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From the Editor

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This is our third issue of Middle-East Journal of Internal Medicine and it is rich with papers from all over the region. I would like to congratulate Dr Al Hasan from Jordan for his study. Dr Al Hasan examined the use of anticoagulation in 1500 patients with atrial fibrillation. His findings illustrate the need for more education to patients and to physicians as well. Dr AL-Youzbaki examined the effect of Depot-medroxyprogesterone (DMPA) injections on the total antioxidant status of patients vs. controls. The study reported persistent increase in the antioxidant status of patients on DMPA as compared to the control group.

In addressing chronic illnesses, the quality of life (QoL) issues need to be examined in patients with chronic medical illness. Dr Yousif from Baghdad conducted health questionnaire interviews on more than 1800 patients with diabetes. His study noted the significant reductions in the scores of all QoL items except vitality, in patients with diabetes. A few of these reductions were related to HbA1c levels. Further studies addressing chronic illnesses in the Middle East are obviously needed.

Dr Muneizel performed a randomized controlled clinical trial comparing the efficacy and side effects of tinidazole compared with metronidazole in the treatment of amoebiasis. The study was well conducted and tinidazole was noted to be more effective than metronidazole in treating patients with amoebiasis. Tinidazole produced fewer and milder side effects when compared with metronidazole.

Dr Rahman conducted a micro-survey study of 170 patients with arsenicosis in Chapai Nawabganj, Bangladesh. Alarming figures were noted as 40 % of patients were housewives who are handling the arsenic contaminated water. Contaminated tube wells were implicated as the cause for the high rates of arsenicosis noted in specific districts from Bangladesh.

Finally, we received two articles from North America. In a review article, Drs Muzaffar and Al Alkahtani discuss the various aspects of thyroid tuberculosis. Dr Shaheen reports a rare case of pulmonary mycobacterium kansasii coinfection in cardiac transplant recipients with invasive pulmonary aspergillosis.

Prevalence of Oral Anticoagulant Use in Patients with Atrial Fibrillation eligible for Anticoagulation at Prince Hashim Military Hospital

ABSTRACT

Objectives: To determine the prevalence of oral anticoagulant use in patients with atrial fibrillation who are eligible for anticoagulation presenting to the medical clinic at Prince Hashim Military Hospital.

Methods: This is a retrospective study that was conducted at Prince Hashim Military Hospital in Zarka during the period from first of January 2006 till first of January 2007. Patients presenting to the medical clinic who were diagnosed to have atrial fibrillation and were eligible for anticoagulation were included. Atrial fibrillation patients with contraindications to anticoagulation were excluded. Medical records were reviewed and information was abstracted. Percentages of AF patients prescribed Salicylates, Warfarin, & antiplatelets were determined. Percentages of therapeutic ,subtherapeutic ,and supratherapeutic International Normalized Ratios were concluded.

Results: A total of one thousand and five hundred patients coming to the Internal Medicine clinic at Prince Hashim Military Hospital met the inclusion criteria of the study. The mean age of patients was seventy two years. The male to female ratio was 3:2. Seven hundred patients (47%) were on Salicylates, six hundred patients (40%) were on warfarin, one hundred patients (6.5%) were prescribed Salicylates & antiplatellets (dihydropyridamole), and one hundred patients (6.5%) were not prescribed any anti thrombotic therapy. The most common indication for anticoagulation in patients on warfarin was age more than 65 years. Only fifty two percent of the patients on Warfarin had their international normalized ratio within the therapeutic range.

Conclusion: Atrial fibrillation anticoagulation is mandatory once indicated. To be efficient the warfarin dose should be adjusted to have an international normalized ratio within the therapeutic range. Anticoagulation clinics are suggested to improve the percentage of atrial fibrillation patients who are well anticoagulated.

Key words: Atrial fibrillation, Anticoagulation, Cerebrovascular accidents, warfarin, international normalized ratio.

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Introduction

Atrial fibrillation (AF) is a growing public health problem affecting approximately 1% of the general population and associated with significant morbidity and mortality.1 Patients with AF have an increased risk of embolic stroke; those with non-valvular AF have at least a 5-fold increased risk, and those with valvular AF have an estimated 17-fold increased risk[1,2].

AF becomes increasingly an important cause of stroke with advancing age. Other risk factors include previous stroke or transient ischemic attack (TIA), hypertension, diabetes mellitus, congestive heart failure, ischemic or rheumatic heart disease, prior thrombo-embolism and female gender. Patients with rheumatic heart disease, prosthetic heart valves, prior thromboembolism and persistent atrial thrombus detected by transoesophageal echocardiography (TOE) are considered to be at highest risk[3,4].

This study was conducted to determine the prevalence of oral anticoagulant (warfarin) use in patients with atrial fibrillation who are eligible for anticoagulation at Prince Hashim Military Hospital.

Methods

This is a retrospective study that was conducted during the period from first of January 2006 till first of January 2007 at Prince Hashim Military Hospital which is a tertiary hospital located in Zarka city, 30 kilometers to the east of Amman the capital of Jordan. Patients presenting to the medical clinic who were diagnosed to have atrial fibrillation and were eligible for anticoagulation were included. AF patients with contraindications to anticoagulation were

excluded. Indications for anticoagulation were defined in accordance to the recommendations published by the American Heart Association as the presence of any of the following variables in the medical record: Advanced age more than 65 years, previous stroke or transient ischemic attack (TIA), hypertension, diabetes mellitus, congestive heart failure. Contraindications to anticoagulation were defined as one the following present in the medical record: Any current gastrointestinal or genitourinary bleeding or any prior gastrointestinal or genitourinary hemorrhage requiring hospitalization, transfusion, surgery, or emergent endoscopy; the presence of liver disease as determined by documented history or clinical suspicion; any central nervous system hemorrhage, hemarthrosis, or bleeding complication requiring hospitalization; history of more than 3 falls in the preceding year; and patients with known ataxia or vertigo. Medical records were retrieved & reviewed, a specially designed abstract record form was used to obtain data regarding age, gender, use of salicylates, warfarin and antiplatelets, indications for anticoagulation and values of measured International Normalized Ratios (INRs) upon arrival to medical clinic for AF patients who were on Warfarin. Therapeutic ranges of INRs were defined in accordance with the fifth edition of the American College of Chest Physicians guidelines for antithrombotic therapy, for non-valvular AF an INR target range of 2.0-3.0 and for AF patients with mechanical valves an INR target range of 3.0 - 4.0. Percentages of AF patients prescribed salicylates, warfarin and antiplatelets were determined. Percentages of therapeutic ,sub-therapeutic ,and supratherapeutic INRs were concluded.

Results

A total of one thousand and five hundred patients coming to Internal Medicine clinic at Prince Hashim Military Hospital met the inclusion criteria of the study. The mean age of patients was seventy two years. The male to female ratio was 3:2. As seen in table (1), seven hundred patients (47%) were on salicylates alone, six hundred patients (40%) were on warfarin, one hundred patients (6.5%) were prescribed salicylates & antiplatelets (dihydropyridamole) and one hundred patients (6.5%) were not prescribed any anti-thrombotic therapy. As demonstrated in Table (2), indications for anticoagulation for patients on warfarin were as follows:

Age more than 65 years in five hundred and eighty patients (97%), hypertension in five hundred patients (83%), heart failure in three hundred patients (50%), diabetes mellitus in two hundred and forty patients (40%) and previous stroke or TIAs in eighty four patients (14%). As illustrated in Chart (1), fifty two percent of the patients on Warfarin (312) had their international normalized ratio within the therapeutic range, thirty one percent of patients on Warfarin (186) had their international normalized ratio in the sub-therapeutic range, and seventeen percent of patients on warfarin (102) had their international normalized ratio in the supra-theraputic range.

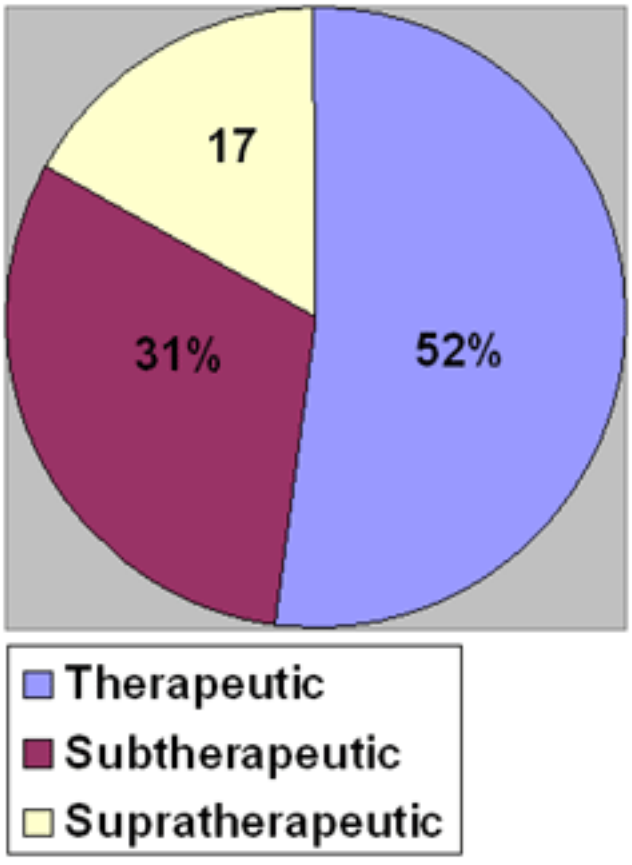
Table 1 Atrial Fibrillation patients eligible for anticoagulation according to anti thrombotic therapy.

