)	51
Total	96 (100%)	47 (100%)	143

Table 5: Type of injury characteristics of the study sample

Type of injury	Group 1	Group 2	Total
Fractures	77 (80.2%)	21 (44.6%)	98
Joint dislocations	2 (2.1%)	3 (6.4%)	5
Soft tissue injury	2 (2.1%)	10 (21.3%)	12
Post-operative	15 (15.6%)	13 (27.7%)	28
Total	96 (100%)	47 (100%)	143

Group 1 (those who had no features of RSD as a control group) were 96 patients, 56 males (58.3%) and 40 females (41.7%) with a ratio of about 3:2. Their age ranged from 20-70 years with an average of 36 years. Sixty five of them had trauma to their upper limb and the rest 31 cases to their lower limb. Seventy seven (80.2%) of them sustained bone fracture, 2 (2.1%) of them with joint dislocation, 2 (2.1%) with soft tissue contusion and ligamental injuries, and 15 (15.6%) cases were post-operative. The patients in this group showed no psychological symptoms apart from mild anxiety due to the concern of the trauma.

Group 2 (those who had features of RSD) were 47 patients, 9 males (19.1%) and 38 females (80.9%) with a ratio of about 1:4. Their age ranged from 35-65 years with an average of 53 years. In 27 patients the triggering trauma was in their upper limb and the rest 20 cases got lower limb trauma. Twenty one (44.6%) of them had bone fracture, 3 (6.4%) of them had joint dislocation, 10 (21.3%) of them had soft tissue contusion and ligamental injuries and 13 (27.7%) were post-operative cases. All the patients of this group had clear psychological disturbance in form of anxiety and depression which had been confirmed by the psychiatrist. Forty five (95.7%) of them had pre-morbid stressful personality (i.e. type A personality), while the other two patients denied any psychological abnormalities before they sustained the trauma and they were of non-stressful personality (i.e. type B personality).

DISCUSSION

The age of the patients which had been included in this study ranged from 20-70 years. The children and adolescent were not included in this study as the personality not fully developed yet.

The age of the patient who did not show the features of RSD (i.e. Group 1) ranged from 20-70 with an average of 36 years, while those who developed RSD (i.e. Group 2) ranged from 35-65 with an average of 53 years. This mean that patients of Group 2 were older than Group 1. This indicate that as the age of the patient increase the risk to develop RSD is more; however, some patients of this study were old age and they did not developed RSD, but most of the patients who developed RSD were at the middle age. This can be explained by that most of the persons at the middle age group are more affected and more aware about life stresses than those who are very young or very old. This does not mean that RSD not occur in age extremities but they have less incidence. Most of the studies 15-19 which described the average age of the patients who developed RSD was at the middle age (which is the period of life from 45 to 64 years), like de Mos *et al* (2007)[15], Puchalski *et al* (2005)[16], Sandroni *et al* (2003)[17], Birklein *et al* (2000)[18] and Rauis (1999)[19].

In Group 1 the male to female ratio was 3:2 while in Group 2 the ratio was 1:4. This indicates that females are more liable to develop RSD than males. In other studies like de Mos *et al* (2007)[15] the females were affected at least three times more often than males, and in Sandroni *et al* (2003)[17] the female to male ratio was 4:1. Even in adolescent patients the RSD is more likely to affect girls (80%) as described by Taylor (2002)[6].

In Group 1, 65 patients got trauma to their upper limb and 31 patients got trauma to the lower limb with a ratio of about 2:1. In Group 2, 27 cases had upper limb trauma and the other 20 cases got lower limb trauma with a ratio of 1.3:1. In both groups the differences between upper limb and lower limb trauma were not significant.

In Group 1, most of the patients sustained significant trauma to their extremities in form of fracture, dislocation or surgical operation; but they did not show the features of RSD. While in Group 2, a significant number of patients (21.3%) got only soft tissue contusion and ligamental injuries but they developed RSD later on. This indicates that type of injury has no role in development of RSD.

Most of the patients of Group 1 had no significant psychological symptoms apart from mild anxiety due to the concern of the trauma especially in the first few weeks of treatment. But in Group 2, all the patients had more clear psychological disturbances in form of anxiety and depression which had been confirmed by the psychiatrist. These psychological features were present at the first few weeks after trauma and become more clear after 6-8 weeks (time of diagnosis of RSD). All of them were examined by the psychiatrist for assessment of their pre-morbid personality before they got the trauma. Forty five patients had stressful personality (Type A personality) before they gained trauma. The other two patients of this group had Type B personality.

