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Chronic Diseases Journal

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The *Chronic Diseases Journal* is a quarterly peer-reviewed scientific journal published by Kurdistan University of Medical Sciences. The manuscripts on the topic of chronic and subacute medical and health conditions and diseases will be published in this journal. This contains all aspects of the chronic and subacute diseases such as control, planning, treatment, patient education, managing guides, policymaking, and biopsychosocial-spiritual factors.

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3. Kuczmarski RJ, Ogden CL, Grammer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Advance data from vital and health statistics. No. 314. Hyattsville, Md: National Center for Health Statistics, 2000. (DHHS publication no. (PHS) 2000-1250 0-0431)

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Chronic Diseases Journal

Editorial

Welcome to the first volume of the Chronic Disease Journal (http://cdjournal.muk.ac.ir), a quarterly peer-reviewed scientific journal published by Kurdistan University of Medical Sciences. The journal contains manuscripts on the topic of subacute and chronic medical conditions and diseases.

The number of medical articles published in Iran has considerably increased during the past decade. The development of any health care system strongly depends on the production, publication, dissemination, and application of updated biomedical knowledge to prevent and treat diseases and improve health services. The most critical role of medical and health professionals is to provide those in need with adequate related knowledge. The quantity of published articles is a commonly used indicator of the scientific level of a country. It also determines a country's contribution to the world science and its status in international academic rankings.

We promise that the Chronic Disease Journal will be a medium for the release of timely and thoughtful information on control, planning, treatment, patient education, management guides, policymaking, and biopsychosocial-spiritual factors in the field of subacute and chronic diseases.

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Nahid Ghotbi,
Editor in Chief, Chronic Disease Journal

Chronic Diseases Journal

Effectiveness of topical Clinda Soap in the treatment of acne vulgaris

Farrokh Rad[1], Mansoor Mirbagheri[2], Mohammad Hossein Pakdaman[3], Roxana Yaghmaee[4], Fardin Gharibi[5]

1 Associate Professor, Department of Dermatology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Pharmacist, Member of the Research Institute Milaco, U.S.A.
3 Chemist, Research and Development, Shadakish Co., Kish, Iran
4 Assistant Professor, Department of Dermatology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
5 Vice Chancellor of Research, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: A variety of drugs can be used for the treatment of acne vulgaris. Every medicine acts against one or some of the mechanisms of the pathogenesis of acne vulgaris. This study was conducted to assess the therapeutic effect of Clinda Soap in the treatment of acne vulgaris.

METHODS: This randomized, double-blind, clinical trial included 82 patients (age: 15-35 years) with mild to moderate acne vulgaris. The study protocol was approved by the ethics committee of Kurdistan University of Medical Sciences (Sanandaj, Iran). The patients were randomized into two groups to receive the standard treatment for acne vulgaris with either Clinda Soap (containing clindamycin hydrochloride 1%, manufactured by Shadakish Company, Iran) or a placebo soap. Both the intervention and control groups were asked to apply soaps twice daily for three months. Monthly examinations were performed by a dermatologist to ensure proper use of the soaps and to assess the rate of recovery and possible complications. Data was analyzed using repeated measures analysis of variance in SPSS.

RESULTS: The mean age of patients was 21.1 ± 4.7 years in the intervention group and 21.5 ± 4.8 years in the control group. The mean duration of the disease was 3.0 ± 1.5 and 3.1 ± 1.8 months in the intervention and control groups, respectively. The mean number of comedones in the two groups had no significant difference at any monthly visit. In contrast, at all visits, significantly fewer papules and pustules were observed in the intervention group than in the control. Significant intra-group and inter-group differences in the number of inflammatory lesions (papules and pustules) were also seen.

CONCLUSION: In general, it can be concluded that Clinda Soap is effective in the treatment of acne vulgaris. The recovery rate of papules and pustules was higher than that of comedones. Easy application of this soap together with its low cost and few adverse effects will increase patients' compliance.

KEYWORDS: Acne Vulgaris, Clinda Soap, Treatment

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Introduction

Acne vulgaris, a common inflammatory disease of pilosebaceous units, is experienced by 80% of adolescents. Increased sebaceous gland secretion, obstruction of pilosebaceous ducts, release of mediators of inflammation, and bacterial colonization are mechanisms involved in the pathogenesis of acne vulgaris. Propionibacterium acnes (P. acnes), a Gram positive anaerobic bacterium, is the dominant microorganism which colonizes pilosebaceous units.[1]

Acne vulgaris often starts in early adolescence

Corresponding Author:
Fardin Gharibi
Email: fardin.gharibi1350@yahoo.com

and its onset is earlier in girls.[2] Its greatest frequency is seen in 14-17-year-old girls and 16-19-year-old boys.[3] Acne is of significance as it is highly prevalent in young adults and its complications such as scarring and poor self-image can lead to anxiety, depression, and social withdrawal.[4,5]

While a variety of medications are available for the treatment of acne, each medicine targets one or some of the factors involving in the pathogenesis of acne. They act through reversing hypercornification of sebaceous ducts, decreasing sebum production, reducing follicular bacteria (in particular P. acnes), or decreasing inflammatory mediators by inhibiting bacterial growth.[6,7] Several topical and systemic medications are used for the treatment of acne. Systemic therapy includes antimicrobial agents, hormone preparations, and isotretinoin. Selection of therapy depends on the clinical variant and severity of acne and previously applied treatments.[8-10] Although systemic and topical antimicrobial preparations have been commonly used to cure inflammatory acne,[11,12] the emergence of resistant microorganisms (particularly P. acnes) has caused some problems in the treatment of acne. Therefore, the use of effective non-antimicrobial preparations should be taken into consideration. Nicotinamide gel has potent anti-inflammatory properties and its use does not promote the emergence of resistant strains of microorganisms.[4]

Systemic antibiotics, especially tetracycline have been used as the treatment of choice for the treatment of acne vulgaris for many years. Long-term use of tetracycline is often associated with gastrointestinal complications. However, application of topical medications brings about fewer side effects.[10] Evaluation of therapeutic responses and finding proper therapeutic regimens in different populations with different genetic and racial characteristics will be valuable for the treatment of acne. Since efficient therapeutic regimens with few side effects are preferred by most dermatologists, we investigated the effects of Clinda Soap (manufactured by Shadakish Co., Iran) on the treatment of acne vulgaris.

Materials and Methods

This randomized, double-blind study was conducted in Besat Hospital (Sanandaj, Iran) from August 2011 to August 2012. It included 106 patients (age: 15-25 years) with mild to moderate acne vulgaris. The severity of acne was determined according to the Global Acne Grading System.[13] Patients with any chronic disease or polycystic ovary syndrome, pregnant and lactating women, patients who had used topical or systemic antibiotics within 30 days before the intervention, and those using acnegenic drugs such as vitamin B_{12}, steroids, anti-tuberculosis drugs, lithium, and phenytoin were excluded from the study.

The study was approved by the ethics committee of Kurdistan University of Medical Sciences (Sanandaj, Iran). It was also registered at Iranian Registry of Clinical Trials (IRCT) with the registration number of IRCT 20100925480n1.

After obtaining informed consent from the patients, block randomization was used to allocate the participants to either intervention (n = 50) or control group (n = 50). Both the patients and the dermatologist were blinded to the grouping and the appearance of the placebo and Clinda Soap were similar. As the standard acne treatment, the two groups received 250 mg oral tetracycline every six hours. The intervention group was instructed to wash the affected areas of the skin with warm water and Clinda Soap and let the lather remain on the skin for three minutes, twice daily, for 12 weeks. Clinda Soap contains clindamycin hydrochloride 1% and has neutral pH. The control group was asked to perform a similar procedure with placebo soap. All patients were visited by our dermatologist every month for three months. Inflammatory lesions (papules and pustules) and non-inflammatory lesions (comedones) were counted and recorded at baseline and every visit.

A total of 24 patients were excluded from the

study because of lack of cooperation, planning for pregnancy, and drug adverse effects. Finally, 82 patients (39 in the intervention group and 43 in the control group) completed the treatment course. The data was analyzed with SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Since the lesions were counted for four times during the treatment course, we used repeated measures analysis of variance to compare the data (The whole process of the study is summarized in Figure 1).

Results

The mean age of the intervention and control groups was 21.1 ± 4.7 and 21.5 ± 4.8 years, respectively. The two groups were similar in the mean duration of the disease (3.0 ± 1.5 months in the intervention group and 3.1 ± 1.8 months in the control group). Sex distribution, family history of acne, and severity of the disease were also similar in the two groups (Table 1).

At the end of the study, there was no significant difference between the two groups in regard to the number of comedones (P = 0.85) (Table 2). In contrast, significantly better recovery rate of papules and pustules was observed in the intervention group (Tables 3 and 4).

Discussion

In our study, the intervention and control groups were matched for demographic characteristics (age, gender, occupation, and severity, duration, and family history of acne). Moreover, no significant differences in clinical variants of acne

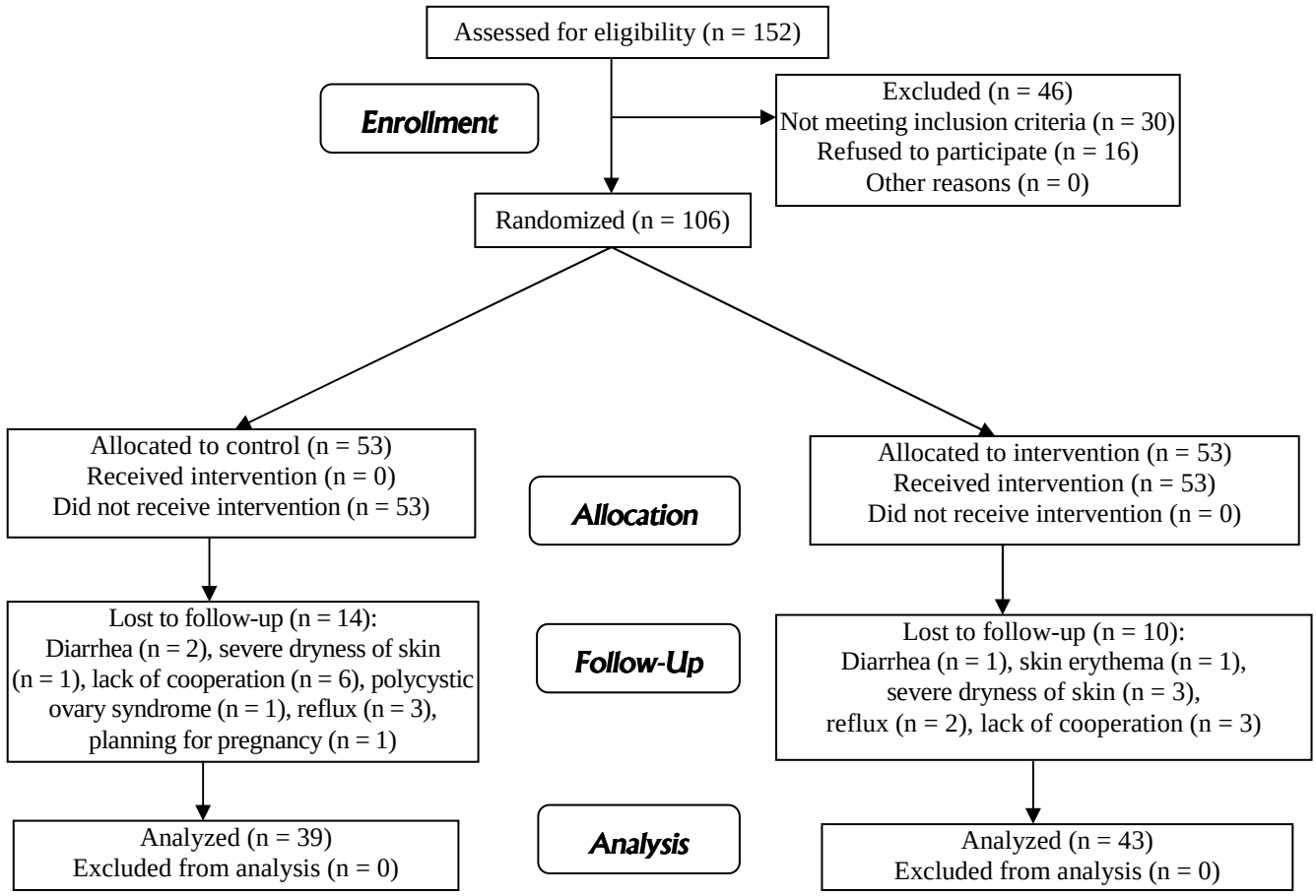

Figure 1. The consort flowchart of the study

Table 1. Demographic and disease-related characteristics of the participants

Variables		Control group	Intervention group	P
Gender	Male	15 (53.6)	13 (46.4)	0.88
	Female	28 (51.9)	26 (48.1)	
Severity of acne	Mild	9 (52.9)	8 (47.1)	0.96
	Moderate	34 (52.3)	31 (47.7)	
Family history	Positive	18 (51.4)	17 (48.6)	0.94
	Negative	25 (53.2)	22 (46.8)	

Values are n (%).

Table 2. The mean number of comedones in the intervention and control groups at different times of treatment course

	Baseline	First month	Second month	Third month
Control group	12.45 ± 4.27	8.83 ± 3.46	6.29 ± 3.27	4.42 ± 2.86
Intervention group	13.11 ± 5.01	8.91 ± 4.57	6.28 ± 3.69	4.37 ± 2.80

Table 3. The mean number of papules in the intervention and control groups at different times of treatment course

	Baseline	First month	Second month	Third month
Control group	9.64 ± 3.83	7.05 ± 3.49	5.15 ± 2.86	2.46 ± 2.67
Intervention group	10.40 ± 4.69	5.04 ± 3.49	2.70 ± 2.48	1.09 ± 1.51

Table 4. The mean number of pustules in the intervention and control groups at different times of treatment course

	Baseline	First month	Second month	Third month
Control group	4.16 ± 1.93	2.83 ± 1.29	2.10 ± 1.35	1.33 ± 0.99
Intervention group	3.81 ± 1.94	1. 46 ± 1.12	0.72 ± 0.99	0.24 ± 0.49

and type and number of lesions (comedones, inflammatory papules, and pustules) were detected between the two groups before the intervention. The two groups were not significantly different in the number of closed comedones at any of the follow-up visits. However, at all visits, fewer papules and pustules were observed in the intervention group than in the control group.

Several different medications such as antimicrobial agents, hormone preparations, oral retinoids, steroids, and topical salicylic acid have been suggested for the treatment of acne vulgaris.[5] In a review article, Del Rosso and Schmidt pointed out that the anti-inflammatory effect of clindamycin has received considerable attention as an essential mechanism for the treatment of acne in the last three decades.[14]

Our evaluations showed that the number of all types of lesions had a decreasing trend in both groups during the treatment. Significantly greater reduction in the number of inflammatory lesions (papules and pustules) was seen in the intervention group. As this difference was more significant for pustules, it can be concluded that Clinda Soap was more effective in the treatment of pustules in comparison to other types of acne lesions. Contrariwise, no significant difference in the number of comedones was detected between the two groups.

In an eight-week study, Shalita et al. found that nicotinamide gel and clindamycin gel did not cause significantly different reductions in the mean number of acne lesions (-14.1 vs. -12.3).[10] These findings are in accordance with the results of our study.

Cunliffe et al. conducted a clinical trial to compare the effects of a topical clindamycin/zinc gel and a topical clindamycin lotion in 246 patients with mild to moderate acne. They concluded that both drugs had similar therapeutic effects.[15] In a study in

Germany, Zouboulis et al. found higher and faster recovery after using a fixed clindamycin phosphate/tretinoin gel than after the application of a clindamycin lotion (Dalacin).[16] NilFroushzadeh et al. reported significantly different reduction in the severity of acne following the use of clindamycin phosphate and salicylic acid lotion, clindamycin phosphate and tretinoin lotion, and clindamycin lotion.[17] Pazoki-Toroudi et al. concluded that the combination of clindamycin and azelaic acid is more effective than either clindamycin or azelaic acid alone.[18] Draelos et al. showed that use of clindamycin phosphate/tretinoin gel together with 4% benzoyl peroxide wash was effective in the treatment of acne. They also found good medication compliance in the patients with acne vulgaris.[19]

Conclusion

The results of this study indicated that Clinda Soap is effective in the treatment of lesions of acne vulgaris, particularly papules and pustules. Considering its low cost, easy use, and few side effects, compliance with this treatment is expected to be favorable.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

We wish to thank the patients and the Deputy of Research of Kurdistan University of Medical Sciences for their support and cooperation.