Antithrombotic therapy	Number of Patients	Percentage
Salicylates	700	47
Oral anticoagulant (Warfarin)	600	40
Salicylates & Antiplatelets	100	6.5
No antithrombotic therapy	100	6.5

Table 2 Distribution of atrial fibrillation patients eligible for anticoagulation according indication of anticoagulation.

Indication for Anticoagulation	Percentage
Age more than 65 years	97
Hypertension	83
Heart failure	50
Diabetes Mellitus	40
Prior Stroke or TIA	14

Chart 1 Measured International Normalized Ratios for atrial fibrillation patients on oral anticoagulants according to the range.



Discussion

Warfarin is efficacious in preventing embolic stroke in patients with AF when INRs are maintained within a

narrow therapeutic range[5,6,7].

A review of the literature showed that only 15-44% of patients with AF without contraindications to warfarin actually receive the drug,[8] which is similar to our finding in this study. Philp A, et al found that 40% of AF patients eligible for anticoagulation used warfarin alone, 28% had antiplatelet therapy alone, 5% used both, 27% had no anti-thrombotic therapy identified.[9]

The mean age of AF patients in the study and the male to female ratio correlate with findings in literature that prevalence of AF is strongly dependent on age. AF is uncommon among individuals < 50 years old. Its frequency rises rapidly from the sixth decade onward, reaching a prevalence of nearly 10% in those > 80 years old.[1,7] AF is more prevalent in men than in women at all ages.[1,7,8,9]

Philp A, et al found that high-risk variables in the non-anticoagulated, warfarin-eligible population were age >65 years (83%); hypertension (70%); congestive heart failure (43%); diabetes mellitus (24%); and prior stroke or transient ischemic attack (14%).[9] These findings are similar to what was found in this study.

The inadequacy of anticoagulation reported in this study is less than that reported by Bungard TJ et al[10,11] and Cohen N et al[12,13] who found respectively that 44.5% and 42.3% of AF patients coming to hospital had sub-therapeutic INRs. A study of 30 long-term care facilities found AF patients to have sub-therapeutic INRs 44.8% of the time.[14] In addition, nearly one-third of all Medicare AF patients prescribed warfarin had an INR below 1.5,[15] This is likely an underestimation, however, as the investigators did not identify patients with INRs of 1.5-2.0.

Finally, an evaluation of a health maintenance organization found AF patients to have sub-therapeutic INRs on only 20% of the days assessed;[6,16] however, the evaluation was conducted at a site that recruited and followed patients for the Boston Area Anticoagulation Trial for Atrial Fibrillation. This study highlights the potential for achieving good anticoagulant control in a clinical setting that is enhanced by participation in clinical trials.

The percentage of Supra-therapeutic INRs in this study is similar to the findings in other studies. Bungard TJ et al[11] found 18.9% of AF patients in the supra-theraputic range while Cohen N et al[12] found 15.6% of AF patients in the supra-therapeutic range. The percentage of therapeutic INRs in this study were more than that reported by Bungard TJ et al[11] and Cohen N et al[12] (36.5% & 42% respectively).

Randomized, controlled trials of warfarin reported patients to be within the stated therapeutic range 64% (range of 44-83%) of the time.[8,13,16,17] Through coordinated, focused delivery of warfarin therapy, anticoagulation-management services report patients to be in the therapeutic range approximately 70% (range of 59-86%) of the time.[17,18] This superior level of anticoagulation translated into improved patient outcomes in terms of the avoidance of thromboembolic and hemorrhagic events, with cost savings to health care systems.[17,19] The superior outcomes that can be achieved through focused management strategies such as anticoagulation-management services suggest that there is much room for improvement in our population for preventing ischemic stroke.

This study has a few limitations. First, it is retrospective and therefore is limited by adequacy of documentation. Secondly, we assessed the adequacy of anticoagulation at only a single time.

Conclusion

Atrial fibrillation anticoagulation is mandatory once indicated. To be efficient, warfarin dose should be adjusted to have an international normalized ratio within the therapeutic range. Anticoagulation clinics are advised to improve the percentage of atrial fibrillation patients who are well anticoagulated in order to avoid the thromboembolic risks of this disease as well as bleeding risks associated with over anticoagulation.

References

1. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. Arch Intern Med 1995;155:469-73.
2. Go AS, Hylek EM, Phillips KA, et al . Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention; the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001; 285:2370-2375.
3. Scholten MF, Thornton AS, Mekel JM, et al. Anticoagulation in atrial fibrillation and flutter.Europace 2005 7(5):492-499; doi:10.1016/j.eupc.2005.05.012.
4. Kalra L, Lip GYH on behalf of the Guideline Development Group for the NICE clinical guideline for the management of atrial fibrillation. Antithrombotic treatment in atrial fibrillation. Heart 2007;93:39-44.
5. Gurwitz JH, Monette J, Rochon PA,et al. Atrial fibrillation and stroke prevention with warfarin in the long-term care setting. Arch Intern Med 1997;157:978-84.
6. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505-11.
7. Singer ED, Albers GW, Dalen JE,et al. Antithrombotic Therapy in Atrial Fibrillation. Chest. 2004;126:429S-456S.
8. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med. 1996; 335:540-6. doi:10.1503/cmaj.061523.
9. Scott PA, Panciol AM, Davis LA, et al. Prevalence of Atrial Fibrillation and Antithrombotic Prophylaxis in Emergency Department Patients. Stroke. 2002;33:2664
10. Oake N, Fergusson DA, Alraven AJ, et al. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. CMAJ. May 22, 2007; 176 (11). doi:10.1503/cmaj.061523.

11.# Bungard TJ, Ackman ML, Ho G, et al. Adequacy of Anticoagulation in Patients with Atrial Fibrillation Coming to a Hospital. Pharmacotherapy 2000:20(9):1060-1065.
12.Cohen N, Almoznino-Sarafian D, Alon I,et al.. Adequacy of anticoagulation in patients with atrial fibrillation: effect of various parameters. Clin Cardiol. 2001 May;24(5):355-7.
13.Go AS, Hylek EM, Borwsky LH, et al. Warfarin Use among Ambulatory Patients with Nonvalvular Atrial Fibrillation: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Annals Of Internal Medicine 1999;131: 927-934.
14.García-García J, Calleja-Puerta S, de la Vega-Cerezales V, et al.Adequacy of anticoagulant prevention in patients with atrial fibrillation. Rev Neurol. 2005 Oct 1-15;41(7):399-403.
15.# Walraven CV, Jennings A, Oake N, Forster AJ. Effect of Study Setting on Anticoagulation Control. Chest. 2006;129:1155-1166.
16.# Birman-Deych E, Radford MJ, Nilasena DS, et al .Use and Effectiveness of Warfarin in Medicare Beneficiaries With Atrial Fibrillation. Stroke. 2006; 37:1070 -1082.
17.Garcia D, Regan S, Crowther M, et al .Implications for Safer Anticoagulation in the Elderly Population Warfarin Maintenance Dosing Patterns in Clinical Practice. Chest. 2005;127:2049-2056.
18.Perez I, Melbourn A, Kalra L. Use of antithrombotic measures for stroke prevention in atrial fibrillation .Heart. 1999; 82:570 -574.
19.# Munschauer FE, Priore RL, Hens M, et al. Thromboembolism Prophylaxis in Chronic Atrial Fibrillation .Stroke. 1997; 28:72 -76.
20.Kalra L,Yu G, Perez I, et al. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness .BMJ. 2000; 320:1236 -1239.
21.Waldo AL, Richard C. Becker RC, Colgan KJ. Hospitalized Patients With Atrial Fibrillation and a High Risk of Stroke Are Not Being Provided With Adequate Anticoagulation .J Am Coll Cardiol, 2005; 46:1729-1736.
22.Gurwitz JH, Terry S. Field TS, Radford MJ, et al. The Safety of Warfarin Therapy in the Nursing Home Setting .The American Journal of Medicine.2007;120:539-544.
23.Reynolds MW, Fahrbach K, Hauch O, et al. Warfarin Anticoagulation and Outcomes in Patients With Atrial Fibrillation. Chest. 2004; 126:1938 -1945.

Evaluating Quality of Life and its Association with Glycaemic Control in Diabetes

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ABSTRACT

Background: Quality of life (QoL) is a multidimensional dynamic concept that has developed from the need to estimate the impact of diseases incorporating an individual's subjective perception of physical, emotional, and social well-being, including both a cognitive component (satisfaction) and an emotional component (happiness). Hemoglobin A1c (HbA1c) is used as a proxy measure of longterm glycemic control in all diabetic research. Although both QoL and HbA1c% are considered essential issues in diabetic management, the relationship between them is not well studied.

Objective: To evaluate QoL in Iraqi diabetic patients and find any association between HbA1c% and the items of QoL.

Methods: A cross-sectional design and a convenient sample of 1840 diabetic patients were recruited in this study for the period from the 1st January, 2006 to 31st December, 2007. Structured questionnaire (SF-36 instrument) was used to collect information from the patients about their QoL, then the results were compared according to their HbA1c% results.