Most of the studies showed that patients with RSD have psychological abnormalities[5-8,16,19-27], but there is controversy in these studies whether these psychological abnormalities are squeals of trauma or they are predisposing factors that make a person liable to develop RSD. Popawski et al28 noted that individuals with psychiatric illness are more prone to develop RSD. Horowitz 29 reported in a group of 11 patients developing RSD subsequent to medical procedures, 7 patients (64%) required psychiatric evaluations, 6 of them appeared to have pre-morbid psychological dysfunction in form of depression and dependent personality with diminished ability to manage (unspecified) life stressors. Hemler et al30 studied military records of 19 patients with RSD who were currently active in the military. They found that 63% of them had reports of interpersonal conflicts, slow rate of promotion and repeated sick calls for non-specific complaints. They conclude that these psychological abnormalities are predisposing factors to RSD. Hootkani *et al*[31] concluded that personal characteristics of patients with distal radius fracture play a role in the incidence of RSD as they found that the presence of type A

personality characters had a significant positive relationship and the presence of type B personality characters had a negative relationship with the incidence of RSD, but they did not found any significant relationship between depression and anxiety of the patients with the occurrence of RSD. Other studies[7,22,27,32] also concluded that psychiatric comorbidity and personality disorders are important etiology and maintenance factors in RSD.

Other researchers[16,25,26] did not find significant psychological differences between RSD and non RSD groups.

The current study agrees that much of the psychological dysfunction associated with RSD is a result of the trauma (that end with prolonged pain and disability), but we suspect that some psychological factors (like anxiety and depression) make one liable to develop RSD, in addition to the pre-morbid stressful personality as can be concluded from the results of this study (45 out of 47 patients had pre-morbid stressful personality which is statistically significant result).

In conclusion, it seems that age (middle), gender (female) and psychological abnormalities (like anxiety, depression, stressful personality,….) are risk factors to develop RSD if such a person sustained trauma or did a surgical procedure. This will help us in predicting this disorder in such persons once they get trauma or when undergo surgery, as early diagnosis has better prognosis. It may play also a role for taking some prophylactic measures to prevent development of such disorder. For that new studies are recommend to be done. The extremity involved in the trauma and the type of injury seems to have no role in development of RSD.

REFERENCES

1. Solomon L, Warwick D, Nayagam S. Apley's System of Orthopaedics and Fractures. 9th edition. London: Hodder-Arnold; 2010. Chapter 23, Principles of fractures; p. 723.
2. Jobe MT, Martinez SF. Peripheral nerve injuries, chapter 62. In: Canale ST, Beaty JH. Campbell's Operative Orthopaedics. 12th edition. Philadelphia : Elsevier-Mosby; 2013. p. 3070-72.
3. Jänig W, Baron R. Complex regional pain syndrome is a disease of the central nervous system. Clin Auton Res. 2002 ;12(3):150-64.
4. Marshall AT, Crisp AJ. Reflex sympathetic dystrophy. Rheumatology. 2000;39(7):692-5.
5. Bruehl S, Carlson CR. Predisposing psychological factors in the development of reflex sympathetic dystrophy. A review of the empirical evidence. Clin J Pain. 1992;8(4):287-99.
6. Taylor LM. Complex Regional Pain Syndrome: Comparing Adults and Adolescents. Topics in Advanced

Practice Nursing eJournal. 2002;2(2). Available from : http://www.medscape.com/viewarticle/430537

7. Vouilloz A , Deriaz O, Rivier G, Gobelet C, Luthi F. Biopsychosocial complexity is correlated with psychiatric comorbidity but not with perceived pain in complex regional pain syndrome type 1 (algodystrophy) of the knee. Joint Bone Spine. 2011;78(2):194-9.
8. Geertzen JH , de Bruijn H, de Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil. 1994;75(4):442-6.
9. Firman G. Diagnostic criteria for complex regional pain syndrome (CRPS). [Internet: medicalcriteria.com]. [cited 2010 Jul 16, updated 2014 Aug 29]. Available from: http://www.medicalcriteria.com/site/en/criteria/64-neurology/282-crps.html
10. Galer BS, Schwartz L, Allen RJ. Loeser JD, Butler SH, Chapman RC,(eds). Complex regional pain syndromes-- Type I: reflex sympathetic dystrophy, and type II: causalgia. In: Bonica's management of pain. Philadelphia: Lippincott Williams & Wilkins; 2001. 388- 411.
11. Quisel A, Gill JM, Witherell P. "Complex regional pain syndrome underdiagnosed". J Fam Pract. 2005;54(6):524–32. Available from: http://www.jfponline.com/index.php?id=22143&tx_ttnews[tt_news]=179014
12. Harden RN, Bruehl SP. Diagnosis of complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. Clin J Pain. 2006;22(5):415-9.
13. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326-31.
14. Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010;150(2):268-74.
15. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker B, Sturkenboom MC. The incidence of complex regional pain syndrome: A population-based study. Pain.2007; 129(1-2): 12-20.
16. Puchalski P, Zyluk A. Complex Regional Pain Syndrome Type 1 after Fractures of the Distal Radius: A Prospective Study of the Role of Psychological Factors. J Hand Surg, Eur Vol 2005; 30(6): 574-580. Available from: http://jhs.sagepub.com/content/30/6/574.short
17. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103(1-2):199.