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Chronic Diseases Journal

Diagnostic value of high sensitivity C-reactive protein in differentiating unstable angina from myocardial infarction

Reza Madadi[1], Katayoon Haddadian[2], Ebrahim Ghaderi[3], Kajal Karimi[1]

1 Associate Professor, Department of Cardiology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Student of Medicine, Department of Cardiology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
3 Kurdistan Research Center for Social Determinants of Health, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: Differentiating between unstable angina and myocardial infarction (MI) is clinically important as they require different treatments. High sensitivity C-reactive protein (hs-CRP) has recently been recognized as prognostic factor in acute coronary syndrome. Since this biomarker may indicate the prognosis of heart disease, identifying its diagnostic value will be clinically important. This study investigated the diagnostic value of the level of hs-CRP in differentiating MI from unstable angina.

METHODS: Blood samples were obtained from all patients with suspected MI or unstable angina at the time of referral. The patients were put in one of the two groups based on final diagnosis. The exclusion criteria were infectious diseases, immune system diseases, history of a recent surgery or trauma, kidney failure, liver failure, cancers, and use of anti-inflammatory drugs. Data was entered in SPSS and analyzed by independent t, Mann-Whitney U and chi-square or Fisher's exact tests. ROC curve was used to determine hs-CRP cut-off point. The sensitivity and specificity were calculated at the cut-off point.

RESULTS: Overall, 60 patients (30 patients with MI and 30 patients with unstable angina) were studied. Hs-CRP level was 3.68 ± 0.86 mg/l in patients with MI and 2.35 ± 1.30 mg/l in patients with unstable angina ($P < 0.001$). The best cut-off point for differentiating unstable angina from MI was hs-CRP levels equal to or greater than 3.27 mg/l. At this cutoff point, the sensitivity and specificity were both 77%.

CONCLUSION: Patients with MI had higher levels of hs-CRP than subjects with unstable angina. Hs-CRP levels equal to or higher than 3.27 mg/l are more likely to be associated with MI. It is recommended to test this biomarker in all patients with acute coronary syndrome.

KEYWORDS: Myocardial Infarction, Acute Coronary Syndrome, Unstable Angina, Diagnosis

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Introduction

Inflammatory marker proteins have been used as a noninvasive method to assess atherosclerosis and prognosis of patients. High sensitivity C-reactive protein (hs-CRP) is an inflammatory marker which has received great attention recently.[1-5] Many studies have evaluated the relationship between this biomarker and the incidence and prognosis of cardiovascular diseases. While some of these studies have suggested an association between hs-CRP and prognosis and mortality of patients, others have suggested opposite results.[6-10] According to a number of studies, hs-CRP concentrations more than 3 mg/l is more associated with disease outcome and may worsen the prognosis in

Corresponding Author:
Katayoon Haddadian
Email: katyhad@ymail.com

patients with acute coronary syndrome (ACS).[11-13]

Research on the value of hs-CRP in the diagnosis of ACS has also reported controversial results.[14-16] However, studies in this field have had shortages and further studies are hence warranted. For instance, although it is important to differentiate unstable angina from myocardial infarction (MI) since they require distinct treatments, no study has assessed the diagnostic value of hs-CRP in differentiating between these two diseases. Considering the fact that increased levels of hs-CRP have been suggested to worsen the prognosis of cardiovascular diseases, evaluating the diagnostic value of this biomarker in distinguishing unstable angina from MI may be clinically important. Therefore, this study investigated the sensitivity and specificity of different levels of hs-CRP in differentiating MI from unstable angina.

Materials and Methods

The study protocol was first approved by ethics committee of Kurdistan University of Medical Sciences (Sanandaj, Iran). The participants were then selected from individuals with chest pain who referred to the emergency ward of Tohid Hospital (Sanandaj, Iran). Patients were only included if the diagnosis of MI or unstable angina was confirmed by a cardiologist. The subjects were selected through convenience sampling until the sample size was reached. Blood samples were obtained from all patients with suspected MI or unstable angina at the time of referral and the participants were categorized based on the final diagnosis. The exclusion criteria were having an infectious disease in the past three weeks, immune system and autoimmune diseases, a history of surgery in the past two months, a history of trauma in the past two months, chronic renal failure, hepatitis, cancers, and use of anti-inflammatory drugs. Using the formula of differences in the mean and having $\alpha = 1\%$, $\beta = 10\%$, and mean hs-CRP of 1.7 ± 09 mg/l for MI and 0.93 ± 09 mg/l for unstable angina,[15] the minimum sample size was calculated as 22 subjects in each group. We studied 30 patients in each group.

After explaining the objectives of the study to the patients, they were asked to sign the consent forms. All patients completed a questionnaire and preliminary examinations (e.g. blood pressure measurement) were conducted under standard conditions.

Data was entered in SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to assess the normal distribution of quantitative data. Quantitative data of the two groups was compared with Student's independent t-test or Mann-Whitney test. Chi-square and Fisher's exact tests were used to compare qualitative data. Receiver operating characteristic (ROC) curve was used to determine hs-CRP cutoff point. The sensitivity and specificity were calculated at the cutoff point.

Results

We studied 30 patients with MI and 30 patients with unstable angina (mean age: 59.8 ± 12.9 years). Females constituted 51.6% of the participants (n = 31). Fifteen subject (25.0%) lived in rural areas and 14 (23.3%) had a family history of MI. Overall, 38 patients (63.3%) were active smokers and 14 (23.3%) were non-active smokers. History of hypertension, diabetes, and hyperlipidemia were reported by 22 (36.6%), nine (15.0%), and 16 patients (26.7%), respectively. The two groups had no significant differences in any variables except smoking. While vomiting was significantly more prevalent in the group with MI, there was no statistically significant differences between the two groups regarding other symptoms (Table 1).

Hs-CRP level was 3.68 ± 0.86 mg/l in patients with MI and 2.35 ± 1.30 mg/l in patients with unstable angina ($P < 0.001$). The best cutoff point for differentiating unstable angina from MI was hs-CRP levels equal to or greater than 3.27 mg/l (Figure 1). At this cutoff point, the sensitivity and specificity were both 77% (Table 2) and the area under the ROC curve was calculated as 0.794 (95% confidence interval 0.68-0.91; $P < 0.001$).

Table 1. Comparison of characteristics of patients with myocardial infarction (MI) and unstable angina

Variables	MI	Unstable Angina	P
Sex			
Male	12 (40)	17 (56.7)	0.196
Female	18 (60)	13 (43.3)	
Place of residency			
Urban	21 (70.0)	24 (80.0)	0.371
Rural	9 (30.0)	6 (20.0)	
Family History of MI	7 (23.3)	7 (23.3)	1.000
Current Smoker	15 (50.0)	23 (76.7)	0.032*
Passive Smoker	8 (26.7)	6 (20.0)	0.542
Hypertension	9 (30.0)	13 (43.3)	0.284
Hyperlipidemia	5 (16.7)	11 (36.7)	0.143
Diabetes	2 (6.2)	7 (23.3)	0.145†
Chest pain	27 (90.0)	29 (96.7)	0.612†
Dyspnea	18 (60.0)	15 (50.0)	0.436
Sweating	18 (60.0)	14 (46.7)	0.301
Vomiting	18 (60.0)	8 (26.7)	0.009*
Level of education**	1 (0-4)	1 (0-4)	0.362§
Diabetes duration (year)	1 (1-1)	8 (3-20)	0.040*
Hypertension duration (year)	9 (3-15)	7 (1-21)	0.689§
Hyperlipidemia duration (year)	1 (1-12)	3 (1-16)	0.524§
Age (year)	59.9 ± 13.1	59.7 ± 12.9	0.945
Body mass index (kg/m^2)	25.7 ± 3.7	26.5 ± 3.5	0.417††
High sensitivity C-reactive protein (mg/l)	3.68 ± 0.86	2.35 ± 1.30	< 0.001††*
Chest pain duration (hour)	2.50 (0.50-80)	3.00 (0.15-24.00)	0.464§
Smoking (Packs/year)	20.50 (0.75-120.00)	19.00 (0.45-100.00)	0.721§

Values are expressed as n (%), mean (range), or mean ± SD; †: Fisher's exact test was applied; ††: Student's independent t-test was applied; §: Mann-Whitney test was applied, Other comparisons were done by chi-square test;* Statistically significant; ** 0: Illiterate; 1: Elementary school; 2: Junior high school; 3: High school; 4: College; MI: Myocardial infarction

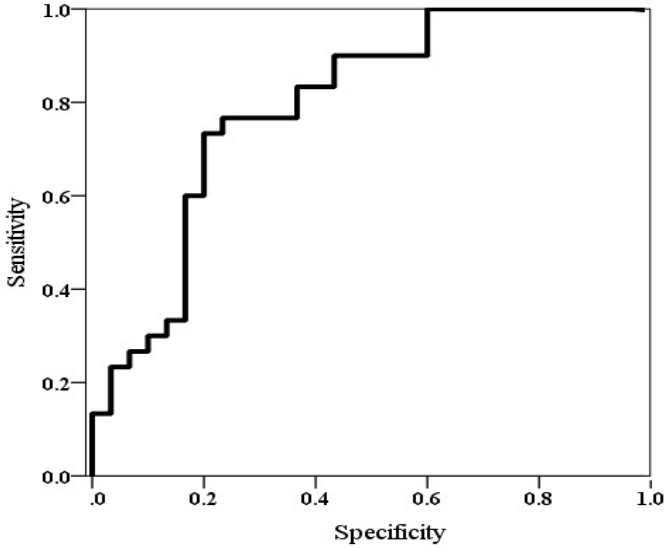

Figure 1. Receiver operating characteristic (ROC) curve to differentiate myocardial infarction from unstable angina (The area under the curve was calculated as 0.794 for 3.27 mg/l; 95% confidence interval: 0.68-0.91; P < 0.001).

Table 2. Calculating sensitivity and specificity of different high sensitivity C-reactive protein (hs-CRP) levels for differentiating myocardial infarction from unstable angina

Hs-CRP (mg/l)	Sensitivity	Specificity
0.22	1.00	0.03
0.45	1.00	0.07
0.71	1.00	0.10
0.85	1.00	0.13
0.94	1.00	0.17
1.06	1.00	0.20
1.22	1.00	0.30
1.43	1.00	0.40
1.85	0.93	0.40
2.15	0.90	0.40
2.26	0.90	0.43
2.48	0.90	0.53
2.65	0.90	0.57
2.79	0.87	0.57
2.96	0.83	0.60
2.99	0.83	0.63
3.17	0.77	0.63
3.24	0.77	0.70
3.27†	0.77	0.77
3.35	0.73	0.77
3.48	0.67	0.80
3.66	0.60	0.80
3.82	0.60	0.83
3.93	0.53	0.83
3.99	0.43	0.83
4.09	0.33	0.87
4.19	0.30	0.90
4.28	0.27	0.90
4.38	0.23	0.97
4.48	0.13	0.97
4.57	0.13	1.00
4.64	0.10	1.00
4.70	0.07	1.00
5.73	0.00	1.00

† The best diagnostic level; Hs-CRP: High sensitivity C-reactive protein

Discussion

In this study, patients in both groups had similar baseline characteristics. Hs-CRP levels were higher in patients with unstable angina than patients in those with MI. The cutoff point for differentiating between the two diseases was calculated as 3.27 mg/l. Accordingly, it seems that hs-CRP could be helpful in differentiating MI from unstable angina.

Several studies have recently shown that inflammation is one of the mechanisms of cardiovascular diseases.[4,5] Zairis et al. found that hs-CRP level is a predictor of mortality over the next five years in patients with ACS[7] and that it may be associated with MI size.[14] Tanaka et al. indicated hs-CRP level to be associated with atherosclerotic plaque rupture, i.e. higher levels were detected in subjects with greater number of ruptured atherosclerotic plaques.[17]

Most previous studies have investigated the prognostic value of hs-CRP in cardiovascular diseases and very few have assessed its diagnostic value in different heart diseases. It is very important to differentiate MI from unstable angina and also to differentiate unstable angina from stable angina since they require different treatment approaches. Thakur et al. found hs-CRP levels to be 1.70 ± 0.75 and 0.93 ± 0.35) mg/l in patients with cardiovascular disease and healthy people, respectively ($P < 0.001$).[4] Yip et al. reported levels of 2.95 mg/l in patients with MI and 1.35 mg/l in subjects with unstable angina ($P < 0.001$). They found this biomarker to be related with disease prognosis and suggested it as an indicator of the amount of attention a patient has to receive.[15] In another study, Yip et al. calculated hs-CRP levels as 2.7 and 1.4 mg/l in subjects with MI and unstable angina, respectively. The values had no relation with gender, smoking, diabetes, body mass index (BMI), or hypercholesterolemia.[18] In contrast, Diercks et al. rejected the diagnostic value of hs-CRP in differentiating acute coronary syndrome from other diseases (area under the ROC curve: 0.49).[16] Amanvermez et al. reported significantly higher level of hs-CRP in patients with MI than in those with unstable angina. While the area under the ROC curve was 0.6 in their study, unfortunately, they did not set a cutoff point.[19]

As it is seen, the mean levels of hs-CRP have been different in previous studies. This might have been caused by different sampling methods or inclusion/exclusion criteria. The higher area under the ROC curve obtained in the

present study compared to those calculated by Diercks et al.[16] and Amanvermez et al. may be justified by our careful consideration over the exclusion criteria (we eliminated conditions which could influence hs-CRP levels). Therefore, it is recommended to use hs-CRP level of 3.27 mg/l to differentiate MI from unstable angina. At this cutoff point, the sensitivity and specificity are both equal to 77%. Additionally, we calculated the sensitivity and specificity of various levels of this biomarker. This allows the physicians to choose the appropriate level and to use suitable diagnostic and treatment approaches in different situations.

Although hs-CRP levels may increase in patients affected by atherosclerosis, such increase can also be caused by the pathology of MI. This provides a means of diagnosing MI. This biomarker can be associated with higher levels of plaque rupture which is probably a reason for its high levels in patients with MI.[17] Patients with unstable angina who have higher levels of hs-CRP have also been suggested to be at greater risk of mortality and MI.[10,20]

Conclusion

Hs-CRP levels were higher in patients with MI than in those with unstable angina. Hs-CPR levels of 3.27 mg/l or higher are in favor of MI. It is recommended to assess this biomarker in all patients with ACS.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Impacts of osteoporosis on quality of life in elderly women

Abolfazl Mohammadbeigi[1], Jafar Hassanzadeh[2], Narges Mohammadsalehi[3], Bagher Nasimi[4], Gholamhossein Ranjbar-Omrani[5]

1 Department of Epidemiology, School of Health, Qom University of Medical Sciences, Qom, Iran
2 Department of Epidemiology, School of Health and Nutrition, Shiraz University of Medical Sciences, Shiraz, Iran
3 Vice Chancellor of Health, Arak University of Medical Sciences, Arak, Iran
4 Shiraz University of Medical Sciences, Shiraz, Iran
5 Department of Endocrinology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Original Article

Abstract

BACKGROUND: Osteoporosis, the most common pathological cause of skeletal weakening and the most common metabolic bone disease, is caused by loss of bone mass density (BMD). Fractures due to osteoporosis will worsen life, increase pain, and decrease quality of life. The present study aimed to determine the impact of osteoporosis on quality of life among elderly women.

METHODS: In a cross-sectional study, 275 postmenopausal women (age: 50-70 years) who were referred to the Namazi Hospital (Shiraz, Iran) were included. BMD was measured according to the World Health Organization (WHO) standards. Women with BMD < -2.5 standard deviation (SD) of the average value in young adults were defined as osteoporosis cases. Women with BMD > 1 SD of the average value were defined as normal cases. Quality of life was measured by Qualeffo-41 Questionnaire and reported on a scale of 100. Data was analyzed in SPSS and P values less than 0.05 were considered significant.