Results: The results of this study revealed that there were significant reductions in the scores of all QoL items except vitality. There was a significant association between HbA1c% with only three (out of 8) items of QoL, these are Role Physical, Social Functioning, and Mental Health.

Conclusions: The study concluded that our diabetic patients had a significant reduction in QoL scores. Role Physical, Social Functioning, and Mental Health are significantly reduced with bad glycemic control.

Keywords: Diabetes, HbA1c, Quality of life (QoL)

Introduction

Diabetes mellitus (DM), the prevalence of which is reaching epidemic proportions in many parts of the world, is an increasingly important public health concern. It is estimated that worldwide in 2007, approximately 246 million people, or 5.9%, in the age group 20-79 have diabetes. Some 80% of these live in developing countries. In the United States, diabetes is present in 8% of the adult population, and is associated with a two-fold increase in age-adjusted mortality[1]. In Iraq, and according to the non-communicable diseases prevalence survey in 2006, the prevalence of DM reaches 10.4% for population 25-65 years of age[2]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels which impose further impact on the daily living of the patient[3].

Physicians have often used Quality of Life (QoL) to measure the effects of chronic illness in their patients to better understand how an illness interferes with a person's day-to-day life. Health-care professionals are becoming increasingly aware of the need to assess and monitor hemoglobin A1c (HbA1c) levels, which reflect diabetic control, and the QoL as an important outcome of diabetes care to help patients in improving their life quality[2,4]. QoL is an important outcome in its own right, but also because it may influence the patient's self-care activities, which may consequently impact on their diabetes control and management[5]. Past research has found, however, that as much as 54% of patient problems and 45% of patient concerns are neither elicited by providers nor disclosed by patients during a typical office visit[6]. QoL is a multifaceted, dynamic concept and refers to functioning and well-being in physical, mental and social dimensions of life, and particular care is needed when defined or assessed. It represents how good or bad a person feels their life to be[7]. This view emphasizes the most essential feature of measuring QoL, which is to capture the individual's subjective evaluation of their QoL and not what others imagine it to be. Clinicians and nurses may feel that because of the enduring relationships they share with their patients they know them well and therefore have a good knowledge of their QoL. However, such impressions can be quite misleading[8]. The literature is full of reports measuring QoL using different questionnaires, but the Medical Outcome Study (MOS) 36 item short course Health Survey (SF-36) and the SF-12 (consists of 12 items and was developed as a shorter alternative to the SF-36) are the most frequently used multi-item QoL instruments[9]. The widespread applicability of the SF-36 (which is used in this study) is apparent in the more than 5,000 publications that have used this measure. The usefulness of the SF-36 in estimating disease burden is illustrated in articles describing more than 130 diseases and conditions.

Among the most frequently studied conditions, with more than 20 SF-36 publications each, are arthritis, back pain, depression, diabetes, and hypertension. 47 Translation of

the SF-36 is the subject of 148 publications, and one or more articles compare results from the SF-36 with those of 225 other generic and disease-specific instruments[10,11].

The aim of this study is the evaluation of QoL in Iraqi diabetic patients by SF-36 instrument and assesses any association with glycemic control measured by HbA1c.

Methods

This is a cross sectional study conducted on 1840 diabetic patients for the period from the 1st January to 31st December, 2007. Participants for the study group were recruited from The Specialized Center for Endocrinology & Diabetes (in Al-Rusafa sector) and The National Center for Treatment & Research of Diabetes in Al-Mustanseria Collage of Medicine (in Al-Karkh sector)-Baghdad. Patients included were at least 18 years and up to 65 years of age.. Ages above or below these limits are not included, and had a minimum of 5 years duration of DM. Those patients with other chronic medical problems (e.g. hypertension, ischemic heart disease, tumors) were excluded.

Glycosylated hemoglobin was measured as HbA1c%, the preferred standard for assessing glycemic control. In non-diabetic people with normal glucose metabolism the HbA1C % level is usually 4%-6%. The patient who manages to keep his/her HbA1C % level below 6.5% is considered to be in group I (Good glycemic control), while those with 6.5% level or more are considered to be in group II (Bad glycemic control)[12].

In both groups, the QoL was measured by the SF-36 Version 2.0, which is a generic instrument composed of 8 multi-item scales (36 items) assessing physical function (10 items), role limitations due to physical health problems (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and emotional well-being (5 items). These eight scales can be aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores. The 36th item, which asks about health change, is not included in the scale or summary scores. It has been claimed that items in the SF-36 questionnaire detect positive as well as negative states of health. In 6 of the 8 scales, patients are asked to rate their responses on 3-point or 6-point grading rather than simply responding yes or no.

For each scale, item scores are coded, computed, and transformed on to a scale from 0 (worst health) to 100 (best health). The subjects' responses are presented as a profile of scores calculated for each scale[10,13]. Crude scores of the 2 summary scales were standardized based on mean = 50 and standard deviation (SD) = 10. The SF-36 is available in multiple languages including Arabic but some modifications were done to fit our social and cultural background. Previous investigations have shown the Arabic version of the SF-36 to be a valid measure of self-reported health status[14,15].

The questionnaires were completed by participants on the same day of HbA1C % measurement. Scoring was the same as above. Total as well as differences between group I and group II regarding SF-36 physical and mental composite scores (PCS and MCS) were computed and then compared with the norm-based scoring (from USA population, 1998 survey) for evaluation.

Data were analysed using descriptive statistics (frequencies and percentages) and analytic statistics (t-test and chi square test) by SPSS, version 11. $P < 0.05$ was considered statistically significant.

Results

A total of 1840 patients were enrolled in the study. The current analyses were conducted with data from the 1,456 patients (79.1%) in which all 36 items were completed and fulfilled the questionnaire criterion (832 in group I and 624 in group II). Demographic characteristics and the mean HBA1c% of the two groups are presented in Table 1.

Comparison of the SF-36 scores for our diabetic patients with that of the standard norms (general population) (16), revealed highly significant differences in all 8 items except vitality, even the physical and mental component summaries showed a highly statistically difference ($P< 0.0001$) (Table 2).

Comparing the results by HbA1C % (between group I and Group II), the only statistically significant differences were for RP, SF, and MH while the others were not. Only Mental but not Physical Component Summary showed the same finding (Table 3).

Discussion

The result has suggested that individuals with diabetes have reduced QoL compared to the general population. This finding agreed with all the studies done before in different parts of the world[17,18,19,20,21]. There are three major explanations as to why diabetes can negatively affect physical well-being. The most potent factor is the development of long-term complications. When patients suffer vision loss, kidney damage, significant heart disease, erection problems, peripheral neuropathy resulting in chronic pain, amputation, and/or difficulty walking, or any of a host of autonomic neuropathy problems (such as gastroparesis or loss of bladder function), there is likely to be a significant drop in perceived quality of life. The patient may now be unable or less able to work, to complete household tasks, or to enjoy pleasurable activities. The patient's ability to function independently may be impaired as well. The second factor is short-term complications. Chronically elevated blood glucose

levels may lead to increased fatigue, sleep problems, more frequent infections, and other associated problems. The third major factor concerns physical symptoms and lifestyle changes resulting from the demands of the diabetes regimen. Finally, when patients are forced (or believe that they are forced) to limit or curtail their activities in order to manage their diabetes effectively, quality of life is likely to be affected. Examples include declining late-night social engagements as a means to avoid dietary lapses or losing one's license to drive due to frequent and severe hypoglycemia. Unpleasant side effects due to prescribed medications may also affect perceived well-being-for example, chronic gastrointestinal distress resulting from specific oral hypoglycemic agents or unsightly lypohypertrophy resulting from repeated insulin injections. To assess this dimension most effectively, evaluation might focus on the patient's perceived distress due to diabetes-specific symptoms as well as the perceived loss of physical function, interference with common role activities (including work, tasks at home, and social and recreational pastimes), and loss of independence due to diabetes[11,17,22,23].

The long-term benefit of glycemic control in diabetes mellitus is to reduce the risk of complications. Since these complications are known to reduce the quality of life, intensified glycaemic control is an important way to reduce risk of complications and improve QoL[18]. However, what is the effect of glycaemic control on QoL? In this study, we found that diabetic subjects with bad glycemic control experienced lowering of mental but not physical QoL as compared to those with good glycemic control. This indicates that the mental component is affected more than the physical component by bad Hb A1C%. The same finding was found in other studies[24,25,26,27,28,29]. Lau Chuen-Yen et al found that improved diabetic control is associated with an improved mental, but not physical, component[30].

The results showed a significant association between HbA1c% with only three (out of 8) items of QoL. These are Role Physical, Social Functioning, and Mental Health. This finding disagrees with previous randomized controlled double-blind trials that showed an improved HbA1c was associated with short-term improvement in QoL and economic benefits in Type II diabetes[23].

Our findings are important for several reasons. Firstly, this is the first study showing the reduction of QoL in Iraqi diabetics using the SF-36 instrument. Secondly, it is assessing the effect of HbA1c% control on QoL of diabetes. Thirdly, the large sample size can increase the power of the study and the results can be readily generalized to the diabetic population at large. However, interventional design would be more appropriate for diabetes with bad glycemic control to assess QoL before and after intervention as it would give us a comparison for the same individual before and after the intervention.