18. Birklein F, Riedl B, Sieweke N, Weber M,Find all citations by this author (default).Or filter your current search Neundörfer B. Neurological findings in complex regional pain syndromes--analysis of 145 cases. Acta Neurologica Scandinavica. 2000;101(4):262-269.
19. Rauis AI. Psychological aspects: A series of 104 posttraumatic cases of reflex sympathetic dystrophy. Acta Orthop Belg 1999; 65(1):86-90. Available from: http://www.actaorthopaedica.be/acta/download/1999-1/10217007.pdf
20. Ciccone DS, Bandilla EB. Psychological dysfunction in patients with reflex sympathetic dystrophy. Pain. 1997;71(3):323-333.
21. Neal LA. Complex regional pain syndrome: the role of the psychiatrist as an expert witness. Med Sci Law. 2009;49(4):241-6.
22. Nelson DV, Novy DM. Psychological characteristics of reflex sympathetic dystrophy versus myofascial pain syndromes. Reg Anesth. 1996;21(3):202-8.
23. Lynch ME. Psychological aspects of reflex sympathetic dystrophy: a review of the adult and paediatric literature. Pain. 1992;49(3):337-47.
24. Hooshmand H, Phillips EM. Psychological Aspects of Reflex Sympathetic Dystrophy (RSD) or Complex Regional Pain Syndrome (CRPS). Available from: http://www.rsdinfo.com/Psychological_Aspects_of_RSD.pdf
25. Lohnberg JA, Altmaier EM. A Review of Psychosocial Factors in Complex Regional Pain Syndrome. J Clin Psychol Med Settings. 2013 20:247–254.
26. Bruehl S , Husfeldt B, Lubenow TR, Nath H, Ivankovich AD. Psychological differences between reflex sympathetic dystrophy and non-RSD chronic pain patients. Pain. 1996;67(1):107-14.
27. Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful Life Events and Psychological Dysfunction in Complex Regional Pain Syndrome Type I. Clinical Journal of Pain. 1998;14(2):143-147. Available from: http://journals.lww.com/clinicalpain/Abstract/1998/06000/Stressful_Life_Events_and_Psychological_.9.aspx
28. Poplawski ZJ, Wiley AM, Murray JF. Post-traumatic dystrophy of the extremities: a clinical review and trial of treatment. JBJS am 1983;65:642-55. Available from: http://jbjs.org/content/jbjsam/65/5/642.full.pdf
29. Horowitz LH. Iatrogenic causalgia: classification, clinical findings, and legal ramification. Arch Neurol 1984;41:821-4.
30. Hemler DE, McAuley RA, Belandres PV. Common clinical presentations among active duty personnel with traumatically induced reflex sympathetic dystrophy. Milit Med 1988;153:493-5.
31. Hootkani AR, Hasankhani EG. Relationship between Anxiety,

Depression, and Personality Type and the Incidence of Reflex Sympathetic Dystrophy in Patients with Distal Radius Fracture. Iran J Med Sci. 2008; 33(2):74-8. Available from: http://ijms.sums.ac.ir/index.php/IJMS/article/view/1687

32. Monti DA, Herring CL, Schwartzman RJ, Marchese M. Personality assessment of patients with complex regional pain syndrome type I. Clin J Pain. 1998;14(4):295-302.

پوختە

تێکچونا ئەرکێ دەماریێت سمپتاوی: ڤەدیتنا هندەك ئەگەرا

پێشەکی: تێکچونا ئەرکێ دەماریێت سمپتاوی چێدبیت ل دەست و پێت مروڤی ئەگەر توشی زەحمەتەکێ یان نشتەگەریەك لێ کر. ئەڤەژی دبیتە ئەگەرێ ئێشانەکا بەردەوام دگەل رەقاتیا گەها و پێتیبونا هەستی. دەست نیشانکرنا ڤێ حالەتی کلینیکیە و گیروبونا ڤێ چەندی کارتێکرنێت خراب ییت هەین.

ئارمانج ژڤێ ڤەکولینێ دەست نیشان کرنا هندەك ئەگەریت ڤێ چەندێ.