RESULTS: The mean quality of life score was 25.5 ± 11.7. According to the definition by the WHO, 70.2% of the participants were affected with osteoporosis. Only 22.3% of osteoporotic women and 30.5% of normal subjects had good quality of life. A significant statistical difference was observed between osteoporotic and normal postmenopausal women in social activities. Overweight and low education were predictors of poor quality of life in multivariate analysis.

CONCLUSION: The imposed financial burden and complications of osteoporosis can affect the patients' quality of life. Health education regarding nutritional behaviors and social activities at adolescence are helpful interventions for decreasing the prevalence of the disease. Since osteoporosis has a gradual, outward, and asymptomatic trend, more attention needs to be paid to preventive and screening programs.

KEYWORDS: Quality of Life, Osteoporosis, Menopause, Female, Qualeffo-41 Questionnaire

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Introduction

Osteoporosis is the most common pathological cause of skeletal weakening.[1] It is also the most common metabolic bone disorder associated with decreased bone mass and quality and increased risk of fracture.[1,2] Due to hormonal changes after menopause,[1] osteoporosis is more prevalent in women than in men.[2]

The gradual development of osteoporosis and the absence of warning signs prevents the patient from noticing the disease until the first fracture occurs.[1,2] Since osteoporosis increases the risk of fractures in femoral and hip bones and the spinal column,[3] it results in high

Corresponding Author:
Narges Mohammadsalehi
Email: nm.salehy@gmail.com

mortality and morbidity and treatment costs. Therefore, the complications of osteoporosis, especially fractures, are major causes of reduced quality of life.[4,5]

The enhanced life expectancy and the overall aging of the population in the current world have increased the prevalence of osteoporosis.[6,7] In fact, femoral fractures are predicted to have increased by 310% in men and 240% in women until 2050. This will raise medical costs from $131,500 in 1990 to $348,000 in 2050.[8,9] Importantly, most of these fractures occur in Latin America and Asia.[2,9,10] According to data form the World Health Organization (WHO), more than 540 million people over 56 years old will live in Asia in 2050 which means more than 50% of fractures will happen in this region.[11] The lifetime prevalence of fractures due to osteoporosis in women more than 50 years old is 40% in the United States and 46% in Sweden.[2] A meta-analysis in Iran showed the mean prevalence of osteoporosis in Iranian women to be 18.9% (range: 1.5% to 43.0%).[3]

Hormonal changes, alcohol consumption, smoking, inactivity, high meat consumption, and menopause before the age of 50 have been proposed as risk factors for osteoporosis.[1,2,8,12] Although the impact of osteoporosis and its complications on quality of life is clear, health-related quality of life in osteoporotic women without fracture has not been adequately assessed.[11,13] The current study aimed to determine the impacts of osteoporosis on quality of life of 50-70-year-old women without fractures.

Materials and Methods

This cross-sectional study was conducted on 50-70-year-old women who referred to Namazi Hospital (Shiraz, Iran) during 2008. After bone mineral density (BMD) measurements, women with BMD more than 2.5 standard deviations (SD) below the mean value for young healthy women (a T-score of < -2.5 SD) were considered as osteoporotic.[2,14] Women with BMD less than one SD below the mentioned mean value (T-Score > -1 SD) were considered as normal.[14] Women with osteopenia, chronic kidney diseases, cancers, respiratory and heart disorders, diabetes, uncontrolled hypertension, and hearing and visual disorders were excluded from the study. Finally, 275 eligible women were included in the study.

The Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41) was used for data collection.[15-17] QUALEFFO-41 has 41 items and measures five aspects of quality of life (pain, physical function, leisure and social activities, general health perception, and mental function). Each item is scored as one-five where one shows the best situation and five shows the worst, i.e. higher scores reflect poorer quality of life. The obtained quality of life scores were compared between osteoporotic and normal women. Since the maximum final score is 100, the quality of life is categorized as good, moderate, and poor if the scores are < 25, 25-75, and > 75, respectively. The reliability of QUALEFFO-41 has been reported as 0.78-0.96 by previous studies.[16,18-21]

The collected data was entered into SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA) and analyzed by Student's t-test, and chi-square and Mann-Whitney nonparametric tests.

Results

The mean age of the subjects was 58.20 ± 5.99 years. The majority of the participants (87.6%) were married and living with their spouse. While most subjects (70.4%) held a high school diploma, 19.3% had not finished high school and 10.9% were university graduates. Osteoporotic women constituted 70.2% of the study sample.

The mean score of quality of life was 31.6 ± 9.58 (range: 5.56-72.83). As table 1 shows, osteoporotic women had higher quality of life scores than normal ones (P > 0.05). Although the mean score of social activities subdomain was significantly higher in osteoporotic women than in the other group (P = 0.002), the two groups had no significant differences in other aspects (pain,

Table 1. Body mass index (BMI), age, and scores of quality of life and its aspects in osteoporotic and healthy elderly women

Variables	Osteoporotic (n=193)		Normal (n=82)		P
	Median	Mean ± SD	Median	Mean ± SD	
BMI (kg/m^2)	28.1	28.1 ± 4.4	25.2	25.7 ± 4.1	< 0.001*
Age (year)	58.0	59.3 ± 6.1	54.0	55.5 ± 4.7	< 0.001*
Quality of life score	31.3	32.2 ± 9.9	31.1	30.3 ± 8.5	0.247
Domain of quality of life					
Pain	35.0	37.5 ± 16.6	35.0	33.6 ± 15.9	0.123
Physical function	10.2	13.1 ± 14.4	10.2	9.9 ± 7.9	0.262
Leisure and social activities	37.8	34.8 ± 15.1	31.7	28.8 ± 13.7	0.002*
General health perception	33.3	37.9 ± 15.7	41.6	40.9 ± 15.6	0.115
Mental function	36.1	37.3 ± 7.4	38.8	38.4 ± 10.1	0.268

*Statistically significant; BMI: Body mass index

physical function, general health perception, and mental function). However, there were significant differences between the two groups regarding age (P < 0.001) and body mass index (BMI) (P < 0.001).

Table 2 shows the relationship of qualitative variables with osteoporosis. As it is seen, while marital status was not significantly related with osteoporosis (P = 0.456), significant relationships existed between osteoporosis and education (P < 0.001) and BMI (P < 0.001). Good quality of life was detected in 22.3% and 30.5% of the osteoporotic and healthy women (P = 0.302).

We used a logistic regression model to adjust the effects of confounding factors in comparisons between subjects with good and moderate quality of life and those with subjects with poor quality of life. According to table 3, being overweight (odds ratio: 3.26; 95% confidence interval: 1.20-8.70) and having low education (odds ratio: 3.43; 95% confidence interval: 1.51-7.79) were predictors of poor quality of life.

Table 2. The relationship between osteoporosis and marital status, obesity, and education level in elderly women

Variable		Osteoporotic women (n = 193)	Normal women (n = 82)	P
Marital status	Single	171 (88.6)	70 (85.4)	0.456
	Married	22 (14.6)	12 (11.4)	
Weight	Normal (BMI < 25 kg/m^2)	94 (48.7)	14 (17.1)	< 0.001*
	Overweight (25 ≤ BMI < 30 kg/m^2)	72 (37.3)	46 (56.1)	
	Obese (BMI ≥ 30 kg/m^2)	27 (14.0)	22 (26.8)	
Education	Lower than high school diploma	52 (26.9)	1 (1.2)	< 0.001*
	High school diploma	122 (63.2)	70 (85.4)	
	University degree	19 (9.8)	11 (13.4)	
Quality of life	Good	43 (22.3)	25 (30.5)	0.302
	Moderate	99 (51.3)	40 (48.8)	
	Poor	51 (26.4)	17 (20.7)	

* Statistically significant; Values are n (%); BMI: Body mass index

Table 3. Predictors of poor quality of life in logistic regression model

Variables		B	P	OR	95% CI for OR
Body mass index	< 25 kg/m^2	0	-	1.00	-
	25-30 kg/m^2	1.18	0.018	3.26	1.20-8.70
Education level	Lower than high school diploma	1.23	0.003	3.43	1.51-7.79
	College degree	0	-	1.00	-

OR: Odds ratio; CI: Confidence interval

Discussion

Osteoporosis is an important health-related problem that reduces quality of life and imposes great financial burden on patients by causing fractures.[12] Due to the gradual and asymptomatic nature of osteoporosis,[13] the disease seems not to affect the quality of life in osteoporotic patients without fracture. In the present study, osteoporotic patients had significantly lower scores in the leisure and social activities subdomain of QUALEFFO-41. In other words, these patients had problems in sports, entertainment, visiting friends, sexual activities, and recreation and were hence in need of help. However, since the disease is asymptomatic in nature,[13] we did not observe any differences between osteoporotic patients and healthy subjects in other aspects of quality of life. Therefore, lack of awareness about the irreversible consequences of the osteorosis disease with physical and psychological changes due to menopause yeilds decreasing in daily activities and increaseing the risk of fractures in elderly women.[6,7,22]

In the present study, the two groups were not significantly different in terms of good quality of life (22.3% vs. 30.5%). In contrast, Bianchi et al. reported a significant difference in this regard (41% vs. 11%).[19] Other studies have also indicated a significant relationship between osteoporosis and quality of life.[16,18,19,23] However, osteoporosis is a multidimensional systemic disease that can affect different aspects of life.[16] Martin et al. discussed that poor quality of life of osteoporotic women can be caused by their fear of future fractures or changes in their lifestyle to prevent fractures.[13]

There was no significant relationship between osteoporosis and mental activities in the current study, i.e. physical inactivity did not decrease mental activity. The same results were found in other studies.[24,25] On the other hand, although we failed to observe a relationship between osteoporosis and general health perception, Silverman confirmed such a relationship.[26]

According to the results of regression analysis, being overweight and having low education could increase the odds of osteoporosis by three times. Hence, increased awareness of people, especially elderly women, may reduce the incidence of osteoporosis. Moreover, since the improved life expectancy and demographical changes in Iran will increase the elderly population in the country, appropriate and continuous screening programs are essential to prevent osteoporosis and its complications.[27]

Conclusion

Osteoporosis without fractures affected only the social activities aspect of quality of life. However, the financial burden due to osteoprosis can affect the quality of life because synergic effect of menopause consequences and osteoporosis complications. Health education about nutritional behaviors and social activities at adolescence will be helpful interventions to decrease the future incidence of osteoporosis. In addition, public sport programs in local parks, periodical visits, and enlivening camping can promote the quality of life in elderly people.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Comparative analysis of morphometric parameters of intercondylar notch in patients with and without anterior cruciate ligament tears

Nazanin Farshchian[1], Satar Sohrabi[2], Mansour Rezaei[3]

1 Assistant Professor, Department of Radiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
2 Resident, Department of Radiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
3 Assistant Professor, Department of Biostatistics, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

Original Article

Abstract

BACKGROUND: Anterior cruciate ligament (ACL) injury is the most common type of ligament injury whose prevalence is higher in athletes. There are different external risk factors for this injury. However, it is important to find its physiological risk factors, as well. This study assessed the relationship between morphometric parameters of intercondylar notch and ACL tears in patients suffering from knee complications.

METHODS: Patients with or without ACL tears who had undergone knee magnetic resonance imaging for any reason were recruited based on inclusion criteria. Intercondylar notch width, femoral bicondylar width, and intercondylar notch index were calculated in both groups. Then, significant variables from univariate analysis were entered in multiple regression analysis with intercondylar notch width, femoral bicondylar width, and intercondylar notch index being assumed as dependent variables.

RESULTS: Overall, 199 participants, including 81 patients with ACL tear and 118 without ACL tear, were evaluated. Multiple regression analysis revealed intercondylar notch width and intercondylar notch index to be less common among women and subjects with ACL tears ($P < 0.001$).

CONCLUSION: Based on the results of this study, there are relationships between ACL tears and being female and intercondylar notch width. Therefore, intercondylar notch index can be used for screening athletes and people at risk of ACL tears.

KEYWORDS: Anterior Cruciate Ligament Tear, Intercondylar Notch, Femoral Bicondylar Width, Intercondylar Notch Index

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Introduction

The knee anterior cruciate ligament (ACL) tear is one of the most serious knee ligament damages that causes short-term functional instability and long-term degenerative joint disease.[1] The incidence of ACL injury among high risk populations has been reported as 70-85 cases per one hundred thousand people.[2-5] About half of patients will develop osteoarthritis over 10-20 years after ACL injury.[6] On the other hand, available ACL reconstructive surgeries are expensive and associated with high levels of morbidity.[7-10]

Risk factors for ACL injury are categorized in two groups of internal and external factors. External risk factors include types of activities especially exercise, clothing, footwear, and

Corresponding Author:
Satar Sohrabi
Email: ss72rad@yahoo.com

environmental causes. Internal causes include anatomical, hormonal, and neuromuscular risk factors.[4] Identifying these risk factors, particularly in athletes, can help predict ACL injury and facilitate the use of preventive measures.

Research has indicated a significant relationship between ACL injuries and morphological parameters of the knee joint, especially intercondylar notch width (INW) index.[11-19] However, a number of studies have failed to find a significant difference in the frequency of ACL injury in patients with or without marked stenosis of intercondylar notch.[20-22] While some previous studies have reported significant large values of most morphometric parameters of the knee joint (e.g. INW and ACL width) in men,[1,15,16,23-25] a few others have rejected such a difference between the two sexes.[26] Similarly, a number of researchers have accepted a family history of ACL injury to increase the risk of ACL injury,[8,27] but others have reported no statistically significant relation between these two.[28]

Considering the inconsistencies in the results of previous studies, further research seems necessary to verify the significance of the mentioned factors in diagnosis of people who are at risk of developing ACL injuries. This study aimed to investigate the relationship between femoral intercondylar notch stenosis and ACL injury in patients with knee problems who referred to Imam Reza Hospital (Kermanshah, Iran) during 2009-10.

Materials and Methods

This cross-sectional, descriptive-analytical study included patients with ACL tear in magnetic resonance imaging (MRI) and individuals who underwent knee MRI for other reasons but did not have ACL tear. Diagnostic criteria included being clinically suspected to ACL tear or showing signal changes in MRI sequence. MRI sequences were produced using a one-tesla MRI scanner (Philips Medical Systems). Morphometric parameters of the intercondylar notch were determined based on T2 axial and T2 coronal sequences. INW (C to D) and femoral bicondylar width (A to B) were calculated according to figure 1. bicondylar width was then divided by INW to calculate the intercondylar notch index. The exclusion criteria were obvious osteoarthritis in MRI, connective tissue diseases, systemic bone diseases, and a history of knee fracture or surgery.

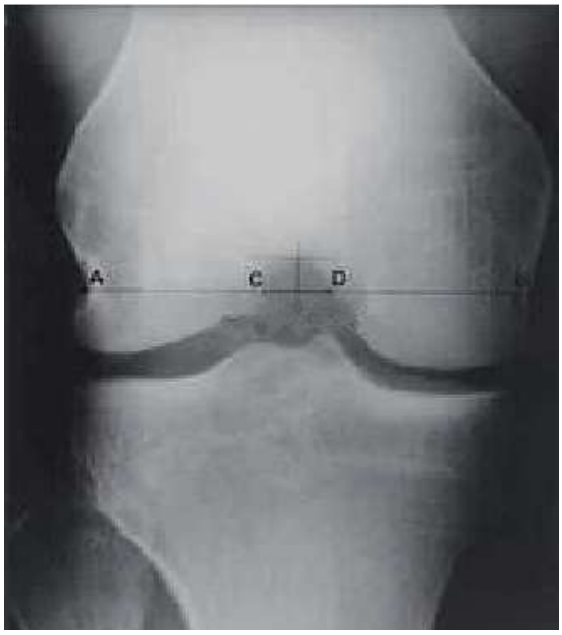

Figure 1. Femoral bicondylar width (A to B) and intercondylar notch width (C to D) were calculated as seen in the figure

Although 260 people had been admitted to the hospital, 61 patients were excluded (48 due to osteoarthritis, seven due to history of a previous surgery, and six due to a history of fracture) and 199 subjects were finally evaluated. Since in this study no intervention was performed on patients and the results were attained based on routine diagnostic procedures, there was no ethical limitation. Nevertheless, patients signed an informed consent after they had been ensured about the confidentiality of their personal information. Although the participants were allowed to quit the study at any point, all subjects completed the study.