Conclusions

Atrial fibrillation anticoagulation is mandatory once indicated. To be efficient, warfarin dose should be adjusted to have an international normalized ratio within the therapeutic range. Anticoagulation clinics are advised to improve the percentage of atrial fibrillation patients who are well anticoagulated in order to avoid the thromboembolic risks of this disease as well as bleeding risks associated with over anticoagulation.

References

1. Gu K, Cowie CC, Harris MI: Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes Care 1998, 21:1138-1145.
2. Non Communicable Diseases Directorate, Ministry of Health-Iraq: Non communicable diseases prevalence survey: 2006.
3. Tuomilehto J, Lindstrom J, Riksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001; 344:1343-1350.
4. Diabetes Control and Complications Trial Research Group. The absence of a glycemic threshold for the development of long-term complications: The perspective of the Diabetes Control and Complications Trial. Diabetes 1999; 45:1289-98.
5. Bradley C. Measuring quality of life in diabetes. Diabetes Ann 1996:207-27.
6. Stewart MA: Effective doctor-patient communication and health outcomes: a review. C MAJ. 1995,152:1423-1433.
7. Rose M, Burkert U, Scholler G, Schirop T, Danzer G, Klapp BF: Determinants of quality of life of patients with diabetes under intensified insulin therapy. Diabetes Care. 1998, 21:1876-83.
8. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GEHM, Wolffenbuttel BHR, Niessen LW. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diab Care: 2002, 25:458-63.
9. Beth D and Robert G. Basic and clinical biostatistics. 14th edition, Lange Medical Book.2004: p 13.
10. Ware JE, Kosinski M, Gandek B: SF-36 ® Health Survey: Manual & Interpretation Guide. Lincoln, RI: QualityMetric Incorporated; 2000.
11. Jaworsk J, Dziemido KP, Kulik TB, Rudnicka- Dorozk E.Frequency of self -monitoring and its effect on metabolic control in patient with type II diabetes ''Ann Univ Mariae Curie Sklodowska [Med] 59 (1) : 2004: 310 -6.
12. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1). Lincoln, RI: QualityMetric Incorporated; 2002.
13. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) project. Journal of clinical epidemiology. 1998; 51(11):903-12.
14. Walters SJ, Munro JF, Brazier JE: Using the SF-36 with older adults: a cross-sectional community-based survey. Age Aging 2001, 30:337-343. Ibtissam Sabbah, Nabil Drouby, Sanaa Sabbah, Nathalie Retel-Rude, and Mariette Mercier. Quality of Life in rural and urban populations in Lebanon using SF-36 Health Survey. Health Qual Life Outcomes. 2003; 1: 30.
15. Gandek B, Ware JE Jr. Methods for validating and norming translations of health status questionnaires : the IQOLA project approach. J Clin Epidemiol. 1998; 51:953-959.
16. Ware JE Jr. SF-36® health survey update. Quality Metric Incorporated (http://www.sf-36.org/tools/sf36.shtml, accessed 21 September 2007).
17. Rubin RR, Peyrot M: Quality of life and diabetes. Diabetes Metab Res Rev 15:205-218, 1999.
18. Watkins KW, Connell CM, Fitzgerald JT, Klem L, Hickey T, Ingersoll-Dayton B: Effects of adults' self-regulation of diabetes on

quality of life outcomes. Diabetes Care 23:1511-1515, 2000.
19. Prospective Diabetes Study Group: Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control. Diabetes Care 22:1125-1136, 1999.
20. American Diabetes Association. Position Statement. Diabetes Care 27:1-143. 2004.
21. Redekop WK. Does improved glycaemic control lead to a better short-term quality of life in diabetes mellitus type 2? JPGM 50 (3): 194 : 2004.
22. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-86, 1993.
23. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: A randomized, controlled, double blind trial. JAMA :80:1490-6, 1998.
24. Weinberger M, Kirkman MS, Samsa GP, Cowper PA, Shortliffe EA, Simel D, et al. The relationship between glycemic control and health-related quality of life in patients with non-insulin-dependent diabetes mellitus. Med Care 32:1173-81, 1994.
25. Bagne CA, Luscombe FA, Damiano A. Relationships between glycemic control, diabetes-related symptoms and SF-36 scale scores in patients with non-insulin dependent diabetes mellitus. Qual Life Res 4:392-3, 1995.
26. Aalto AM, Uutela A, Aro AR. Heath related quality of life among insulin-dependent diabetics: Disease-related and psychosocial correlates. Patient Educ Couns 30:215-25, 1997.
27. Ahroni JH, Boyko EJ, Davignon DR, et al. The health and functional status of veterans with diabetes. Diabetes Care 17:318-21, 1994.
28. Jacobson AM, DeGroot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. Diabetes Care 17:267-74, 1994.
29. Anderson RM, Fitzgerald JT, Wisdom K, et al. A comparison of global versus disease-specific quality-of-life measures in patients with NIDDM. Diabetes Care. 20:299-305, 1997.
30. Lau Chuen-Yen, Qureshi AK, Scott SG. Association between glycaemic control and quality of life in diabetes mellitus. 50(3): 189-194, 2004.

Table 1. Percentage Distribution of the Respondents according to Selected Characteristics

Characteristic	Group I (N = 832)	Group II (N = 624)	Total (N = 1456)	p value1
Age (mean±SD) in years	38.7 (12.4)	40.1 (13.9)	39.4 (13.15)	0.07
Gender Male Female	522 (62.7%) 310 (37.3%)	393 (63%) 231 (37 %)	915 (62.8%) 541 (37.25)	0.925
Duration of DM (years) Mean (SD)	8.9 (3.6)	9.3 (3.9)	9.1 (5.7)	0.21
HBA1c Mean (SD)	4.7 (1.4)	7.9 (2.3)	6.3 (1.85)	<0.01

1 P values are for comparison between the 2 groups. t-test was used for continuous variables, and chi square test was used for categorical variables.

Table 2. Mean scores and standard error of the 8 scales with summary measures of mental and physical health for the studied sample as compared with the standard norms.

SF 36 Scale	SF 36 Score		p value2 (CI) 3
	Total Sample Mean (SE1)	Standard Norms Mean (SE1)	
Physical Functioning (PF)	72.13 (1.04)	83.0 (0.07)	<0.0001 -12.12 to -9.62
Role Physical (RP)	66.35 (0.81)	77.9 (0.11)	<0.0001 -13.37 to -9.72
Bodily Pain (BP)	66.34 (0.86)	70.2 (0.07)	<0.0001 -5.08 to -2.63
General Health (GH)	57.69 (0.70)	70.1 (0.06)	<0.0001 -13.52 to -11.29
Vitality (VT)	56.50 (0.83)	57.0 (0.06)	0.3738 -1.60 to 0.60
Social Functioning (SF)	75.30 (0.74)	83.6 (0.07)	<0.0001 -9.49 to -7.10
Role Emotional (RE)	70.53 (1.11)	81.1 (0.09)	<0.0001 -12.21 to -8.92
Mental Health (MH)	65.35 (0.57)	75.2 (0.05)	<0.0001 -10.76 to -8.93
Physical Component Summary 4	46.95 (0.36)	50 (0.03)	<0.0001 -3.57 to -2.52
Mental Component Summary 4	46.25 (0.33)	50 (0.03)	<0.0001 -4.27 to -3.23

1SE= Standard Error, 2 P values, t-test was used for the difference between the 2 groups. 3 95% confidence Interval for the difference , 4Summary standardized value

Table 3. Mean scores and standard error of the 8 scales with summary measures of mental and physical health for the two and total studied groups.

SF 36 Scale	Group I score Mean (SE1)	Group II score Mean (SE1)	Total score Mean (SE1)	p value2 (CI) 3
Physical Functioning (PF)	73.07 (1.14)	71.18 (0.94)	72.13 (1.04)	0.2222 (-1.15 to 4.93)
Role Physical (RP)	69.33 (0.95)	63.38 (0.67)	66.35 (0.81)	<0.001 (3.51 to 8.38)
Bodily Pain (BP)	67.44 (0.88)	65.24 (0.84)	66.34 (0.86)	0.0786 (-0.25 to 4.65)
General Health (GH)	58.67 (0.80)	56.72 (0.6)	57.69 (0.70)	0.0660 (-0.13 to 4.03)
Vitality (VT)	56.40 (0.79)	56.60 (0.87)	56.50 (0.83)	0.8658 (-2.52 to 2.12)
Social Functioning (SF)	78.34 (0.82)	72.26 (0.66)	75.30 (0.74)	<0.001 (3.90 to 8.25)
Role Emotional (RE)	70.02 (1.32)	71.04 (0.90)	70.53 (1.11)	0.5514 (-4.38 to 2.34)
Mental Health (MH)	69.88 (0.62)	60.82 (0.52)	65.35 (0.57)	<0.001 (7.39 to 10.72)
Physical Component Summary4	47.1 (0.41)	46.8 (0.31)	46.95 (0.36)	0.5816 (-0.76 to 1.36)
Mental Component Summary4	47.5 (0.39)	45.0 (0.27)	46.25 (0.33)	<0.001 (1.50 to 3.49)

1SE= Standard Error, 2 P values t-test was used for the difference between the 2 groups. 3 95% confidence Interval for the difference , 4Summary: standardized value

Nitroimidazoles in The Treatment of Intestinal Amoebiasis

ABSTRACT

Objective: Entamoeba histolytica is one of the common intestinal protozoans in the Middle East. Treatment of infection has some difficulties by metronidazole because of the long course of therapy and various side effects. The objective of this study was to determine efficacy and side effects of tinidazole compared with metronidazole in the treatment of amoebiasis in Jordanian patients.