نەخوش و ریکێت ڤەکولینێ: دڤێ ڤەکولینێدا ئەو نەخوش ڤەگرتن ئەویت توشی زەحمەتەکێ بوین یان نشتەگەری کرین بو دەست و پێێت خو کرین. ئەو نەخوشێت هیمایێت تێکچونا ئەرکێ دەماریت سمپتاوی لێ دیار نەبون بونە گروپێ ١ و ییت لێ دیار بوین بونە گروپێ ٢.

ئەنجام: نەخوش هەمی ١٤٣ بوون. ل گروپێ ١ ریژا نێرا بو مێیا ٣:٢ و ناڤنجیا ژییێ وان ٣٦ سال بون. ٣٦ ژ وان توشی زەحمەتەکێ ببون ل دەست تێت وان و ٣١ ل پێت وان. ئەڤانە هیچ هیمایێن دەرونی ییت نە سروشتی ل دەف وان نەبون. ل گروپێ ٢ ریژا نێرا بو مێیا ١:٤ و ناڤنجیا ژییێ وان٥٣ سال بون. ٢٧ ژ وان توشی زەحمەتەکێ ببون ل دەست تێت وان و ٢٠ ل پێت وان. هەمی نەخوشێت ڤی گروپی هیمایێت دەرونی ییت نە سروشتی ل دەف هەبون و ٤٥ ژ وان هندەك تێکچوونێت دەرونی هەبون بەری توشی ڤێ زەحمەتێ ببن یان کەساتییەکا نازك هەبوو.

دەرئەنجام: ژی (ناڤنجی) ، رەگەز (مێ) و کەساتییا نازك ژ وان ئەگەرانە کو هیمایێت تێکچونا ئەرکێ دەماریێت سمپتاوی لێ دیار ببن ئەگەر ئەڤە توشی زەحمەتەکێ ببن یان نشتەگەریەك بو دەست و پێت خو کرن و چ جیاوازی نینە چ دەست بیت یان پێ بیت.

الخلاصة

اختلال الجهاز العصبي السمبثاوي الانعكاسي: ملاحظة بعض العوامل المؤدية لها

الخلفية: اختلال الجهاز العصبي السمبثاوي الانعكاسي يحدث عادة في اطراف الجسم بعد تعرضها لاصابة. انه تسبب الام مزمنة، تورم مع تحدد حركة المفاصل و نخر موضعي للعظام. التشخيص دائما سريري و التأخر في ذلك ذو عواقب سيئة. لذلك توقع هذه الحالة مهم و ذلك من خلال ملاحظة بعض العوامل المؤدية لها.

الهدف من هذه الدراسة هو القاء الضوء على بعض العوامل التي قد تؤدي لها.

المرضى و طرق البحث: تضمنت الدراسة المرضى الذين تعرضوا لشدة خارجية او اجروا عمليات جراحية في اطرافهم. الاطفال و الذين لديهم اصابة واضحة في العصب استثنوا من الدراسة. الذين لم يظهر عليهم علامات الحالة صنفوا ضمن المجموعة ١ و الذين ظهرت عليهم صنفوا ضمن المجموعة ٢ .

النتائج: العدد الكلي للمرضى كانوا ١٤٣ . في المجموعة ١ كانت نسبة الذكور للاناث ٣:٢ و متوسط اعمارهم ٣٦ سنة. ٦٣ منهم لهم اصابة في الطرف العلوي و ٣١ في الطرف السفلي. و لم يكن لديهم اي علامات نفسية غير اعتيادية. في المجموعة ٢ نسبة الذكور الى الاناث ١:٤ و متوسط اعمارهم ٥٣ سنة. ٢٧ منهم كانت لهم اصابة في الطرف العلوي و ٢٠ منهم في الطرف السفلي. كل المرضى في هذه المجموعة كانت لهم علامات نفسية غير اعتيادية ٤٥ منهم كانت لهم مشاكل نفسية قبل الاصابة او لهم شخصية انفعالية.

الاستنتاجات: العمر (المتوسط)، الجنس (الانثى) و الشخصية الانفعالية تعتبر عوامل مؤدية لظهور علامات اختلال الجهاز العصبي السمبثاوي الانعكاسي اذا تعرضوا لشدة خارجية او اجروا عملية جراحية في اطرافهم و لا يهم طرف علوي او سفلي.

پەربەندا ٩ ژمارە ٢

كانونا ئێكێ ٢٠١٥

زانكويا دهوك
كوليژا پزيشكى

گوڤارا پزيشكى يا دهوكێ

گوڤارا فەرمى يا كوليژا پزيشكى يا دهوكێ

ISSN: 2071 - 7326