The data was entered into SPSS for Windows (version 11.5, SPSS Inc., Chicago, IL, USA). The

mean values of INW, femoral bicondylar width, and intercondylar notch index in the two groups with and without ACL injuries were compared using Student's independent t-test. Chi-square test was used to analyze qualitative variables. Significant variables in univariate analysis were entered in multiple regression model with INW, mean femoral bicondylar width, and intercondylar notch index as dependent variables.

Results

This study included 199 patients (81 cases with ACL tear and 118 cases without ACL tear) of whom 75 subjects (37.7%) were female. The mean age of patients was 32.6 ± 7.9 years. The two groups had no significant differences in terms of gender distribution (P = 0.18) or mean age (P = 0.91). Knee trauma was due to tensile stress in 51 patients (25.6%) and a direct blow to the knee in 70 patients (35.2%) (Table 1).

No statistically significant difference was observed between the two groups regarding the distribution of injury to the bones adjacent the knee. The group with tear had a greater percentage of trauma to bones surrounding the knee (P < 0.001). The two groups were significantly different regarding the distribution of fractures in the bones adjacent to the knee and the group with tear had a greater percentage of rupture in bones surrounding the knee (P < 0.008). However, there was no significant correlation between these two variables (Table 2).

The mean INW was 22.63 ± 3.25 and 21.4 ± 2.78 mm in the groups with and without ACL tear, respectively (P = 0.004). The mean femoral bicondylar width was 76.00 ± 5.97 mm and 79.39 ± 5.38 mm in the groups with and without ACL tear, respectively (P < 0.001). The mean intercondylar notch index was 0.30 ± 0.04 and 0.27 ± 0.03 in the groups with and without ACL tear, respectively (P < 0.001) (Table 1). The mean INW and intercondylar notch index were significantly lower in women than in men (P < 0.001). Multiple regression analysis showed that INW and intercondylar notch index in women with ACL tear were lower than other groups (Table 3).

Table 1: Characteristics of the two groups with and without anterior cruciate ligament (ACL) tears

Variable	Without ACL tear (n = 118)	With ACL tear (n = 81)	P
Sex			
Female	49 (41.5%)	26 (32.1%)	0.170
Male	69 (58.5%)	55 (67.9%)	
Injury to the bones adjacent to the knee			
Yes	8 (6.8%)	24 (29.6%)	< 0.001
No	110 (93.2%)	57 (70.4%)	
Breaking the bones adjacent to knee			
Yes	1 (0.8%)	7 (8.6%)	0.008
No	117 (99.2%)	74 (91.4%)	
Age (year)	32.5 ± 8.0	32.7 ± 7.6	0.910
Intercondylar notch width (mm)	22.63 ± 3.25	21.40 ± 2.78	0.004
Femoral bicondylar width (mm)	76.00 ± 5.97	79.39 ± 5.38	< 0.001
Intercondylar notch Index	0.30 ± 0.04	0.27 ± 0.03	< 0.001

Values are n (%) or mean ± SD; ACL: Anterior cruciate ligament

Table 2. The morphometric parameters of femoral bicondylar and intercondylar notch in the two sexes

Variable	Gender		P
	Male	Female	
Intercondylar notch width (mm)	23.36 ± 3.06	20.09 ± 1.93	< 0.001
Femoral bicondylar width (mm)	77.71 ± 6.23	76.84 ± 5.49	0.310
Intercondylar notch index	0.302 ± 0.041	0.262 ± 0.027	< 0.001

Values are mean ± SD; SD: Standard deviation

Table 3. The morphometric parameters of femoral bicondylar and anterior cruciate ligament (ACL) tears in the two sexes

Variable		Beta coefficient value		Beta confidence interval		P	R^2
		Standardized	Non- Standardized	minimum	maximum		
Intercondylar notch width	Constant coefficient	24.056	-	23.492	24.620	< 0.001	
	ACL tear	-1.563	-0.247	-2.303	-0.823	< 0.001	0.319
	Being female	-3.421	-0.532	-4.172	-2.670	< 0.001	
Femoral bicondylar width	Constant coefficient	76.239	-	74.986	77.491	< 0.001	
	ACL tear	3.334	0.275	1.690	4.978	< 0.001	0.080
	Being female	-0.555	-0.045	-2.221	1.112	0.512	
Intercondylar notch index	Constant coefficient	0.316		0.309	0.324	< 0.001	
	ACL tear	-0.032	-0.383	-0.042	-0.023	< 0.001	0.359
	Being female	-0.043	-0.498	-0.052	-0.033	< 0.001	

ACL: Anterior cruciate ligament

Discussion

The most common type of ACL injury is ligament damage which was reported in about 3.2% of men and 3.5% of women over a four-year period.[29] It is more common in athletes and has several environmental risk factors.[6,8,30,31] Recognizing the physiological risk factors of this problem can help identify and protect people at risk.

We found significantly higher INW and intercondylar notch index in the group without ACL tear than in those with the tear. However, the mean width of femoral bicondylar was significantly higher in the group with ACL tear than in the other group. In multiple regression analysis, INW and intercondylar notch index were lower in subjects with ACL tear and women than in other groups.

Several studies with contrasting results have been conducted in this field. Lombardo et al. did not find a significant difference in mean intercondylar notch index in athletes with and without ACL injuries (0.235 vs. 0.242).[20] However, Schickendantz and Weiker[21] and Teitz et al.[22] reported a significant difference in intercondylar notch index between people with and without ACL tears. Souryal et al. calculated the mean intercondylar notch index as 0.2238 in the normal group, 0.2248 in the acute tear group, and 0.1961 in patients with two-sided ACL injuries and suggested the difference between the first and third groups to be statistically significant.[12] Good et al. reported the mean INW as 16.1, 18.1, and 20.4 mm in patients with chronic ACL injuries, acute injuries, and normal knees, respectively.[14] In another study, Souryal et al. reported that people with smaller intercondylar notch are less likely to suffer from traumatic knee injuries. They thus introduced the mean intraocular notch stenosis as a risk factor for noncontact tensile ACL injuries.[15] As we obtained similar results, this index can be used to identify and screen athletes vulnerable to ACL tears. It can also be considered as a risk factor for posterior cruciate ligament (PCL) tear since Davis et al. showed a significant relationship between ACL and PCL.[16] Wada et al. suggested the mean INW to be significantly lower in knees with ACL laxity or tear than in those with normal ACL.[17] Stijak et al. observed a significant difference in intercondylar notch index between people with ACL injury and those without it.[18]

In the only available Iranian study in this field, Alizadeh and Kiavash showed the mean intercondylar notch index to be significantly different in healthy subjects and the group with ACL tear (0.298 vs. 0.296).[19] The age range of the participants in the mentioned study increased the probability of osteoarthritis and might have been a confounding factor. However, the exclusion criteria and the restricted age range in the present study reduced the effects of age as a confounding factor. While the findings of Alizadeh and Kiavash[19] were not consistent with ours, various studies have indicated a

relationship between intercondylar notch stenosis and ACL tear.[32] Stijak et al. showed that the INW and ACL are significantly higher in men than in women.[1] Souryal et al.[12] and Dienst et al.[24] found higher intercondylar notch index in men than in women. Murshed et al. reported similar results about the INW and epicondylar notch width.[23]

Since the current study had a cross-sectional design, it could not precisely prove the cause. Hence, obtaining more accurate results requires further comprehensive, cohort studies on athletes to measure these indexes before starting professional sport careers and evaluate the level of ACL injuries.

Conclusion

Based on the results of this study, ACL tears are related with being female and intercondylar notch stenosis. Therefore, this index can be used for screening athletes and people who are at risk of developing ACL tears.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Risk factors of chronic obstructive pulmonary disease in men and women in Sanandaj, Iran

Naseh Sigari[1], Fatemah Alhani[2], Jamal Seidi[3], Ghader Salehnejad[4], Alireza Gharib[5], Roshani Daem[6]

1 Department of Internal Medicine, School of Medical Sciences, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Associate Professor, Department of Nursing, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
3 Department of Nursing, Kurdistan University of Medical Sciences, Sanandaj, Iran
4 Department of Nursing, Kurdistan University of Medical Sciences, Sanandaj, Iran
5 Deputy of Research and Technology, Kurdistan University of Medical Sciences, Sanandaj, Iran
6 Assistant Professor, Department of Biostatistics and Epidemiology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world. While smoking has been identified as the main cause of COPD in many studies, other causes may include environmental pollution and genetic vulnerability in both genders. Considering lifestyle of rural women, and the old structure of Sanandaj (Kurdistan Province, Iran) which is different with other parts of the country, this study compared the risk factors for COPD in men and women.

METHODS: In a descriptive, analytic study 400 subjects of both genders (200 female and 200 male) were evaluated. The files of patients with COPD admitted to Besat Hospital (Sanandaj, Iran) during 2006-11 were randomly selected using a systematic sampling method. The sampling continued until a total of 200 patient files were collected in each group. Eventually, data was analyzed with SPSS.

RESULTS: Smoking was the major risk factor (56.5%) for COPD in both men and women (n = 226). While only 32.5% of women (n = 65) had a history of smoking, the rate was as high as 80.5% in men (n = 161). Most women (60.5%) were more exposed to fossil fuel smoke than men. Fisher's exact test results showed a significant difference in the risk factors (including Smoking and tobacco use, Exposure to fossil fuel smoke and air pollution) and the type of jobs between the two genders.

CONCLUSION: Based on the results of our study, it is better to obtain an accurate history of exposure to smoke of wood or biomass and a history of residing in rural areas as the main risk factors for developing COPD in patients who have no history of high-risk occupations or other risk factors of the disease (e.g. smoking).

KEYWORDS: Chronic Obstructive Pulmonary Disease, Epidemiological Study, Risk Factors

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world. Regardless of gender, tobacco use is the major cause of COPD. However, other causes may include air pollution and genetic susceptibility.[1,2] Several studies have suggested fossil fuel fumes as an etiologic factor for development of COPD. This association has been reported to be significant in females. Fossil fuels like firewood, charcoal, animal waste, and plants are used in baking, cooking, heating, and

Corresponding Author:
Fatemah Alhani
Email: alhani_f@modares.ac.ir

home lighting.[3] In developing countries, fossil fuels are the main cause of indoor pollution and studies have shown that the inhalation of these pollutants are responsible for lung diseases, particularly COPD.[4]

A great deal of recent research in developing countries has reported symptoms of obstructive lung disease in persons without previous history of cigarette smoking or occupational or industrial exposure. Bronchoscopic procedures revealed black particles in the airways of these patients (anthracosis). Since most of these patients have been in contact with fossil fuels, pollutants inhaled from such fuels could be the main culprit of COPD.[5-10] The majority of the mentioned studies have been performed in developing countries such as Turkey, Iran, India, Mexico, Bolivia, Tanzania, Kenya, Nepal, China, and rural areas of South Korea.[11-20]

The incidence of obstructive lung disease after exposure to fossil fuels occurs mainly in women. In 2009, some cases of COPD with anthracosis were reported. They were mostly rural women with long-standing history of exposure to fossil fuels.[4] Based on numerous clinical experiences, COPD is observed in non-smoking women as well.[4] However, in 2008, Seidi found the majority (97%) of patients with COPD and a history of smoking in Sanandaj (Kurdistan Province, Iran) to be male.[2] Therefore, it is necessary to identify gender-related risk factors of COPD and to compare them with other related studies. Kurdish women have a traditional lifestyle in the old dwellings of Sanandaj. Considering the increased indoor fossil fuel pollutants in recent years and previous research in this field,[2,4] this study was conducted with a particular emphasis on gender-based risk factors of COPD. It eventually evaluated the risk factors for developing COPD in female and male populations in the city of Sanandaj.

Materials and Methods

This descriptive, analytic (cross-sectional) study included 400 (200 male and 200 female) patients with COPD admitted to Besat Hospital (Sanandaj) from 2006 to 2011 during which a total of 400 subjects for both sexes were included in the study. The study protocol was approved by the ethics committee of Kurdistan University of Medical Sciences, Sanandaj, Iran).

During the study, 2000 files were randomly selected for each gender. Then, systematic sampling was used to select one case from every 10 files. In order to start sampling, file number seven was chosen among files one to 10 at random. Other files were then selected by adding multiples of 10 to seven. Therefore, files seven, 17, 27, and so on were until a total of 200 files were collected in each group.

We only considered bronchitis and emphysema as COPD. Hence, asthma, pneumonia, and other respiratory diseases were excluded from this study. After obtaining permissions from Besat Hospital, questionnaires containing questions on the history of COPD were filled out based on patient files. Diagnosis of COPD had been confirmed through spirometry as a standard test (the spirometric values were recorded in patient files). Patients with productive cough for more than three months in two consecutive years and forced expiratory volume in 1 second (FEV1) to forced vital capacity (FEV1/FVC) of less than 70% were considered to have COPD. These patients' conditions did not improve in spite of receiving bronchodilators.

Patient history including clinical symptoms such as cough, sputum, and dyspnea, chest X-ray, arterial blood gas measurements, history of smoking, exposure to fossil pollutants, history of previous exposure to chemical warfare, history of medications, and Alpha1-antitrypsin values (for patients younger than 45 years of age) were also recorded in the specified questionnaires.

The collected data was analyzed using Fisher's exact test to compare statistical differences between male and female groups. All analyses were performed with SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA).

Results

The mean age of all subjects was 67.45 ± 1.21

years (66.61 ± 1.36 years in men and 68.30 ± 3.70 years in women). Overall, 124 female patients (62.0%) were housewives or stayed at home because of poor health or senility. Most men (n= 144; 72.0%) and 70 women (35.0%) were farmers or had a lifetime history of agricultural work. Although 110 women (55.0%) and 137 men (68.5%) were urban dwellers, about 360 patients (90.0%) from both sexes had spent more than 40 years of their lives in rural areas. Fisher's exact test results showed significant differences in risk factors and types of jobs between the two genders. However, men and women were not significantly different in terms of seasonal incidence and exacerbation.

Smoking was the major risk factor of COPD in both men and women (n = 226; 56.5%). Meanwhile, only 41 women (20.5%) versus 161 men (80.5%) were smokers (P < 0.001) (Table 1). In contrast, significantly higher number of women had the history of exposure to fossil fuel smoke [131 women (65.5%) vs. 29 men (14.5%); P < 0.001] (Table 1). The presence of other factors, e.g. infection and genetic factors, had been recorded for eight women (4.0%) and 10 men (0.5%).

Moreover, when exposed to cigarette exposure, men had 9.407 times higher chance of developing COPD than did women (P < 0.001; 95% confidence interval: 5.930-14.92). On the other hand, exposure to fossil fuel smoke increased the risk of developing COPD 0.855 times more in women than in men (P < 0.001; 95% confidence interval: 0.808-0.905). Finally, male and female patients did not have any significant differences in other risk factors like infection and genetic abnormalities (P = 0.400, 95% confidence interval: 0.488-3.270) (Table 2).