Patients and Methods: Over an interval period of one year duration, starting July 2005 through July 2006,a randomized controlled clinical trial was carried out on 66 subjects (42 males, 24females) with Entamoeba histolytica infestation who presented to out-patients clinic or emergency room in Queen Alia Military Hospital in Jordan ,infected patients were treated with either tinidazole or metronidazole (Tinidazole 2gm single dose orally for 3 days and metronidazole 2gm single dose orally for 3 days). Parasitological cure was documented when there were 3 successive negative stool examinations for entamoeba histolytica at 1-2 weeks after therapy.

Results: 27 of 32 patients (87.5%) treated with tinidazole and 23 of 34 patients (67.5%) treated with metronidazole had parasitological cure. Cure rates between two groups were significant statistically (P<0.01). No major side effects were observed except 13 cases in metronidazole group who had nausea, epigastric pain, mild headache and some had metallic taste. Three cases in tinidazole group had nausea, dizziness and headache.

Conclusion: Tinidazole was more effective than metronidazole, produced fewer and milder side effects, and is recommended with high efficacy in treating intestinal amoebiasis.

Key-words: Amoebiasis, Treatment, Nitroimidazo, Metronidazole.

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Introduction

Entamoeba histolytica is the etiological agent of amoebic dysentery. Worldwide, 40-50 million symptomatic cases of amoebiasis occur annually and 70,000 to 100,000 deaths are due to this infection.[1] Molecular phylogeny places entamoeba on one of the lowermost branches of the eukaryotic tree, closest to dictyostelium. Although the organism was originally thought to lack mitochondria, nuclear-encoded mitochondrial genes and a remnant organelle have now been identified.[2,3] Unusual features of entamoeba include polyploid chromosomes that vary in length; multiple origins of DNA replication; abundant, repetitive DNA; closely spaced genes that largely lack introns; a novel GAAC element controlling the expression of messenger RNA; and unique endocytic pathways.[4,5,6,7] There are two distinct, but morphologically identical species of Entamoeba: Entamoeba histolytica, which is pathogenic and Entamoeba dispar, which is non-pathogenic.[15]

Ingestion of the quadrinucleate cyst of E. histolytica from fecally contaminated food or water initiates infection. Infection with E. histolytica may be asymptomatic or may cause dysentery or extra intestinal disease. Asymptomatic infection should be treated because of its potential to progress to invasive disease. Patients with amebic colitis typically present with a several-week history of cramping abdominal pain, weight loss, and watery or bloody diarrhea. The insidious onset and variable signs and symptoms make diagnosis difficult, with fever and grossly bloody stool absent in most cases.[8,9,10] Therapy for invasive infection differs from therapy for noninvasive infection. Noninvasive infections may be treated with paromomycin. Nitroimidazoles, particularly metronidazole, are the mainstay of therapy for invasive amebiasis.[11] Nitroimidazoles with longer half-lives (namely, tinidazole, secnidazole, and ornidazole) are better tolerated and allow shorter periods of treatment.

Approximately 90 percent of patients who present with mild-to-moderate amebic dysentery have a response to nitroimidazole therapy. Parasites persist in the intestine in as many as 40 to 60 percent of patients who receive nitroimidazole. Therefore, nitroimidazole treatment should be followed with paromomycin or the second-line agent diloxanide furoate to cure luminal infection. Metronidazole and paromomycin should not be given at the same time, since the diarrhea that is a common side effect of paromomycin may make it difficult to assess the patient's response to therapy.[12,13,14] In this study we assess the efficacy of the 2 nitroimidazoles available in Jordan, tinidazole and metronidazole.

Patients and Methods

The efficacy and tolerability of metronidazole and tinidazole were evaluated in a randomized clinical trial performed with 66 patients who attended the out-patient clinic and emergency room in QAMH. The study period was 12 months from July 2005 to July 2006. The subjects (24 females and 42 males) were randomly allocated to two groups: experiment group (n=32) were given tinidazole and control group (n=34) were given metronidazole

[Table 1]. In group one, metronidazole 2gm as a single dose orally for 3 days), and in group two, tinidazole 2 gm single dose orally were prescribed respectively.[16] Patients were followed for three weeks after the end of therapy for the presence of entamoeba histolytica in their stool. Clinical and parasitological follow-up was carried out before, and at 7, 14, and 21 days after treatment and the outcome of treatment was noted. Parasitological cure was documented when there were three consecutive negative stool examinations for entamoeba histolytica at 1-3 weeks after therapy termination.

Results

As illustrated in Table 1 the sample size of both groups was almost identical 32 (48.5%) and 34 (51.5%)of tinidazole and metronidazole respectively. The males constituted the majority of patients 42 (63.6%) while the females were 24 forming 36.4% of the patients, The male to female ratio was 1.75:1.

The age distribution of patients ranged from 16 years to 68 years, the commonest age group was among 20 years-40 years making up around half of all patients (48.5%) as shown in Table 2.

28 of 32 patients (87.5%) treated with tinidazole and 23 of 34 patients (67.5%) treated with metronidazole had parasitological cure. Cure rate between the two groups was statistically significant ($P<0.01$). No major side effects were observed except two cases in the metronidazole group who had mild headache and abdominal pain for two days and three cases in tinidazole group who reported nausea, dizziness and headache. Efficacy of two regimens in term of drug are presented in [Table 3]. Tinidazole appears to be safe having a few ignorable side effects and produced a significant cure rate, more effective than metronidazole.

Discussion

A 2 gm single dose for 3 days regimen of tinidazole had excellent effectiveness in treatment of amoebiasis as compared with metronidazole. Introduction of nitroheterocyclic drugs in the late 1950s and the 1960s heralded a new era in the treatment of infections caused by a range of pathogenic protozoan parasites.[17] Metronidazole is the drug now most widely used in the treatment of anaerobic protozoan parasitic infections caused by G. intestinalis, Trichomonas vaginalis and Entamoeba histolytica.[18,19] Although various drugs have been available for several decades to treat this infection, none of them is entirely satisfactory due to high incidence of undesirable side effects and a significant failure rate in clearing parasites from the gastrointestinal tract.[19,20] Some evidence suggests that drug resistance may be responsible for these failures.[21,22] Unfortunately, failures in treatment of amoebiasis with standard metronidazole therapy have been reported in five to 20% cases. In the event of overt clinical resistance to metronidazole in entamoeba histolytica strains, tinidazole could be an alternative treatment. A key issue should be keeping in mind the documented cross-resistance between currently used nitroimidazole drugs .As such the choice of drug will differ in each case depending on the local conditions and keeping in view the sensitivity of parasite strain. Moreover, perhaps treatment of all asymptomatic entamoeba histolytica infections in developing countries hyperendemic for the disease is doubtful because of rapid reinfection. Clinical metronidazole resistance in Trichomonas vaginalis has also been documented previously.[22] Single dose therapy with tinidazole is effective in the metronidazole-resistant strains of T. vaginalis which could be another advantage of this drug.

Conclusions

Tinidazole was more effective than metronidazole produced fewer and mild side effects. We recommend tinidazole as drug of choice for treatment of amoebiasis because of its efficacy, and desirable tolerance. This preparation is preferred to metronidazole in the treatment of entamoeba histolytica infection as a considerable advantage in low socio-economic communities. Moreover, this drug may be tried and used if other agents failed in the treatment of clinical amoebiasis.

References

1. World Health Organization. WHO/PAHO/UNESCO report: A consultation with experts on amebiasis. Mexico City, Mexico28-29 January, 1997.Epidemiol Bull PAHO. 1997; 18:13-14.
2. Mai Z, Ghosh S, Frisardi M, Rosenthal B, Rogers R, Samuelson J. Hsp60 is targeted to a cryptic mitochondrion-derived organelle ("crypton") in the microaerophilic protozoan parasite Entamoeba histolytica. Mol Cell Biol 1999; 19:2198-2205. [Free Full Text]
3. Tovar J, Fischer A, Clark CG. The mitosome, a novel organelle related to mitochondria in the amitochondriate parasite Entamoeba histolytica. Mol Microbial 1999; 32:1013-1021. [CrossRef][ISI][Medline]
4. Willhoeft U, Tannich E. The electrophoretic karyotype of Entamoeba histolytica. Mol Biochem Parasitol 1999;99:41-53. [CrossRef][Medline]
5. Dhar SK, Choudhury NR, Mittal V, Bhattacharya A, Bhattacharya S. Replication initiates at multiple dispersed sites in the ribosomal DNA plasmid of the protozoan parasite Entamoeba histolytica. Mol Cell Biol 1996;16:2314-2324. [Abstract]
6. Singh U, Rogers JB, Mann BJ, Petri WA Jr. Transcription initiation is controlled by three core promoter elements in the hgl5 gene of the protozoan parasite Entamoeba histolytica. Proc Natl Acad Sci U S A 1997;94:8812-8817. [Free Full Text]
7. Saito-Nakano Y, Nakazawa M, Shigeta Y, Takeuchi T, Nozaki T. Identification and characterization of genes encoding novel Rab proteins from Entamoeba histolytica. Mol Biochem Parasitol 2001;116:219-222.
8. Adams EB, MacLeod IN. Invasive amebiasis. I. Amebic dysentery and its complications. Medicine (Baltimore) 1977;56:315-323. [Medline]
9. Aristizabal H, Acevedo J, Botero M. Fulminant amebic colitis. World J Surg 1991;15:216-221. [CrossRef][Medline]
10. Ellyson JH, Bezmalinovic Z, Parks SN, Lewis FR Jr. Necrotizing amebic colitis: a frequently fatal complication. Am J Surg 1986;152:21-26.
11. Powell SJ, MacLeod I, Wilmot AL, Elsdon-Dew E. Metronidazole in amoebic dysentery and amoebic liver abscess. Lancet 1966;2:1329-