Discussion

We found men to be more affected with cigarette smoke while women were more likely to experience the side effects of fossil fuels. Many studies have identified smoking and air pollution as main causes of COPD regardless of gender.[1,21-23] However, the lifestyle of rural women in Kurdistan Province, smoke from the conventional home oven, old houses in villages, and old structure of the city of Sanandaj were the main culprits behind COPD. Overall, 32.5% of women and 80.5% of men were smokers. On the other hand, 65.5% of women and 16.0% of men were exposed to fossil fuel smoke. A meta-analysis by Halbert et al. suggested smoking, air pollution, and occupation as the main risk factors for the disease.[21] In large and industrial cities, air pollution is the most important risk factor for the incidence and aggravation of COPD.22 Halvani and colleagues detected occupation-related

Table 1. Distribution of absolute and relative risk factors of chronic obstructive pulmonary disease in male and female patients (n = 200 each) admitted to Besat Hospital in Sanandaj, Iran

	Female		Male		Fisher's exact test results
	Number	Percent	Number	Percent	
Smoking and tobacco use					
Yes	61	30.5	161	80.5	df = 1 P < 0.001
No	159	69.5	39	19.5	
Exposure to fossil fuel smoke and air pollution					
Yes	131	65.5	29	14.5	df = 1 P < 0.001
No	59	34.5	171	85.5	

Df: Degree of freedom

Table 2. Odds ratio (OR) and 95% confidence interval (CI) of risk factors of chronic obstructive pulmonary disease in male and female patients (n = 200 each)

Variables	OR	95% CI	P
Smoking	9.407	5.930-14.923	< 0.001
Fossil fuel smoke and air pollution	0.855	0.808-0.905	< 0.001
Other factors (genetic and infection)	1.260	0.488-3.270	0.405

OR: Odds ratio; CI: Confidence interval

risk for COPD in 77.7% of patients. They reported high-risk occupations for men and women as bakery (54.4%) and agricultural jobs (46.6%), respectively.[23]

Two-thirds of women and one fifth of men in the present study had no history of smoking. Wood smoke exposure was prevalent in more than half of the women and about 90.0% of patients had a history of living in rural areas. The results of our study suggest obviously different epidemiological results in male and female patients with COPD. This is consistent with many studies on the causes of COPD in which the gender differences was included in the study[24-35] (Table 3), nevertheless the results were different when the gender was not included in the study.[1,2]

Generally, etiologic diagnosis of COPD in non-smokers is a major medical challenge.[5] A closer look at the results of this study and other parallel studies indicates the importance of household contact with contaminants as an etiologic cause of COPD especially in women. In recent years, many studies have shown that contact with fossil fuel smoke is a major cause of airway diseases such as anthracosis of the airway. In this regard, Amelie presented his first report by which 10 female patients with symptoms of COPD had airways anthracosis.[24] A great number of other studies have also reported a higher prevalence of anthracosis in women.[24-34]

The high prevalence of COPD among our non-smoking, female participants could be explained by their contact with fossil fuel smoke. Most rural houses, where rural women spent most of their time cooking and baking, lack adequate ventilation and are thus polluted with carbon particles. Our study didn't explain a history of significant risk factors such as smoking in patients with respiratory problems such as symptoms of chronic obstructive pulmonary disease. Therefore, elements such as having close contact with fossil fuel smoke, place of residence, and house ventilation have to be considered as main components in history taking. Appropriate measures should then be taken for faster detection and elimination of these risk factors.

The female/male ratio of bronchitis caused by exposure to fossil fuel smoke was 11/121 which is consistent with the results of some other relevant studies.[24-34] These studies reported the higher prevalence of COPD in

Table 3. Distribution of published studies considering male and female components, on the incidence of bronchitis caused by smoke exposure of burning fossil fuels

Country	Number of patients	Mean age of the patients	Female to male ratio	Author
Iran	778	63	399/372	Sigari and Mohammadi[34]
	102	60-62	42/60	Amoli[24]
	34	61.8	15/19	Hemmati et al[30]
	40	70	14/26	Sigari and Bahari[3]
	63	60	-	Mirsadraee and saeedi[27]
	47	70	24/23	Najafizadeh et al[25]
	10	62.5	0/10	Amoli[26]
	96	68.2	44/52	Aslani et al[28]
South Korea	54	75	19/35	Jang et al[32]
	166	72.5	23/143	Gupta and Shah[29]
	54	67	16/38	Kim et al[35]
	22	55-84	8/14	Bekci et al[31]
	28	64	8/20	Chung et al[7]
Turkey	27	68.8	25/2	Torun et al[8]
UK	7	71	5/2	Wynn et al[33]

women than in men to be justified by women's contact with household pollutants like fossil fuels, poorly ventilated kitchens, and insanitary dwellings.[24-34] The first study in this field was published by Amoli in 1998. It presented 10 female patients with a long history of contact with pollutants inside the house.[24] Other studies revealed higher female to male ratio in patients exposed to fossil pollutants.[7-35]

Numerous recent studies have evaluated bronchitis due to exposure to fossil fuel smoke in rural communities especially in women exposed to fuels from animal and firewood. Sigari and Bahari found that the majority of patients with anthracotic bronchitis were either housewives residing in rural areas or male farmers who developed COPD as a result of smoking.[3] Since the target population in this study has mainly been rural women, the findings of Sigari and Bahari are comparable to ours. The high prevalence of COPD in rural housewives or those live in the outskirts of urban areas could be explained by exposure to indoor carbon contaminants. In previous studies, the incidence of bronchitis and respiratory symptoms were higher among rural women who used firewood or biomass as fuel for food preparation.[2,4-6,8-15]

In patients with respiratory symptoms and COPD who have no specific history of risk factors, not only the occupational history of the patient, but also the use of firewood or biomass for cooking and heating has to be particularly considered. At last housekeeping in rural areas and outskirts of urban areas should be considered as an important risk factor and bronchitis caused by exposure to smoke from burning fossil fuels in women and to a lesser extent in men should be considered as an important factors in contracting the disease.

Conclusion

Some studies have introduced tobacco smoking as the main cause of COPD in both genders. Similar to previous research, fossil fuel smoke was another important risk factor for the disease. Thus, it is better to obtain an accurate history of exposure to smoke from firewood or biomass and the history of residing in rural areas as main risk factor of COPD patients with no history of high-risk occupations or smoking.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

A survey of factors related to urine iodine levels in elementary school children, Kurdistan, Iran

Mehdi Zokai[1], Amin Amini[2], Farzam Bidarpoor[1], Mohammad Tamimi[3]

1 Kurdistan Province Health Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Nutritionist, Kurdistan Province Health Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
3 Food and Drug Deputy, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: Iodine deficiency disorders (IDD) control program has two important factors: annual monitoring of urine iodine levels and controlling iodized salt consumed in the community. Preserving the iodine indexes in different level is important now too. This survey determined factors affecting median levels of urine iodine levels in students of Kurdistan Province (Iran).

METHODS: This cross-sectional study selected 255 8-10-year-old students using cluster random sampling. Data was obtained by a questionnaire and urine analysis. The collected data was analyzed by Mann-Whitney and Kruskal-Wallis tests, Spearman correlation, and multiple regression. All analyses were performed using SPSS.

RESULTS: The median urine iodine level of the studied school children was 9.7 µg/dl. There was no significant relation between urine iodine level and sex, place of residence (rural/urban areas), and household iodized salt intake (r = 0.188, P = 0.003). Overall, 119 families (46.7%) did not appropriately protect their iodized salt. The amount of iodine in salt and the condition in which salt is kept had relationships with children's urine iodine levels.

CONCLUSION: Low median level of urine iodine in students, low household iodized salt, and high use of salt with lesser iodine than the standard value showed that the IDD program in Kurdistan Province has not been successful. Therefore, there is a risk for increased prevalence of Goiter in the region. We recommend interventional programs to improve the current status in the province.

KEYWORDS: Goiter, Urine Iodine, Iran

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Introduction

Iodine is an essential element for human body which changes to thyroid hormones (triiodothyronine and thyroxine) after absorption in the thyroid gland. Thyroid hormones are necessary for normal brain development and brain function, especially during pregnancy. Iodine deficiency disorder (IDD) leads to various types of diseases such as goiter, hypothyroidism, mental retardation, psychosomatic disorders, neural auditory disorders, and cretinism.[1-3] According to the World Health Organization (WHO), about 1.6 billion men are at risk of IDD in over 130 countries of the world. Approximately 50 million of these people have different degrees of mental disorders due to IDD.[4,5] Since iodine is mainly excreted through urine, urinary iodine is a major indicator of iodine deficiency and a simple method to monitor iodine status of a community.[6,7] In 1994, the national IDD prevention and control program made the production of iodized salt mandatory in Iran.[3,6] Consequently, the WHO introduced Iran as one of the two IDD-free Middle Eastern countries. Unfortunately, assessments of iodized salt consumption and urinary iodine in the national

Corresponding Author:
Farzam Bidarpoor
Email: fbidarpoor2003@yahoo.com

monitoring of goiter revealed increasing number of students with iodine levels lower than 50 µg (moderate and severe iodine deficiency). In recent years, the prevalence of severe, moderate, and mild forms of IDD in Kurdistan (a province in Iran) has been as high as 11.6-31.6%.[8,9] This change can be considered as a warning about the reducing effects of the IDD prevention and control program and the probable recurrence of high prevalence of goiter. Kurdistan is a mountain province in Iran whose people are likely to develop iodine deficiency. This study evaluated the factors related to the urine iodine excretion in elementary school students of Kurdistan Province.

Materials and Methods

This cross-sectional survey was performed after obtaining approval from the ethics committee of Kurdistan University of Medical Sciences (Sanandaj, Iran). The statistical population consisted of 8-10-year-old schoolchildren and their parents who lived in Kurdistan Province in 2010. In total, 48 clusters (elementary schools) were systematically selected. After referring to the attendance office in each school and accessing student lists, one subject was randomly selected from the second grade, two from the third grade, and two from the fourth grade. The participants' parents were asked for their permission and urine samples were then collected according to national guideline and regulations. A questionnaire was filled out for each household. The questionnaire consist of observation and sampling of salt and measuring of iodine concentration in salt by iodine kit. For better accuracy, iodine content of salt samples was also determined by iodometry. The purity of samples was analyzed in the Food and Drug Laboratory of Kurdistan University of Medical Sciences.

Based on standard definitions, urine iodine levels lower than 2.0 µg/dl, between 2.0-4.9 µg/dl, and 5.0-9.9 µg/dl represent severe, moderate, and mild iodine deficiency, respectively. On the other hand, levels above 10 µg/dl are considered normal. Salts containing less than 20 gammas iodine lack the standard level of salt. Salt iodine levels of 20-55 and over 55 gammas are standard and higher than standard, respectively. Iodized salt should be kept in dark and closed containers away from light.

Data collected via questionnaires was analyzed using Mann-Whitney and Kruskal-Wallis tests and Spearman correlation. Variables with a significance level of less than 0.25 were entered into the multiple regression model. All analysis were performed in SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

As the quantitative variables did not have a normal distribution, they were expressed as median and range. The median urine iodine level was 9.7 µg/dl among the schoolchildren of Kurdistan Province (9.9 µg/dl in boys and 9.5 µg/dl in girls; P = 0.386). Children in urban areas had higher urine iodine levels than those in rural areas (10.5 vs. 8.3 µg/dl; P = 0.054). There was no significant correlation between urine iodine level and weight (r = -0.078; P = 0.220) or height (r = -0.016; P = 0.800). However, a positive significant correlation was found between urine iodine level and bulk salt (r = 0.188; P = 0.003). A negative significant correlation was also detected between urine iodine level and body mass index (BMI) (r = -0.173; P = 0.006). The urine iodine level lower and higher than 10 µg/dl were seen in 51.8% and 48.2% of the participants, respectively (Table 1, Figure 1).

The median of urine iodine level was 10.4 µg/dl in eight-year-olds, 8.9 µg/dl in nine-year-olds, and 10.5 µg/dl in 10-year-olds (P = 0.627). Parents with higher levels of education had children with higher median urine iodine. About 119 families (46.7%) did not keep their salts in appropriate conditions and the median iodine was 27.8 (range: 0-105.5) gamma in their salts. In 90 salt samples (35.3%), iodine was lower than the standard range. Moreover, 175 families (68.6%)

Table 1. Urine iodine levels in schoolchildren of Kurdistan Province, Iran

Variables	n (%)	Median	Minimum	Maximum	P
Sex					
Male	128 (50.2%)	9.9	2.0	40	0.380
Female	127 (49.8%)	9.5	1.0	40	
Place of residence					
Rural	114 (44.7%)	8.3	2.0	40	0.050
Urban	141 (55.3%)	10.5	1.0	40	
Age (years)					
8	62 (24.3%)	10.4	2.3	40	0.620
9	97 (38.0%)	8.9	1.0	40	
10	96 (37.6%)	10.5	2.0	40	
Salt usage					
In the beginning of cooking	175 (68.6%)	9.7	1.0	40	0.900
At the end of cooking	80 (31.4%)	9.5	2.0	40	
Salt storage conditions					
Good	136 (53.3%)	11.1	2.0	40	0.010
Poor	119 (46.7%)	8.9	1.0	40	
Father's education					
Not educated	30 (11.8%)	8.0	2.0	40	
Elementary school	99 (38.8%)	8.7	1.0	38.5	0.090
Junior high school	49 (19.2%)	10.5	2.9	40	
High school	12 (4.7%)	11.1	3.5	16.5	
College	65 (25.5%)	11.9	2.6	35.2	
Mother's education					
Not educated	95 (37.3%)	9.3	1.0	40	
Elementary school	84 (32.9%)	8.0	2.3	40	0.150
Junior high school	24 (9.4%)	11.4	3.2	39.1	
High school	10 (3.9%)	13.6	6.0	40	
College	42 (16.5%)	11.8	2.6	34.2	

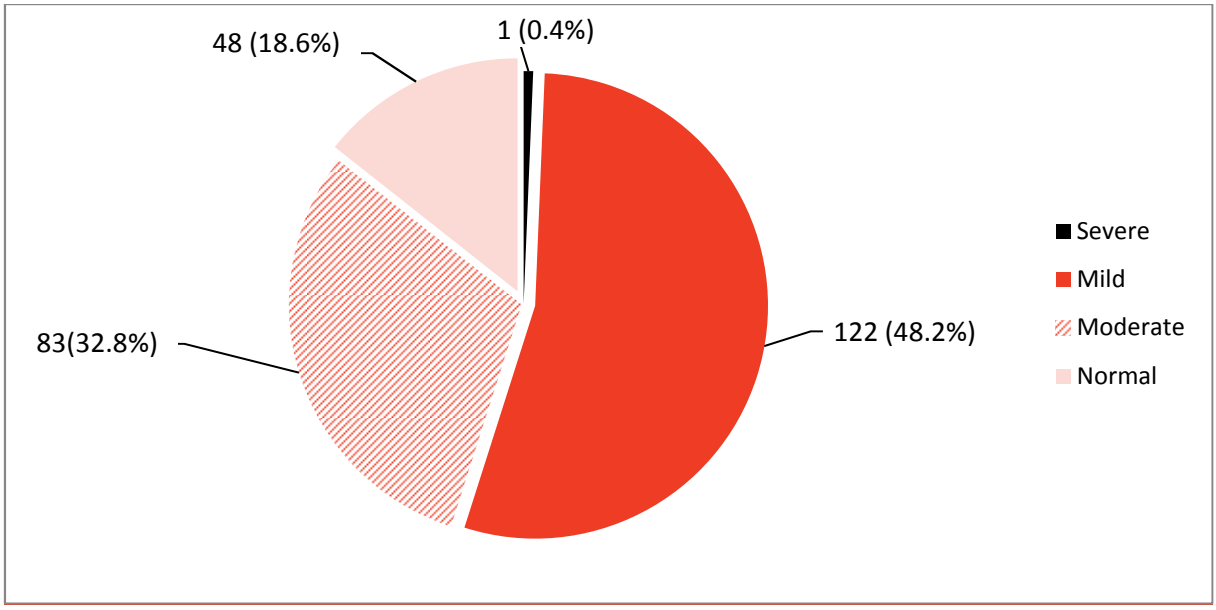

Figure 1. Severity of iodine deficiency according to urine iodine levels (< 2.0 µg/dl: severe deficiency; 2.0-4.9 µg/dl: moderate deficiency; 5.0-9.9 µg/dl: mild deficiency; and ≥ 10 µg/dl: normal range).

Table 2. Results of multiple regression analysis to evaluate the potential relations between urine iodine level and different factors (father's education, place of residence, salt storage conditions, salt iodine, and body mass index were entered into the model but the last three finally remained).

Model	Unstandardized Coefficients		Standardized coefficients	95% confidence interval for beta		P
	Standard Error	Beta		Lower bound	Upper bound	
Constant	4.127	19.342	-	27.473	11.211	< 0.001
Salt storage conditions	1.185	-2.847	-0.153	-0.512	-5.182	0.017*
Salt iodine	0.035	0.095	0.168	0.165	0.025	0.008†
Body mass index	0.234	-0.487	-0.132	-0.026	-0.948	0.038‡

* Inappropriate storage conditions lead to decreased urine iodine level; † Higher iodine content of salt correlated with higher urine iodine level; ‡ Higher body mass index correlated with lower urine iodine level

added salt to food in the beginning of cooking (wrong use).

After controlling confounding factors by multiple regressions, urine iodine level was found to have positive, significant relations with iodized salt consumption and appropriate method of keeping salt. On the other hand, urine iodine level was negatively related with BMI (Table 2).

Discussion

We found the median urine iodine level to be 9.7 µg/dl in the students of Kurdistan Province (51.8% had urine iodine levels lower than 10 µg/dl). On the other hand, 46.7% of families did not keep iodized salts in suitable conditions and 68.6% added salt to food incorrectly. The median iodine content of salts was 27.8 gamma. Urine iodine level was significantly related with iodized salt consumption, appropriate protection of salt, and BMI.

A survey in Tehran (Iran) reported the median urine iodine as 9.4 µg/dl (10.9 µg/dl in urban areas and 8.0 µg/dl in rural areas) with no difference between the two sexes. While urine iodine levels higher than 10 µg/dl were seen in 45.6% of the subjects, the corresponding values were 5-9.9 µg/dl in 33.6% and lower than 4.9 µg/dl in 20.8%. The majority of the study sample (54.9%) used non-iodized salt and 47.9% kept salt in inappropriate conditions. Iodine content was less than 15 gamma in 62.5%, 15-30 gamma in 25.6%, and 30-50 gamma in 31.3% of the study sample.[10] A study in Azerbaijan (Iran) found the median urine iodine and the mean iodine of salt samples to be 11.9 µg/dl and 32.36 ppm, respectively.[11] The median urine iodine in schoolchildren of Yazd (Iran) was 24.8 µg/dl (5.8% of urine samples had iodine levels lower than 5 µg/dl). Almost half the studied families (48.0%) kept salt in good conditions.[9]

In France, Pouessel et al. suggested median urine iodine level not to be related with age, sex, place of residence, social status, or job.[12] Gur et al. reported urine iodine levels lower than 10 and 5 µg/dl in 46.2% and 13.9% of Turkish students, respectively. The prevalence of IDD increased in families with low-educated parents and poor and more populated families. While 44.4% of families used iodized salt, it did not affect IDD rate.[13]

In order to control IDD in a region, the WHO policies and regulations have to be followed. Accordingly, IDD is controlled when over 90% of families have urine iodine levels higher than 10 µg/dl through the use of iodized salt, urine iodine levels below 10 µg/dl are found in less than 50% of the population, and urine iodine levels below 5 µg/dl among are only detected in less than 20% of the population.[14] The median urine iodine levels in schoolchildren of Kurdistan Province were recorded as 25.8, 16.0, and 14.7 µg/dl in 1992, 2001, and 2007, respectively.[8,9,15,16] As it is seen, the values have had a decreasing trend. While 51.8% of urine samples had less than 10 µg/dl iodine, the rates were 14.2%, 19.7%, and 35.0% in 1992, 2001, and 2007, respectively.[8,9,15,16] Differences in the

findings of various studies could have been due to behavioral and environmental factors. In general, the above-mentioned trends indicate insufficient iodine supply in Kurdistan Province. We found level of iodine in salt to be correlated with urine iodine levels, i.e. iodized salt is a very important source of iodine for human body.

Lowe levels of urine iodine in children of rural areas confirms their access to non- or low-iodized salt, and inappropriate keeping of salt, and low knowledge in rural society. Therefore, the IDD prevention and control program has not been successful.

The mean iodine content of salts used in the studied households was 27.8 gammas. However, this amount has been calculated as 30 gammas in 2007.[15] In spite of public education programs and collection of non-iodized salts at the provincial level, 35.5% of salt samples in the present study had less iodine than the standard range. Hence, either a lot of non-iodized salt is still in the market or salt is not kept in good conditions. Although a previous study revealed that 87.5% of salts used in Kurdistan Province are iodized, demographic data collected by health employees in villages suggested the rate to be as high as 98.0%[17]. Since this very high rate seems to be the result of inaccurate measurements performed by health employees, it is necessary to find out the exact rate of iodized salt consumption through census in the beginning of each year and to assess the iodine content of salts using iodine measurement kits.

In the present study, inappropriate conditions of storing salt was related to decreased iodine level in urine. Considering the fact that 46.7% of families did not store salt in suitable conditions, public education in this field is warranted. Adding salt in the beginning or end of cooking does not affect urine iodine level. The observed relation in this study was probably caused by using non-iodized salt for cooking since iodized salt changes the taste of foods. Thus, qualitative research would be is essential to better clarify this relation.

Reducing urine iodine is important since studies in some countries have shown increased prevalence of IDD and its complications as a result of previously implemented IDD control programs. For example, the former Soviet Union produced a lot of iodized salt and designed an exact plan to control and monitor iodine deficiency during 1955-70. Consequently, the prevalence of goiter was reduced to less than 5% in a national survey in 1969. However, the gradual increase of iodine deficiency was again observed in the 1970s when the surveillance system and preventive programs had terminated. Finally, by 1991, the whole IDD control system had been inactived.[18] A similar trend was seen in Australia after reduced production and use of iodized salt.[19,20]

Conclusion

Our findings indicated the possible failure of the IDD control program in Kurdistan Province. Therefore, iodized salt production factories have to be supervised and the public has to be educated on appropriate use of iodized salt. In the absence of periodic revisions to IDD control programs, the incidence of goiter and other iodine-related disorders may start to increase again.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Effectiveness of an educational intervention on pain duration and severity of herniated disc

Kheiriollah Moradi[1], Mokhtar Yaghoubi[2], Daem Roshani[3], Alireza Gharib[4]

1 Department of Nursing, Islamic Azad University, Sanandaj Branch, Sanandaj, Iran
2 Department of Nursing, Kurdistan University of Medical Sciences, Sanandaj, Iran
3 Department of Epidemiology, Kurdistan University of Medical Sciences, Sanandaj, Iran
4 Deputy of Research and Technology, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: One of the causes of low back pain is herniated disc that puts pressure on the nerve roots and cause pain radiating down the legs. Specific body movements tend to aggravate pain. Among treatment approaches, patient education could be considered as an effective way of pain management. We did not find any study showing the effects of educational intervention on pain management in searched medical literature. This study aimed to investigate effects of educational intervention on the level of pain due to herniated disc.

METHODS: In this study, 83 patients with lumbar disc pain were selected and pain intensity and duration were recorded based on a scale from one to ten. The average pain intensity and duration before and after intervention were recorded. Then the data were analyzed using SPSS software.

RESULTS: Frequency of L4-L5 herniated disc was 39.7%, L5-S1 was 36.1% and L4-S1 was 24.1%. Mean intensity of pain before intervention was 8.33. After intervention, duration of pain decreased from 8.34 ± 0.73 to 6.76 ± 5.54 ($P < 0.001$) and mean duration of pain before and after intervention were 65.6 ± 5.21 and 53.5 ± 5.83 minutes, respectively ($P < 0.001$).

CONCLUSION: Educational intervention for patient with lumbar herniated disc could be used as a practical complementary method beside other therapeutic approaches in the treatment of low back pain.

KEYWORDS: Educational Intervention, Pain, Herniated Disk, Low Back Pain

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Introduction

Low back pain is a common and costly medical conditions.[1,2] In 75% of the patients, their condition is improved by treatment but in 25% it deteriorates despite treatment.[3,4] One of the causes of low back pain is bulging or herniated disc which causes pressure on the nerve roots and radiation of pain to lower limbs.[5] Dislocation of back vertebra mostly occurs in L4-L5 and L5-S1 and its diagnosis is achieved by straight leg raise test (SLRT), magnetic resonance imaging (MRI) and CT-scan.[6] Some activities may cause increased intraspinal pressure (bending down, getting up fast from a lying position, sneezing and coughing) which may cause increased pain. This may cause aggravation of pain and changes in the spinal cord mechanics and ultimately body forms.[6] Low back pain may cause limitation in movement and weakness in hip muscles.[5] The most common reason for limitation of movement in patient under the age of 45 is low back pain which occurs mostly with increasing age.[7]

Relationship between some background conditions and low back pain as well as long period of standing, sitting and heavy works has been confirmed. Other psychological reasons like

Corresponding Author:
Mokhtar Yaghoubi
Email: mokhtar-yaghobi@muk.ac.ir

routine and monotonous jobs, low levels of job satisfaction, and stressful jobs has been mentioned as related to low back pain.[8,9] Statistics have shown that from 32711 patients referred to health clinics, 7935 cases had chronic low back pain.[10] Side effects of chronic low back pain include depression, loss of job, and sleep disorder.[11] Treatments are surgical and therapeutic including non-steroidal and corticosteroid medications.[6]

Obviously exclusive therapeutic or surgical intervention may not be successful in treating these patients; furthermore, surgery has its own side effects. It seems that rehabilitation treatments like physiotherapy and aerobic exercises as well as walking and swimming are effective on decreasing duration and severity of pain.[5] A study done by Selkowitz et al. showed that one hour patient education in a session could affect on level of awareness in patients under micro discectomy surgery.[12] Sherman et al. study showed that combination of Yoga and physical exercise in addition to self-care education improves function and decrease chronic low back pain.[13] Another study done by Deyo et al. showed that patient education caused job satisfaction and decreased job absenteeism with a rate of 80%.[14] Another study by Schectman et al. showed that patient education in low back pain caused behavioral change leading to decrease in pain.[15] Patient education is one of the responsibilities of health care team. With regard to the conducted studies, no exclusive study has been done to evaluate the effect of patient education on the level of pain due to herniated disc. Considering low cost and limited side effects as well as ease of implementation, this study was conducted to evaluate the effect of education on herniated disc pain.

Materials and Methods

The study was a before after clinical trial. The subjects were patient with low back pain referring to the Besat Clinic in Kurdistan University of Medical Sciences, Iran. Non-probability sampling method was used during which patient did not have equal chance for entering into the study and only patients were chosen who had pain due to herniated disc. Sample size was determined based on Cochran's formula at $\alpha = 0.05$ with power of 80%, resulting in a total of 83 patients. Data gathered using: 1) Demographic questionnaire, 2) numeric pain scale (0-10) for pain assessment before and after the intervention, and 3) table for pain duration in minutes before and after the intervention. Considering the validity and reliability of the instruments, the numeric measurement tool for pain has been used in many countries and its reliability has been approved. Test-retest reliability of the survey instruments was assessed using 10 patients of sample population in a period of one week by Pearson's correlation coefficient ($r = 96\%$) showing good reliability of the instrument.

The research team attended the location and after examining the venue and subjects, based on demographic data and other factors started to choose subjects according to inclusion criteria: 1) One month pain duration, 2) pain should be due to herniated disc, 3) no lumbar canal stenosis or other conditions, 4) being literate, and 5) using the same medication during the study. Exclusion criteria were: 1) Failure to follow instructions, 2) changes in medication, 3) having other diseases related to the spinal cord, and 4) not willing to participate in the prospective study.

Informed consent was obtained from the patients knowing that they could be excluded from the study upon their request. The patients were informed that they could use their prescribed medication including naproxen 500 mg twice daily, Depomedrol injection (prednisolone) 40 mg and Kopex topical gel twice daily after the intervention. During the course of the study, the subjects were examined by neurosurgeons using MRI and SLRT test to diagnose the herniated disc. Before intervention, information regarding pain intensity and duration were collected (83 patients).

Practical patient education was given to the subjects in the physician clinic and after that

hand out were distributed among them. A sample of patients education instructions is: Refraining from exercises which induce intracranial pressure like bending down and tensions due to coughing and sneezing; resting on a firm floor; proper weight lifting technique; semi-sitting position lead to back muscle relaxation; patients should place a pillow between their knees while they are in a lateral position; in the time of getting up from the lying position the patients should first rest on his/her side and get up while he/she puts pressure on the bed; using wet and hot compress help relaxation of the tense muscles in the back region; walking in the water pool and refraining from hyperactivity due to its negative effect on adjacent muscles in the vertebral column; and hanging from a horizontal bar several times a day. In case these managements did not reduce the pain, patients should refer to the physician for further follow-up. Then the duration and intensity of pain chart was distributed among patients to be filled out at home and they were reminded to deliver them in their next clinic referral. The patients learned to fill out intensity and duration of pain chart and were informed that in case they were unable to fill out the form they would be excluded from the study. Finally, data were recorded and analyzed using SPSS (version 19; SPSS Inc., Chicago, IL., USA). For comparing duration and intensity of pain before and after intervention, paired t-test was conducted with regard to the normal distribution of both variables.

Results

Mean age of the subjects was 37.5 years with a range between 18-65 years, 51 (61.4%) patients were male, and 55 (66.3%) patients were married. The results showed that bending of the leg caused aggravation of the pain in all of the patients. The SLRT test was positive in 75 (90%) patients. In 33 (39.7%) patients in L4-L5, in 30 (36.1%) patients in L5-S1, and in 20 (24.1%) patients both had disc herniation. 71 (85%) patients had pain in the time of getting up from bed. Pain increased in 73 (88%) patients with activity and in 61 (73%) subjects with sneezing or coughing. 68 (80.7%) patients had gait disorder. 73 (84%) patients had foot paresthasia. 29 (34%) subjects were obese. The results are shown in table 1.

Discussion

The results revealed that mean intensity of pain before and after intervention were (8.33 and 6.76) respectively; along with mean duration of pain before intervention was 65.6 minutes that was reduced to 53.5 minutes after intervention. The results showed that patients with improper physical activities had more pain. Another factor in our study was obesity which involved 29 patients with herniated disc. Risk factors included low back pain, lifting of heavy objects, torsion of the waist, and continuous and severe body movement, and obesity. Most of the herniated discs were in L4-L5 and L5-S1.[6] In our study, most of the cases had L4-L5 disc herniation (39.7%); however, disc herniation in L5-S1 (36.1%) had the most frequency. In patients with herniated disc in L4-S1 which involved all 3 vertebras, the rate was 24.1%. The results showed that mostly one of the vertebras was involved and when both of the vertebras were involved, patients had more pain which could be considered as an important finding.

Table 1. Mean intensity and duration of pain due to disc herniation in patients with lumbar disc herniation

		Mean ± SD	Mean difference (95% CI)	t	P
Pain intensity	Before After	8.34 ± 0.73 6.76 ± 5.54	1.41 (1.24-1.57)	17.3	< 0.001
Pain duration (minutes)	Before After	65.6 ± 5.21 53.5 ± 5.83	12.1 (11.2-12.9)	21.3	< 0.001

CI: Confidence interval; SD; Standard deviation

The results of the study showed that mean intensity and duration of pain before intervention were decreased after intervention In comparison with other studies, the study done by Selkowitz et al. revealed that one hour patient education in one session in cases undergoing microdiscectomy causes increased awareness resulting in decreased pain.[12]

However, in our study, patient education three times a week (each time half an hour) was conducted during which educational pamphlet was distributed among the patients. In another study, 101 patients with chronic back pain were chosen for a 12 weeks yoga training course. For waist function, 24 digits Ronald scale and 11 digit pain intensity scales were used. Results showed that yoga was more effective than educational booklet on patients and in decreasing their chronic back pain.[13] Concerning pain management in patients with disc hernia, we used only one method but they used two therapeutic methods. We recommend that in future studies, effect of yoga on decreasing pain due to disc hernia should be considered. Another study showed that patient education caused patient satisfaction leading to 80% reduction in absenteeism.[14]

In our study practical patient education and proper body movement like getting up from bed side and lying down as well as controlling sneezing and coughing caused less pain and more satisfaction in second and third sessions. Schectman et al. showed that education causes change in behavior and reduced pain in the patients suffering from acute low back pain,[15] which is congruent with our study.

Another study by Cherkin et al. showed that in patients with low back pain both exercise and manual therapy on the spine had better results compared with educational booklet; however, the latter were more cost effective.[16] With regard to lower cost of patient education in our study, patients were more willing to benefit from it. In a study entitled "patient education, the base for neurophysiologic low back pain", intervention was given to the patient for a 4 weeks period and the patients were divided into two groups. One group received physiotherapy and the other only received education. In line with our study, no significant difference was observed between the two groups.[17] Another study by Saicheua et al. entitled "documents and findings in physical and cognitive alteration among patients with low back pain after patient education" showed that teaching physical activity has a great influence on pain relief resulting in improving physical function[18] which is congruent with our findings.