1331. [Medline]
12. Blessmann J, Tannich E. Treatment of asymptomatic intestinal Entamoeba histolytica infection. N Engl J Med 2002;347:1384-1384. [Free Full Text]
13. McAuley JB, Herwaldt BL, Stokes SL, et al. Diloxanide furoate for treating asymptomatic Entamoeba histolytica cyst passers: 14 years' experience in the United States. Clin Infect Dis 1992;15:464-468. [Medline]
14. McAuley JB, Juranek DD. Paromomycin in the treatment of mild-to-moderate intestinal amebiasis. Clin Infect Dis 1992;15:551-552. [Medline]
15. Diamond LS, Clark CG. A redescription of Entamoeba histolytica Schaudinn 1903 (emended walker, 1911) separating it from Entamoeba dispar Brumpt, 1925. J Eukaryot Microbiol. 1993;40:340-4. [PubMed]
16. A comparative study of tinidazole and metronidazole as a single daily dose for three days in symptomatic intestinal amoebiasis.
17. Drugs. 1978; 15 Suppl 1:19-22. No abstract available.
18. PMID: 350563 [PubMed - indexed for MEDLINE]
19. Campbell WC, Rew RS. Chemotherapy of Parasitic diseases, New York: Plenum Press 1986; 146-7.
20. Upcroft JA, Campbell RW, Benkali K. Efficacy of new 5-nitroimidazoles against metronidazole-susceptible and resistant Giardia, Trichomonas & Entamoeba spp. Antimicrob Agents Chemother 1999;43:73-6.
21. MacMillan JA, DeAngelis CD, Feigin RD, Warshaw JB. Oski's Pediatrics: Principles and Practice. Philadelphia, Lippincott Williams &Wilkins 1999; 1176-7.
22. Misra PK, Kumar A, Agarwal V, Jagota SC: A comparative clinical trial of albendazole versus metronidazole in children with giardiasis. Indian Pediatrics 1995;32(7):779-82.
23. Romero-Cabello R, Robert L, Munoz-Garcia R, Tanaka J. Randomized study comparing the safety and efficacy of albendazole and metronidazole in the treatment of giardiasis in children. Rev Latinoam Microbiol 1995;37(4):315-23.
24. Lacy E. The role of the cytoskeletal protein, Tubulin, in the mode of action and mechanism of drug resistance to benzimidazoles. Internl J Parasitology, 1988;18(7):855-936.

Table 1 Number of patients allocated to therapy

DRUG / SEX	TINIDAZOLE	METRONIDAZOLE	TOTAL
MALE	19(45%)	23(55%)	42(63.6%)
FEMALE	13(54%)	11(46%)	24(36.4%)
TOTAL	32(48.5%)	34(51.5%)	66(100%)

Table 2 Age distribution of patients

AGE / SEX	<20YRS	20-40YRS	>40YRS	TOTAL
MALE	11(26%)	19(45%)	12(29%)	42(63.6%)
FEMALE	9(37.5%)	13(54%)	2(8.5%)	24(36.4%)
TOTAL	20(30.3%)	32(48.5%)	14(21.2%)	66(100%)

Table 3 The efficacy of treatment

Efficacy			
Drug	**effective**	**Non effective**	**Total**
Tinidazole	28(87.5%)	4(12.5%)	32(48.5%)
Metronidazole	23(67.5%)	11(32.5%)	34(51.5%)
Total	51(77.2%)	15(22.8%)	66(100%)

Basic Characteristics of Arsenicosis Patients and their Treatment Outcomes from a Micro-Survey Study in Chapai Nawabganj District with Special Reference to Bangladesh

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ABSTRACT

This study is based on 170 arsenicosis patients from Nawabganj district. Basic Characteristics (demographic, socio-economic, household and mass-media) of the patients, their present arsenicosis condition, treatment outcome and different problems faced by them, have been investigated in this study. The study reveals that most of the patients are in the age group 25 to 60 years and male patients constitute 49.4% and the remaining are female. It is also found that of the total patients 47.1% have no educational attainment, 40.6% patients are housewives. 54.1% of the patient's households obtain their drinking water from tubewells and 53.5% use tubewell water for cooking purposes. Among the total arsenicosis patients, 47.6% patients are in Phase I (Melanosis, keratosis). Besides arsenicosis, 14.1% patients are also suffering from diabetes mellitus and 11.2% are suffering from asthma. We found from this study that, among the various types of problem faced by arsenicosis patients (mental, social, invitation cases, physical), 98.8% fhave mental problem from arsenicosis. This study also indicates that out of 84 male patients 59 are partially improved and 25 had no improvement after taking some treatment. But in female counterparts out of 86 patients 42 were partially improved and 43 remained unchanged. Finally Regression analysis indicates that population per square kilometer has a significant effect on contaminated tubewells per square kilometer in 52 districts out of 64 in Bangladesh.

Key words: Arsenicosis, melanosis, keratosis, contamination.

Introduction

Arsenic contamination in ground water has become a formidable issue of life and death in Bangladesh. More than 80 million people living in the country are under the risk of arsenic poisoning (Rahman Z. 2003). The number of people affected by this arsenic disaster is among the greatest of any disease facing the world today. Out of 64 districts 61 are already affected by arsenic contamination. About 130 million people are vulnerable to arsenic.

After independence, tube wells were first introduced for access to unpolluted drinking water in Bangladesh, with the collaboration of UNICEF; after which the people of Bangladesh were habituated to drink water from tube wells. But, in recent past it has been discovered that the opinion of UNICEF was wrong. Setting up tube wells everywhere in Bangladesh has created a serious question. In 1993, it was first discovered after diagnosing patients with arsenicosis that water of tubewells is contaminated with arsenic beyond the permissible level of 0.05 milligram per litre. It is being estimated that more than 50 percent of the tubewells in 62 out of 64 districts contain more than .05 mg of arsenic per litre of water (Momotaj H. et al.: 2001).

People who drink arsenic contaminated water for 5 to 10 years, have an 85 percent risk that 10 percent would develop cancer. Consumption of arsenic contaminated groundwater over a prolonged period of time has adverse health effects like-arsenical dermatosis, hyperkeratosis and several other symptoms of arsenicosis (Goriar et al., 1984; Chakraborty et al., 1987; Guha Mazumder et al., 1988; Das et al., 1996).

The geochemical processes involving leaching of continental rocks as well as sediment, govern mobilization of arsenic in groundwater. Anthropogenic inputs particularly due to the application and the use of arsenical wood preservatives (Bhattacharya et al. 1996, 1998) as well as pesticides could also lead to significant emission of arsenic in groundwater, especially under anoxic conditions.

In 1987, the first arsenicosis patient of Baroghoria at Nawabganj district in Bangladesh was identified afterwards the Department of Public Health Engineering confirmed the presence of arsenic in tubewells in the

same district in 1993. Consequently 8 arsenicosis patients were detected through the DPHE survey. In 1994, then the Public Health Engineering Department (PHED) argued that about 8 million people belonging to 61 of 64 districts have been affected with arsenicosis. Therefore, immediate action must be done to provide safe water for affected people and the information on the background characteristics of the study population is essential for interpretation of the study results and examination of any cause-effect relationship among the study variables. This is also essential because these characteristics are supposed to influence the norms, values and beliefs, expectations and aspirations of the people and consequently their family building.

In this study an attempt has been made to investigate the basic characteristics (demographic, socio-economic, household and mass media), different types of problem, treatment outcomes of the arsenicosis patients and also to examine the effect of population per square kilometer (measured as population density) on arsenic contaminated tubewells per square kilometer on a country level (Bangladesh).

Patient and Methods

The data for this study came from 170 arsenicosis patients of Nawabganj district. The list of the patients was provided by the Civil Surgeon office of Nawabganj district. Data was collected from these 170 arsenicosis patients by personal interview method in June 2006. For the purpose of knowing the differentials of various characteristics of arsenicosis patients we performed bivariate analysis. Finally regression analysis is performed to know the effect of population density on arsenic contaminated tubewells.

Basic Characteristics: Demographic, Socio-economic, Household and Mass Media Related Characteristics

Demographic Characteristics

Age of the Patients: For arsenicosis patient's age is a very important factor. In this analysis, age is grouped according to adult, active and inactive population. From Table 1, we see that the mean age of the patients was 31.77 years and the median age was 30.00 years, which bmeans most of the patients were middle aged. Again, from this we also observed that the persons of the age group 25-60 constitute the maximum percentage, which is 55.3%, and more than half of the total, much greater than the other groups that contain 41.2% and 3.5% for the age group 25 years and below and 60+. A study also shows that, children below 7 years of age showed no manifestations of arsenicosis (Khan A.W. et al.; 1997). Another study shows that, most of the arsenicosis patients were between 10 to 39 years of age (Ahmad M.H. et al.; 1999). But in our study we found that most of the patients were 25 to 60 year's age, which is the most active population. A survey study found that most of the arsenicosis patients with neoplastic skin lesions were in the middle age group (Jalil M. A. et al.; 1998)

Sex of the patients: From Table 1 we found that the arsenicosis patients who are male constitute 49.4% whereas that of females constitutes 50.6%, i.e.; the number of women slightly exceeds the number of men. Women are the worst sufferers because they are more malnourished than men and are less able to deal with arsenic that attacks their bodies (Rahman Z. 2003). The prevalence of arsenic was quite high and males were more vulnerable to arsenic contamination (Kadono T. et.al.; 2002). But here in my study females are higher, albeit a little bit, than males. A study showed that, the majority (59.4%) of the arsenicosis patients were female, (Khan A.W. 1997).

Marital status: Marital status is another important characteristics of the arsenicosis patients. Marriage is almost universal in Bangladesh. Marital status is an important factor in population studies. From Table 1, we found that out of 170 patients 118 are married, which constitutes 69.4% of the total and we conclude that since the main affected group of arsenicosis is above age 15, hence the maximum number of patients are found to be married. Again 24.7 percent were found uto be nmarried and only 5.9 percent are divorced or widowed and the causes of the divorce may be due to the affect of arsenic. There are some instances of arsenic-affected husbands divorcing their arsenic-affected wives blaming the disease on the women. Arsenic-caused separation is also common (Rahman, Z. 2003).

Socio-economic Characteristics

Patients' Education: Education is the single most important indicator of the socioeconomic status of an individual which affects almost all aspects of human life, including demographic and health behavior. It is a key determinant of the lifestyle and status an individual enjoys in a society. Studies show that literacy plays an important role in suffering from arsenicosis. Of the total arsenicosis patients 47.1 percent have no educational attainment, i.e., never attended school, 11.8 percent have the educational attainment of primary level and it amazing that 41.2 percent patients, who have passed secondary or higher education are suffering from arsenicosis.

Patient's Occupation: Patient's occupation is one of the most important indicators of socioeconomic status of the patients. From Table 1, we found that 40.6 percent of patients were housewives; this also may indicate that housewives who are handling arsenic contaminated water have more exposure to the risk of arsenicosis. We also observed that 15.3 percent were students, 15.9 percent were servicemen which includes businessmen, teachers and serviceman and 28.2 percent of the patients had occupations in the day laborer group, which includes

farmers, day laborers and patients of other groups.

Monthly Income: Monthly income and income source is another important indicator of the socioeconomic status of the patients. Since the majority of the patients mainly come from the groups of housewives and students these are considered as outside the labor force and have no income. Hence a large percentage (81.8%) fall into the category who have monthly income of below 2000 T.K., the minimum income to spend a month for a person, 14.1 percent have a monthly income of between 2000 to 5000 T.K. and only 4.1 percent have a monthly income above 5000 T.K.

Ownership of Land: Having and owning land is a good economic indicator. Among the patients 44.1 percent have land of their own and 55.9% do have not their own land, so they are dependent on others' land or working outside agricultural work for their livelihood. Hence we easily understand that many of the patients come from the low economic level.

Electricity, Source of Drinking and Cooking Water: Electricity itself is considered as an indicator of modernization and households having electricity are, in general, indicative of a higher socioeconomic status. Table 1 shows that about 51.2 percent of the patients' households have electricity. Tubewells are the major source of drinking water of the patients in Nawabganj as well as in Bangladesh. 54.1 percent of the patient households obtain their drinking water from tubewells. A great number of the patient's households (45.9%) depend on the surface water such as wells, ponds, bills and rivers. Again for cooking purpose the majority of the patients, 53.5 percent, use water from tube-wells and also a good percentage (41.8%) use well water. Hence we may conclude that, since the majority of persons depend on tubewells for drinking and cooking purpose they are under risk of contaminationj by arsenic.

Sanitary Facility: The majority (94.7%) of the households of the patients have sanitation facilities; however, 77.6 percent have hygienic toilets such as septic tanks (22.9%), high quality hole (53.5%) and 18.3 percent have the sanitary facility of kancha latrines while 5.3 percent have no facility at all.

Mass-Media Related Characteristics

Access to mass media is an important factor for the rise in consciousness of the patients. Some selected mass media related characteristics are discussed in Table 1. Access to modern mass media, such as listening to radio, watching T.V., reading newspapers may have an effect on the awareness of the arsenic contamination and suffering from arsenicosis in a country like Bangladesh, because modern mass media offers different programs relating to arsenic contamination. So if in their leisure time patients were listening to radio or watching T.V. or reading newspapers then they can learn about arsenic and can prevent that. Patients were asked about what they do in their leisure time. Whenever asked about listening to radio we get 32.4, 15.9 percent were watching T.V. and only 1.8 percent read newspapers in the leisure time.

Arsenicosis Condition, Place of Treatment and Side-effects

Phases of Arsenicosis and Manifestations: According to the clinical manifestation arsenicosis has three phases. In different phases from table 2, we observed that 47.6 percent of arsenicosis patients are in the first phase and 52.4 percent are in the second phase. There is no evidence of patients who are in phase three. All the three stages of manifestations of arsenicosis were observed in Bangladesh. But the majority of the patients were found in the initial and second stage (Khan A.W. et al., 1997). Hence these stages of arsenicosis are curable if the treatment is proper and mainly that is nothing but drinking arsenic free water and eating nutritious food. Again from Table 2 we observed that 19.4 percent were suffering from melanosis, 22.9 percent suffering from keratosis and only 5.3 percent from both melanosis and keratosis. The above total 47.6 percent of patients are in phase one. Another 52.4 percent of patients were found in the second phase, who were suffering from Hyper-keratosis with melanosis and keratosis. A study shows that, the most commonly observed clinical manifestations were melanosis and keratosis (Ahmad S.A. et al., 1997). In this study, above half of the patients were found in the second stage and also treated as hyperkeratosis.

Duration of the Disease: Since the first patients of arsenicosis were detected in 1993 at the Barogharia, Nawabganj district the duration should not be more than 10 years. In this study, when the duration of the disease was found some respondents trelated that their clinical manifestation were observed for more than ten years and while it was very few it provides evidence of the lack of proper health facilities situated in Bangladesh. From the Table we observe that 65.9 percent have had the disease less than 5 years, 30 percent 5-10 years and only 4.1 percent more than ten years.

Place of Treatment: Some types of ointment are also suggested for relief from arsenicosis. The government, along with some NGO's provides this type of treatment. From Table 2, we observe that all the patients take their treatment and among them 89.4 percent from the NGOs, only 1.2 percent from the Thana Health Complex, and the rest, 9.4 percent, from other places like from India or other personal. NGOs play a great role in the treatment and mitigation of arsenic in Nawabganj as well as in Bangladesh ((Khan A.W. et al.,1997).

Side Effects: From the Table we observe that, among the arsenicosis patients 14.1 percent were suffering from Diabetes Mellitus, 11.2 percent had asthma and also

some were suffering from high blood pressure, heart disease, malaria and jaundice. Hence we can say that, arsenicosis patients have a greater chance of having diabetes mellitus. In 1996, two of the authors conducted a survey of the prevalence of diabetes mellitus among 163 subjects with keratosis, taken as exposure to arsenic and 854 unexposed individuals. The results corroborate earlier studies and suggest that arsenic exposure is a risk for diabetes mellitus. (Tondel M. et al.; 1999)

Problems faced by arsenicosis Patients

These include mental, social and physical problems that are observed among the arsenicosis patients. The frequency of some selected problems is presented in Table 3. We observed that almost all the patients, 98.8 percent of patients, have mental problems from suffering from arsenicosis. They were taking arsenicosis as a kind of skin disease and that looks ugly to them so theyare mentally affected. Some questions were also asked about family problems due to suffering from arsenicosis but all the results were found that they experience no family problems. They were also asked about social problems; only 2.4 percent trelated that they feel some social problem such as taking arsenic free water from others' houses or are not invited to social ceremonies, but the majority of the patients, 97.6 percent, did not feel any social problems. In the case of invitations to social ceremonies 89.41 percent patients were told that they were invited toall the social ceremonies and 10.59 percent patients related that they were not invited to social ceremonies. Many of the arsenicosis patients have become socially segregated. Nobody tries to understand the fact that the diseases were not a result of any sin (Rahman Z.; 2003)

On the basis of physical problems we also observed from the table that, 45.2 percent of the total patients have no physical problems as a result of suffering from arsenicosis, and of those who feel physical problems among them 43.5 percent have problems related to walking. Again 59.5 percent patients were suffering from other physical problem like wearing clothes, eating, bathing etc and especially women have problems related to cooking, working under the sun etc.