A study done by Bharpayma named "comparison of the effects of medical education method on decreasing functional instability of lumbar spine", showed that before the exercise there was no significant difference between two groups according to functional instability of lumbar vertebra. Before this exercises, there was also no significant difference between two groups based on functional instability of lumbar spine. Patients in both groups after the exercises showed significant improvement in symptoms of functional instability of lumbar spine. In addition, there was no significant difference after the workouts in patients. The results showed that both methods could decrease pain and other signs and both methods have similar effect on clinical manifestation of functional instability in lumbar spine.[19]

With flexion of the foot and physical activity in these patients, pain severity increases. Even coughing and sneezing increase the pain. Brunner et al. believed some activities increase intra cranial pressure (like bending, getting up from a lying position, tensions due to sneeze, and coughing) which in turn increases the level of pain. This pain causes vertebral and postural deformity in body which was in line with our study.[6] The results showed that after disc herniation, patients had paresthesia resulting in movement disorders due to changes in natural body mechanics because of pain. Sometimes we may face deformities in body posture and movements. Other signs and symptoms involved muscle atony, changes in tendon reflexes, and loss of sensation. Other

accompanying signs and symptoms include loss of muscle tone, alteration in tendon reflex and parasthesia.[20] The result of our study confirms this finding.

Risk factors include low back pain, lifting of heavy objects, torsion of the waist, and continuous and severe body movement and obesity. However, we may find patients suffering from low back pain without aforementioned risk factors.[21,22] In a study in 2001 in Thailand, 78.4% of patients had disc herniation in the vertebral column, most of them were 26 to 35 years of age. Most risk factors in these patients had a history of prolonged heavy weight lifting.[23] This is analogous to our study in which most of the patients with low back pain were male candidates.

With regard to the above mentioned studies, patient education could be considered as a pain management approach and in case of combining with other therapeutic methods could even be more effective; hence our patients used medication in the time of intervention. In order to decrease the amount of error, each patient was considered as its own control and every patient used the same medication during the intervention period.

Conflict of Interests

Authors have no conflict of interests.

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Chronic Diseases Journal

Treatment of Behcet's disease

Fereydoun Davatchi[1], Nasrin Moghimi[2], Mohammad Mousavi[3], Alimohammad Fatemi[4]

1 Professor, Division of Rheumatology, Shariati Hospital AND Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
2 Assistant Professor, Department of Rheumatology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj AND Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
3 Assistant Professor, Department of Rheumatology, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord AND Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
4 Assistant Professor, Department of Rheumatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan AND Behcet's Unit, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Review Article

Abstract

Behcet's disease is a systemic disease classified among vasculitides. Major manifestations are mucous membrane lesions (oral aphthosis and genital aphthosis), skin manifestations (pseudofolliculitis, erythema nodosum), ocular manifestations (uveitis, retinal vasculitis), joint manifestations, vascular lesions (small to large vessel thrombosis, aneurysm), gastrointestinal manifestations, orchiepididymitis, and some rare manifestations like cardiac, pulmonary, and renal impairment. Diagnosis is mainly clinical. The International Diagnosis Criteria for Behcet's Disease may be of help. The gold standard of treatment for mucocutaneous lesions is colchicine. In refractory cases, levamisole, thalidomide, and dapsone may be of help. For major organ involvement like the eyes and the brain, immunosuppressive drugs and prednisolone are the gold standard. In refractory cases, biological agents are the last resort. For gastrointestinal manifestations, sulfasalazine and prednisolone are the first-line treatment. For vascular involvement, the first line treatment was anticoagulation, but recently it was shown that immunosuppressive drugs and prednisolone were confirmed to be the best. In all refractory cases and for all different organs, the last resort is biological agents.

KEYWORDS: Behcet's Disease, Treatment, Manifestation, Diagnosis

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Introduction

Behcet's disease (BD) is a multisystemic disease classified among vasculitides.[1-3] The main pathologic feature is leukocytoclastic vasculitis. The disease is mainly seen along the historical Silk Road, but can be seen nowadays all over the world with a prevalence going from 0.64 (Yorkshire) to 300 (Turkey) per 100,000 inhabitants.[4-11] The prevalence in Iran was estimated from 16 to 80 patients per 100,000 inhabitants.[12-14]

The men to women ratios are from 0.38 in the US[15] and 0.63 to 1.00 in Korea[16] to 3.40 in Saudi Arabia[17] and 1.00 to 4.90 in Kuwait.[18]

BD is a disease of the youth but can be seen at any age.[3,10] The mean age goes from 40 years (Brazil) to 20.8 years (Ireland), but the majority of countries are between 25 and 30 years. In Iran, the mean age is 26 years with a standard deviation of 11.3. At the onset of the disease, the youngest was 1 year old and the oldest 70 years.[19]

Corresponding Author:
Fereydoun Davatchi
Email: fddh@davatchi.net

Clinical manifestations of the BD are dominated by mucous-membrane manifestations [oral aphthosis (OA), genital aphthosis (GA)], skin manifestations [pseudofolliculitis (PF), erythema nodosum (EN), skin aphthosis], and ocular manifestations [anterior uveitis (AU), posterior uveitis (PU), retinal vasculitis (RV)]. In Iran, OA was seen in 97.3% of patients with 95% confidence interval (95%CI) of 96.9-97.7%. GA was seen in 64.6% (95%CI: 63.4-64.7), PF in 54.5% (95%CI: 53.3-55.7), skin manifestations in 64.9% (95%CI: 63.7-66.1), ocular manifestations in 56.8% (95%CI: 55.6-58), EN in 22.5% (95%CI: 21.5-23.5), skin aphthosis in 7% (95%CI: 6.4-7.6), AU in 41.2% (95%CI:40-42.4), joint manifestations in 37.4% (95%CI: 36.2-38.6), cataract in 19.6% (95%CI: 18.6-20.6), mono-arthritis in 7.6% (95%CI: 7-8.2), PU in 44.9% (95%CI: 43.7-46.1), RV in 32.1% (95%CI: 31-33.2), arthralgia in 17.2% (95%CI: 16.3-18.1), oligo-arthritis in 16.8% (95%CI: 15.9-17.7), ankylosing spondylitis in 2% (95%CI: 1.7-2.3), neurological manifestations in 3.7% (95%CI: 3.2-4.2), peripheral lesions in 0.3% (95%CI: 0.2-0.4), central manifestations in 3.5% (95%CI: 3.1-3.9), isolated headache in 7.9% (95%CI: 7.2-8.6), gastrointestinal manifestations in 7.4% (95%CI: 6.8-8), gastroduodenitis in 2.4% (95%CI: 2-2.8), peptic ulcer in 1.3% (95%CI: 1-1.6), chronic diarrhea in 2.2% (95%CI: 1.8-2.6), rectorrhagia in 1% (95%CI: 0.8-1.2), abdominal pain and nausea in 1.9 (95%CI: 1.6-2.2), vascular involvement in 8.3% (95%CI: 7.6-9), phlebitis in 5.7% (95%CI: 5.1-6.3), large vessel involvement in 1.7% (95%CI: 1.4-2), superficial phlebitis in 2.2% (95%CI: 1.8-2.6), cardiac manifestations in 0.6% (95%CI: 0.4-0.8), pulmonary manifestations in 0.9% (95%CI: 0.7-1.1), and epididymitis in 4.7% (95%CI: 4.2-5.2).[19]

Laboratory findings in Iran[19] were as: normal erythrocyte sedimentation rate (ESR < 20) in 46.5% (95%CI: 45.3-47.7), ESR between 20 and 50 in 32.6% (95%CI: 31.5-33.8), ESR between 51 and 100 in 13.8% (95%CI: 13-14.6), and ESR superior to 100 in 1.3% (95%CI: 1-1.6). Abnormal urine sediment was seen in 12.2% (95%CI: 11.4-13.0) of patients. Proteinuria was detected in 2.2% (95%CI: 1.8-2.6), cast in 0.2% (95%CI: 0.1-0.3), and hematuria in 6.3% (95%CI: 5.7-6.9). Like most of BD symptoms, abnormal urine sediments were transient. Renal biopsy was done in 18 patients for persistent proteinuria (WHO type II: 3 cases, type III: 7 cases, type IV: 5 cases, type V: 2 cases, and amyloidosis: 2 cases). Pathergy test was positive in 52.5% of patients (95%CI: 51.3-53.7). HLA-B5 was checked in 6261 patients and was positive in 53.3% of them (95%CI: 52.1-52.1). HLA-B51 was checked in 1534 patients, it was detected in 47.9% of them (95%CI: 45.2-50.4). HLA-B27 was checked in 5933 patients, it was detected in 8.6% of them (95%CI: 7.9-9.3).

Disease Classification: 98.3% of the patients in Iran were classified by the International Criteria for Behcet's Disease.[19] Looking at previous criteria for Behcet's disease, the rate of classification (sensitivity) was 97.2% with the Iran Classification Tree, 86.3% with the Korean criteria, 86.1% with the Japanese revised criteria, 81.0% with Dilsen revised criteria, and 78.0% with the International Study Group (ISG) criteria.[19]

BD progresses by repeated cycles of attacks and remissions. After the attack, the healing process starts and lasts for several days to several months. Then the remission occurs. However, it is not a definitive remission. A new attack will occurs after several days of remission to several months, or even years, and everything starts all over again. For short attacks, the healing is complete and the tissue or the involved organ returns to its pre-attack state without any sequel. If the healing process takes long, sequels may appear. Longer the healing process, more chance to get sequels. Sometimes, before the healing process completes, a new attack occurs, aggravating the precedent attack. This is what usually happens with ocular lesions, where from one attack to another, lesions accumulate and progress toward severe loss of vision or blindness. In the past, the majority of BD patients with ocular lesions became blind in few years. Benezra and Cohen said in the past that after 10 years 74% of ocular

involvement of BD lead to the loss of useful vision, no matter what treatment was used.[20] However, this is no more the case.[21]

Treatment

The aim of the treatment in BD is to accelerate the healing process and to prevent from sequels. If possible, it has to maintain the remission by preventing from new attacks. There are two categories of lesions.

The first category comprises those manifestations that produce some burden without serious complications (e.g. mucocutaneous or many types of joint manifestations). These lesions do not require aggressive treatment, because complete healing is not indispensable and usually a shorter healing time with longer remission period will suffice. Not all patients in this group need treatment, especially those with very mild manifestations of short duration and long remission. In this group, colchicine is the first line, followed by levamisole, thalidomide, dapson, and non-steroidal anti-inflammatory drugs (NSAID) are the mainstay.

The second group of lesions comprises those producing major morbidities. Among them are ocular lesions, as seen before, neurological manifestations, major vascular lesions (large vessel thrombosis, aneurysm), and the rare cardiopulmonary lesions. This group needs aggressive and early treatment. For them, immunosuppressive drugs, whether in mono therapy or combination therapy, associated to corticosteroids, is the first line treatment. In resistant cases biologic agents will be of help.

Both groups may benefit of symptomatic or local treatments.

Colchicine

Colchicine is the first line treatment for mucocutaneous lesions of BD. It was first used in 1977 by Mizushima[22] and Haim and Friedman-Birnbaum.[23] Its efficacy raised some polemics, especially after the surveys of Aktulga et al.[24] and Yurdakul et al.[25] despite several case reports attesting its efficacy.[26-31] A double blind control study of colchicine versus placebo, by Davatchi et al. showed its efficacy for mucocutaneous lesions and mild forms of joint involvement.[32] The starting dose is 1 mg daily, taken at night. In some resistant cases it may be raised to 1.5 to 2 mg daily. Side effects are rare, mainly in the form of diarrhea especially in those taking more than 1 mg daily. In very rare cases, abnormality of liver function tests (LFT) as elevation of hepatic enzymes can be seen, necessitating the discontinuation of colchicine if the abnormal LFT persists. However, in the study of Davatchi et al., side effects were the same in the colchicine and the placebo group, with no statistically significant difference between them.[32]

Colchicine has to be continued for longtime. Its discontinuation will result in the return of attacks to their original state (rate of recurrence and duration).

Levamisole

It is an immunomodulatory drug first used by Hamza and Ben in Tunisia.[33] It was followed by de Merieux et al.[34] who used it in 11 patients. More reports came later by Hamza et al.,[35] and Davatchi et al.[36] The indication is like colchicine, but for patients not responding to it.[37] Side effect is classically agranulocytosis. Therefore, regular CBC has to be done to discover it. We never observe it.[36] The same was for de Merieux et al.[34] The classic dose is 150 mg daily, 3 consecutive days per week. Upon good results, the dose may be decreased to two or one day per week.

Levamisole was rather forgotten in the past decades; but a new report from Sun et al. opened new insight into the mechanism of the drug and its benefits in concomitant use with colchicine. They observed a significant decrease of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) in 64 patients with mucocutaneous lesions.[38]

Thalidomide

It is an experimental drug used in resistant cases of BD.[1] It is not for daily or routine use.[2] It was used for all kinds of manifestations.[39] The main indication is mucocutaneous manifestations

resistant to other treatments.[40] The treatment starts with 200 mg daily. As soon as possible, upon the remission of symptoms, the dose is decreased to 100 mg daily, and if possible to 50 mg as the maintenance dose.[39] The safe dose, without side effects, would be 50 mg taken at night, 3 nights per week.[40] Side effects are mainly peripheral neuropathy and drowsiness. In difficult cases, the classical dose still can be used monitoring closely the neuropsychological manifestations.[41] Later, a double-blind, controlled study demonstrated the effectiveness of thalidomide in the treatment of mucocutaneous lesions of BD.[42] Sayarlioglu et al. used it successfully in a case of intestinal perforation not responding to Immunosuppressive drugs.[43] Thalidomide has been lately shown to be not only an anti-inflammatory drug, but also an immunoregulatory drug by decreasing the TNF-α receptor levels, cluster of differentiation 8 (CD8)/CD11b+ and CD16/CD56+ cells. On the other hand CD4+CD45RO+ T cells and gammadelta+ T cells increased after treatment.[44]

Dapson

It is an anti-leprotics agent used in resistant cases of mucocutaneous lesions successfully.[45] Not all authors agree with its efficacy in all resistant cases.[46] It is used as 50-100 mg daily. Side effects are hemolysis, liver toxicity, and hypersensitivity syndrome. It has recently been successfully used by Joshi and Mamta in pyoderma gangrenosum.[47]

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are mainly used for joint manifestations of BD.[2,37,48] As they are transient and follow the general scheme of attack and remission, and also as they go to remission without joint destruction (no sequels), no aggressive treatment is needed. NSAIDs have to be started at full dose and then tapered to a moderate dose until arthritis subsides. Usually, this will not take more than a few weeks. In case of resistant cases, especially in the rare chronic polyarthritis forms, disease-modifying antirheumatic drugs (DMARDs) will be necessary. The best choice will be methotrexate with low dose prednisolone.

Another indication of NSAIDs is EN, with or without joint manifestations, starting with a high dose and then adjusting to the need.

For superficial phlebitis and mild forms of deep-vein thrombosis, DMARDs can be used, always starting with a high dose and then adjusting.

Local treatment

Steroids are indicated in different situations. For mild oral aphthosis with few attacks per year (less than one attack per month), systemic medication is not necessary. Triamcinolone in Orabase, an ointment that stick to the mucosa, is indicated if an aphthous lesion is too painful. It is to used in local application up to 4 times a day. For resistant genital aphthosis, local (in situ) injection of triamcinolone acetonide may help, but is not always efficient.[2,37]

Benzoyl peroxide is an antiseptic used locally for genital aphthosis to accelerate the healing process.

Immunosuppressive and immunomodulatory drugs

They are used for lesions of high morbidity like ocular, central nervous system (CNS), vascular, gastrointestinal, and all other resistant manifestations of the disease. The main products used in BD are cyclophosphamide, chlorambucil, azathioprine, methotrexate, and cyclosporine. They are all to be used in association with prednisolone.

In the past, cyclophosphamide for BD was used as oral tablets with the dose of 2-3 mg/kg daily. It was used in combination with prednisolone.[49] The results in ocular manifestations were very interesting.[48] It is now used in pulse therapy.[50-56] Pulse cyclophosphamide (PCP) dose is usually 750 mg per square meter of body surface (around 1000 mg), in perfusion, once monthly. It is combined with daily prednisolone (0.5 mg/kg). Once a good response is obtained, prednisolone is gradually tapered to the minimum dose maintaining the good result. After 6 monthly doses, pulses are given as bimonthly, then once every 3 months, and finally as needed (pro re nata or PRN). PCP is an effective treatment.

Good results are not due to the combined steroids but to PCP itself, as shown in a double blind control study of PCP versus placebo, receiving both equal doses of prednisolone.[57] Results are interesting.[58,59]

Chlorambucil was one of the first cytotoxic drugs to be used for the treatment of ophthalmologic manifestations of BD.[60] It is used as 0.2 to 0.3 mg/kg body weight. Prednisolone is associated as 0.5 mg/kg body weight daily. Upon obtaining good results, prednisolone is tapered gradually. In a longitudinal study on 89 patients with a mean follow-up duration of 26.2 ± 2.6 months, all parameters of the eyes [mean VA, inflammatory index of the AU, PU, RV, and the total adjusted disease activity index (TADAI)] improved significantly.[61]

Azathioprine (AZA) was used early in the treatment of BD.[62,63] Results were not satisfactory because used at low dose (2 mg/kg daily).[64] A controlled study in 1990 showed its effectiveness in BD.[65] A more recent work, on 2000, showed its efficacy in ocular lesions of BD, in 32 patients. The result of the disease activity index of AU, PU, the TADAI, and the mean VA improved significantly, but not the mean retinal vasculitis.[66] A recent work from 2010 showed also good response with azathioprine, but less in those having retinal vasculitis.[67]

Methotrexate (MTX) was first used in ocular manifestations of BD at a low dose of 7.5 mg weekly in the 1990[68] and 1998.[69] Higher dose (15 mg weekly) at the beginning of the treatment were used later, in 2003.[70] In resistant cases, doses up to 25 mg weekly may be used. It is mainly indicated in PU (mainly particularly posterior uveitis) . It is less efficient in RV. A longitudinal study of 15 years follow-up on 597 patients with BD (4462 eyes in the years of follow-up) showed an improvement of 47% of VA, an improvement of 89% of PU, and an improvement of 55% of RV.[71] MTX can be used for other manifestations of BD, mainly for mucocutaneous and joint manifestations when resistant to other treatments.

Cyclosporine A is an immunomodulator acting principally on interleukin-2 (IL-2). It is highly effective in transplanting organs and in many autoimmune diseases.[1,2] Its efficacy was demonstrated in BD.[72,73] New formulation in microemulsion, as we use today, was tested in ocular lesions with good results, where the ocular attacks decreased in 78.6% of patients.[74] Cyclosporine was used in pyoderma gangrenosum of BD[74] and found, in 2003, to be very effective in unresponsive to other treatments.[75] These results were later confirmed in 2008.[76] It was also used in recurrent cutaneous polyarthritis nodosa-like lesions.[77] However, the main indication is ocular lesions, especially uveitis.[78-82] The mechanism of action has been broadened in BD. It has been shown , in BD uveitis that when combined to prednisolone, it down-regulates the natural killer cell-like effector functions of CD8brightCD56+ T cells.[78] Importantly, the production of interleukin-17, which plays an important role in all autoimmune diseases, is inhibited by cyclosporine A.[82] Cyclosporine is used as 5 mg/kg by oral route. As soon as a therapeutic response is obtained, the drug must be reduced to the minimum dose that keeps the patient in remission. Side effects are important; especially nephrotoxicity that leads to renal insufficiency.[83] The use of cyclosporine in BD is associated with the occurrence of neurological manifestations, which appear as a complication of the treatment and necessitate the interruption of cyclosporine therapy.[81-85]

All immunosuppressive drugs are efficient in major organ involvements of BD, mainly ocular manifestations.[21,58,59,79,86-90] A study comparing the efficacy of all immunosuppressive drugs among 1494 patients with ocular manifestations of BD (posterior uveitis and/or retinal vasculitis) followed the patients longitudinally for up to 15 years (7685 eyes-years of treatment). It showed that there was no statistically significant difference between their efficacies on visual acuity. However, combination therapy of PCP (1 g monthly) + azathioprine (2-3 mg/kg daily) + prednisolone (0.5 mg/kg daily) was more effective on retinal vasculitis than the others.

Methotrexate, on the other hand, was mainly effective on uveitis, and had the least efficacy on retinal vasculitis.[89]

Biological Agents

Interferon alpha (INF-α-2a and INF-α-2b) was the first biological agent used for BD in 1986 by Tsambaos et al.[91] It was first used in milder forms of the disease (mucocutaneous and articular manifestations) but the real indication is ocular manifestations. Kotter et al. used INF in high doses of 9 million international units (IU) daily. However, lower doses of 3 million IU three times a week have also used, but with fewer efficacies. Kotter et al. recommended to start the treatment with 6-9 million IU per day (subcutaneous injections) and to reduce the dose to 4.5 million IU daily after 4 weeks. After another 4 weeks, they recommended to reduce the dose to 3 million per day. The maintenance dose after complete remission will be 3 million IU three times per week. It is recommended to continue INF at least for 8 weeks after complete remission.[92]

Side effects are numerous, mainly a flu-like syndrome necessitating the use of NSAIDs to overcome the reaction. The local reaction on the site of injection is very frequent and varies from a rash to pyoderma gangrenosum (although the latter is of exception). A case of pathergy has also been reported on the site of injection.[93]

Results on eye lesions (from different reports) seem very good. Kotter et al. evaluated the highest number of patients (50 patients) and reported the response rate as 92%. The mean visual acuity rose from 0.46 to 0.81 after 6 months.[94] In 2006, INF was used for refractory cystoid macular edema with good results in 11 out of the 15 eyes.[95] In a study in 2008, only 71.9% of the eyes responded.[96] While, in another study in the same year, the improvement was 88% of the eyes[97] (very close to the rate reported by Kotter et al.[94]). Findings on mucocutaneous and articular manifestations are less impressive and less complete.[98,99] Many recurrences are seen during the treatment, Kotter et al. concluded that INF should be reserved for more serious lesions of the disease like ocular lesions.[94]

Anti TNF-α has recently been used in BD. There are sparse reports on few cases.

Etanercept is a soluble receptor intercepting circulating TNF-α before it reaches its receptors on the cell surface. Only a double-blind, controlled study by Melikoglu et al. in Turkey has assessed the efficacy of etanercept on mucocutaneous lesions. Patients received 25 mg injections twice weekly for 3 months. There was a statistically significant reduction in mucocutaneous and articular attacks during the therapy. It is important to note that not all lesions responded to the treatment and after discontinuation, there was an exacerbation of attacks.[100] The latter will largely limit the use of etanercept in treatment of BD as the disease is chronic and lasting for several decades. Melikoglu et al. also tested etanercept for ocular lesions in an open study on 10 cases. Patients were already receiving already azathioprine, cyclosporine, and prednisolone. All medications continued with the adjunction of etanercept, except cyclosporine. The results were not satisfactory after 9 months of treatment since there was no statistically significant improvement of visual acuity (mean before 0.34, mean after 0.54).[101]

Infliximab is a monoclonal antibody for TNF-α. It was used by Sablé-Fourtassou et al. in 2002. They used it in a dosage of 5 mg/kg by infusion. It was given on the classic schedule of week 1, 2, 6, 14, and then, after every 8 weeks. They used it in 3 patients for duration of 5 to 9 months and reported an excellent result. Visual acuity improved significantly reaching almost the normal value in nearly all patients. The patients were on INF before getting infliximab. They were obliged to stop it because of side effects or inefficacy.[102] Sfikakis et al. presented the effects of short-term use of infliximab on uveitis in 5 patients. The treatment response was dramatic.[103] Many case reports have clarified the effects of infliximab in few patients. There are 11 reports on 10 cases or more,[104-114] all on ocular manifestations except one.[111] Among them, only 2 reports are on more than 20 cases.[106,113] Infliximab is also effective in the treatment of other manifestations, and among them, intractable

gastrointestinal manifestations.[115-117] Arida et al. reviewed 88 articles on a total of 325 cases treated with infliximab. They reported the improvement of oral ulcers 91%, genital ulcers 96%, skin lesions 77%, erythema nodosum 81%, ocular lesions 89%, gastrointestinal manifestations 91%, neurological manifestations (central) 90%, joint manifestations 94%, and thrombophlebitis 70%.[117]

Adalimumab is a humanized anti-TNF-α monoclonal antibody. Arida et al. could find 13 articles on adalimumab (on a total of 28 patients). The results of improvement were 73% in oral ulcers, 86% in genital ulcers, 80% in skin lesions, 100% in erythema nodosum, 100% in ocular lesions, 100% in gastrointestinal manifestations, 100% in neurological manifestations (central), and 60% in joint manifestations.[117] The same authors also reviewed 12 articles on etanercept (totally on 37 patients) and reported improvements in 82% of oral ulcers, 71% of genital ulcers, 67% of skin lesions, 100% of erythema nodosum, 60% of ocular lesions,100% of neurological manifestations (central), and 100% of joint manifestations.

Rituximab is an anti-CD20 antibody which depletes B-lymphocytes.[118,119] It was used in connective tissue diseases and vasculitides, but not in BD. Recently it was used for intractable eye lesions of BD in one case with good results.[120] A randomized controlled study of patients with intractable retinal vasculitis with cystoid macular edema resistant to immunosuppressive drugs compared rituximab (10 cases) with combination therapy of PCP and azathioprine (10 cases). Patients on rituximab improved while patients on immunosuppressive combination therapy did not.[121]

As suggested by the above-mentioned experiences, etanercept may be partially effective in mucocutaneous lesions of BD but not much effective in ocular manifestations. Infliximab was effective in short- and mid-term studies of ocular manifestations (maximum 3 years of follow-up in prospective studies). However, all the presented experiences are on few cases and practically short-term treatment. Since attacks of ocular lesions in BD continue for many years, it is important to have a controlled study on a large number of patients lasting for several years to judge the real efficacy of infliximab (as has been performed in case of immunosuppressive drugs). For now, the best indication of anti-TNF therapy will be the control of intractable ocular attacks, mainly the retinal vasculitis. Adalimumab was effective in the few studied cases, but only on short-term therapy. None of the previous studies were a randomized, controlled trial comparing the drug with a gold standard. The only study of this kind was with rituximab.

How to treat patients in the daily practice

It is important to keep in mind that: 1. BD progresses by repeated cycles of attack and remission, 2. not all patients with BD need treatment, and 3. not all of those needing treatment require aggressive treatment.[1,2,37] The aim of the treatment is to: 1. accelerate the healing process, 2. prevent from sequels, and 3. prolong or maintain remission.[122] BD lesions are of two kinds: 1. Those producing some burden, like the majority of mucocutaneous lesions, joint manifestations, and some vascular manifestations like superficial phlebitis. For these lesions, complete healing is not indispensable. Faster healing, shorter healing time, fewer attacks, and longer remissions are sufficient. 2. Those producing high morbidity, like ocular manifestations, neurological manifestations, and the majority of vascular lesions especially large vein thrombosis and arterial aneurysm, and many of gastrointestinal manifestations.[3,19,123] For these lesions, quick and complete healing along with is mandatory; otherwise sequels will appear. Apart quick and complete healing, long or definitive remission to prevent sequels are necessary. In case of slow healing process and frequent attacks, lesions accumulate from one attack will persist until the next and lead to another, leading to sever impairment of the involved organ. A good

example is eye lesions that progress toward sever loss of vision or blindness in few years.[1]

For lesions producing some burden, the first line of treatment is colchicine (1 mg at bedtime). In case of resistance or side effects, the treatment is changed to levamisole. In resistant cases, combination of both is of help. MTX or AZA with low dose prednisolone, or thalidomide or dapson will be other choices when higher resistance is observed. For patients having 3 or 4 attacks of oral aphthosis per year, there is no need for systemic treatment. Local treatment, in case of an abnormally painful attack, will usually suffice. The best local treatment (particularly Orabase) will be adequate for abnormally painful attacks. Pimecrolimusis triamcinolone in Orabase, which is an ointment can be used in adheres to the oral mucosa. Pimecrolimus ointment can be used in case of isolated genital aphthosis or long duration aphthous ulcer.[124] Intralesional injection of triamcinolone acetonide may also be used for intractable genital aphthosis.

For articular manifestations, NSAIDs for few to several weeks are usually sufficient. If not, MTX at low dose (7.5 mg weekly) + low dose prednisolone is the best choice. However, other choices can be used like levamisole, AZA, or cyclosporine A.

For the second type of lesions, those with high morbidity, immunosuppressive drugs are mandatory for lesions with high morbidity. A short course of moderate-dose (20-30 mg/day) prednisolone should suffice a single for eye lesion (i.e. lesions, if the patient has only uveitis, and if uveitis is an isolated anterior uveitis). Usually prednisolone at moderate doses of 20 to 30 mg per day is largely sufficient. A short course of few weeks will suffice.

However, isolated anterior uveitis is rare in BD. Usually the patients have a panuveitis or posterior uveitis alone. In these cases, the first line immunosuppressive drug will be MTX at 15 mg weekly, with prednisolone 0.5 mg/kg daily in divided doses. After controlling the inflammation, the dose of prednisolone will be tapered gradually, every month to every 3 months, to arrive to a maintenance dose of 7.5 mg weekly. It is wise to continue at this dose for several months before deciding to further taper and eventually stop the medicine. If the inflammation does not recur, MTX can be gradually tapered (by steps of 3 t0 4 months) until it is stopped. At each level of tapering of the drugs, if the inflammation recurs, and depending on its importance, one or several steps are taken back.

If at the beginning of the treatment the eye does not respond, an escalation of drug is initiated as: increase of weekly dose of MTX will increase up to 25 mg, change of MTX will be replaced with AZA, change to combination therapy with PCP + AZA + prednisolone will be prescribed. Inefficacy of all these methods will necessitate the substitution of immunosuppressive + AZA + prednisolone as described before. If still no benefit, change of immunosuppressive strategy with to biological agents.

If eye lesions are retinal vasculitis, with or without posterior uveitis, the first line of treatment will be combination therapy with PCP + AZA + prednisolone (0.5 mg/kg daily). After controlling the inflammation, prednisolone dose will be tapered gradually, every month to every 3 months, to arrive to a maintenance dose of 7.5 mg daily. If the inflammation does not recur after 6 PCP, the rhythm of once monthly pulse is decreased to once every two months and then to once every 3 months. If still in remission, PCP will be stopped after 3 to 4 PCP, and the patient will continue on AZA alone. After several months at this regimen, the tapering will start again with prednisolone, exactly as for uveitis alone, and then with AZA.

At any step, if the inflammation recurs, the treatment will get one to several steps depending on the importance of the new attack. If the combination does not work, AZA can be changed to MTX or to cyclosporine A. If still no improvement, biological agents have to start, if the patient can afford it.

For neurological manifestations, the same treatment scheme as for retinal vasculitis is used,

except prednisolone is to be given as 1 mg/kg daily. In case of treatment escalation and change of immunosuppressive drugs, cyclosporine is to be avoided, because of its neurological side effects.

For vascular involvement, the classic strategy was the prescription of anticoagulants. However, new experiences and papers are more and more in favor of immunosuppressive drugs + prednisolone for these cases. Depending on the site and the form of the lesion, anticoagulation may be given, but not for longtime as in the past.[125-129] Ahn et al. demonstrated that adding anticoagulants did not improve the results obtained by immunosuppressive drugs + prednisolone in deep vein thrombosis.[126] However, for superficial vein thrombosis and some restricted and mild forms of deep vein thrombosis, NSAIDs may be enough. In such cases, trying NSAIDs before opting for the aggressive treatment will be beneficial.

For gastrointestinal manifestations, the first treatment to try is sulfasalazine (2 g daily) + prednisolone in low to moderate doses. If not sufficient, immunosuppressive drugs are necessary. In case of resistance to the treatment, biological agents are the last resort.

Conflict of Interests

Authors have no conflict of interests.

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