Age, Marital Status and Education by Sex Differentials of Arsenicosis Patients

We observed from Table 4 that the arsenicosis patients of both sexes were almost the same for all ages. Female patients of age 25-60 and 60 have more arsenicosis. There was a significant trend for the prevalence rate both in relation to exposure levels and to dose ($p<0.05$) to be regardless of sex. there is a higher prevalence rate of arsenic lesions in males than females, with a clear dose-response relationship (Tondel M. et al., 1999).

According to marital status we observe that, married females have more exposure to the risk of arsenicosis than unmarried females. This may be the results of married women having more contact with the arsenic contaminated water for not only drinking but also cooking, washing and bathing purposes, than males. Again in the case of unmarried situations, males have more exposure to the risk of arsenicosis.

From Table 4 we also observed that, of the total 80 illiterate patients of arsenicosis the majority (53) patients were female. A study shows that, female arsenicosis patients were mostly illiterate.(Ahmad Sk.et al.,1999). In case of primary education, males and female patients were the same but females were very much lower in the case of secondary and higher education and out of 70 patients who had the experience of secondary or higher education, only 23 were female and the rest were male.

Effects of Arsenicosis Patients in Different Phases by Age, Sex and Their Improvement Situation

Age, Sex and Different Phase of the Patients: Age is an important indicator of the various phases of the arsenicosis patients. From Table 5 we observe that, Phase 1 is mainly observed at age 25 and age 25-60 and phase 2 is also observed in the majority number in the same group. Above age 60 arsenicosis patients were not frequent. As the clinical manifestations of arsenicosis develop after 2 to 20 years after the intake of arsenic contaminated water, so after age 15 the arsenicosis patients were frequently observed. Again from Table 6 we observed that, among male patients 44 were in phase 1 and 40 were in phase 2, out of 84 patients and out of 86 female patients 37 were found in phase 1 and 49 were found in phase 2. Hence we conclude that more female patients were observed in phase 2 and male patients were observed more in phase 1. This may be that females always intake less nutritious food than males and are more involved with arsenic contaminated water for drinking, cooking, washing and other household work. It is noted that males who showed clinical manifestations of arsenicosis in phase 1 quickly turn into phase 2.

Age, Sex and Improvement of the Arsenicosis Patients: Though arsenicosis has no specific treatment, mild cases have shown to be improved by withdrawing further intake of arsenic contaminated water and by taking good diet and vitamin A, E & C at initial and second stages of toxicity. Distribution of improvement of arsenicosis patients by age and sex are present in Table 6.

From the total 170 arsenicosis patients, we observed that in Table 6, only 1 patient was totally improved after taking the minimum treatment available and drinking arsenic free water; 101 patients were partially improved and 68 remained unchanged after taking the treatment. Among the 101 partly improved patients 41 were from age group 25 and below, 56 from age group 25-60, and only 4 patients were from above age 60. It is also observed that, out of 94 patients in the age group 25-60 and among

them 56 patients were partially improved after taking treatment, i.e.; drinking arsenic free water. Again 41 and 4 patients were partially improved from the age group 25 and below and 60+, respectively. Hence we may conclude that adult and active age group were more susceptible to improvement from arsenicosis than the older age group.

Again from Table 6 we found that, out of 84 male patients 59 were partly improved and 25 had no improvement. But in female counterparts 42 were partly improved and 43 remained unchanged out of 86 female patients. Again we see that, total 101 patients were partly improved and among them more than half (59 patients) were male and 42 patients were female. And we also observe that, only one female patient was found to be entirely improved after maintaining the treatment. Male patients were found to be partly, or more improved than females. It may be noticed that male members of the family had better and more nutritious food than females and are also more conscious about arsenic.

Arsenic Scenario at a Glance: Bangladesh

A decade has passed since the arsenic problem in Bangladesh was identified. The government, private sector and non-government organizations have developed a variety of strategies and technologies to mitigate the problem. It is high time that national progress and plans for supporting affected communities and extending mitigation are comprehensively reviewed, to ensure affected communities are supported within the shortest possible time.

Arsenic contamination in groundwater is a deadly devastation for safe water supply through pump technology in Bangladesh. It is estimated that 95% of the population relies on groundwater for drinking purposes and over a quarter of Bangladesh is affected by this new problem (DPHE/BGS/DFID, 2000). In 1993, the Department of Public Health Engineering (DPHE) traced arsenic in tubewell water in the north-eastern part of the country. Since then, the situation has been aggravated. WHO declared arsenic contamination as a 'Major Public Health Issue' in 1996 and informed the Bangladesh Government to deal with the problem on an emergency basis. The World Health Organization (WHO) revised its original guideline value for arsenic in drinking water 0.05 mg/L (WHO, 1994) to a provisional guideline value 0.01 mg/L (WHO, 1993). The level recommended by the Bangladesh Government is 0.05 mg/L (DoE, 1991).

Department of Public Health Engineering (DPHE), British Geological Survey (BGS) and Mott MacDonald Ltd. survey throughout Bangladesh revealed that 27% of the shallow tubewells are contaminated with arsenic above the level of 0.05 mg/L and 46 % of the shallow tubewells tested are contaminated with arsenic above the WHO guideline value 0.01 mg/l (ppb). Eight of the 61 sampled districts had no samples exceeding the Bangladesh standard for arsenic (0.05mg/l). It has also been found that, generally, not all tubewells in an area are affected by arsenic. However, the BGS-DPHE studies finally gave an estimation of the number of the population exposed to arsenic concentration as above 0.05 mg/l (50 ppb) and 0.01 mg/l (10 ppb) to be 35.2 million and 56.7 million respectively. Based on Upazilla statistics the exposure levels to arsenic exceeding 0.05 mg/l (50 ppb) and 0.01 mg/l (10 ppb) were estimated as 28.1 million and 46.4 million respectively. District wise percentage distribution of tubewells with arsenic contaminated water are presented in Figure 1.

Model Building and Statistical Analysis

Regression analysis is a statistical technique for investigating and modeling the relationship between variables. Applications of regression are numerous and occur in almost every field. We have a number of sample observations on population per square kilometer and contaminated tubewells per square kilometer of 52 districts, out of 64 districts in Bangladesh. The data was collected from the 2001 census of Bangladesh which was conducted by Bangladesh Bureau of Statistics (BBS). In census 2001, male and female patients were found, to be 16,624 and 13,698 respectively out of a total 30,322 patients. The number of contaminated tubewells was 1,440,409. Plotted observations (Figure 2) suggested that there is a strong statistical relationship between contaminated tubewells per square kilometer (CT/sq. km) and population per square kilometer (P/sq.km). To determine a linear relationship between the response variable Y (represented as CT/sq.km) and the regressor variable X (represented as P/sq. km), the following regression model is assumed:

$$Y = \beta_o + \beta_1 X + \varepsilon \quad \text{... (1)}$$

The simple correlation coefficient is a measure of the linear association between Y and X. We obtained the correlation coefficient between CT/sq. km and P/sq. km (r= .50) and coefficient of determination (R^2) is approximately 0.25, that is 25% of the variability in CT/sq. km (Y) is accounted for the regression model. Results in Table 7 suggest that the overall regression is highly significant ($p<10^{-7}$) indicating CT/sq. km may have a significant relationship with P/sq. km. We performed a test on individual regression coefficient (Table 7) to determine if P/sq. km has a significant influence on CT/sq. km relationship. Since the absolute value of the test statistic to (t^0=4.096) in Table 8 is greater than the true value of t (t=2.101), we may reject H_0 . $ß_1 = 0$ and calculate that P/sq. km or X, contributes significantly to the model. Thus, the fitted model in equation (1) is

CT/sq. km = -5.486+.02065 P/sq. km

The frequency distribution of the residuals is shown

as a histogram in Figure 3, which is slightly negatively skewed with mean zero and standard deviation 0.99. Also from the normal probability test (Shown in Figure 4) we may conclude that the residuals obtained from the fitted model are approximately normally distributed.

Summary and Conclusion

From this study we found that the mean age of the patients was 31.77 years. It indicates that the patients were mostly middle aged. The maximum number of patients were from the very low-income group. The patients were continuing to drink tubewells water, which is the main source of arsenic contamination. Their health condition is not so good and and they are suffering from some kind of diseases throughout the year. All the patients feel mental problems and are facing some sort of social and physical problems. Their access to mass-media is not satisfactory. Various differentials of arsenicosis patients by age, sex, education, treatment and improvement are also observed in this study. We found that female arsenicosis patients were mostly illiterate. Both married males and females ahave more exposure to the risk of arsenicosis than their unmarried counterparts. Distribution of improvement of arsenicosis patients by age showed that adult and active age group was more susceptible to improvement from arsenicosis than the older age group, and male patients were found to be more improved than females. We also observe from regression analysis that population per square kilometer (population density) has a significant effect on the arsenic contaminated tubewell per square kilometer at the country level.

The situation of arsenic contamination is aggravating fast and the number of patients is increasing tremendously. Experts fear Bangladesh is not far from an arsenic disaster if the situation stays unchanged. The damage has already been done and it will intensify over the years if measures are not taken immediately to contain it and further aggravation. Researchers, doctors, donor partners should put forward their helping hands to the government to solve this disaster. It is not a question of which country's people are suffering, it is the suffering of mankind. Everybody should come forward to save these sufferers.

Recommendation

The following steps may be recommended in view of the observed findings:

i. Proper steps should be taken to identify the arsenicosis patients with their particular disease and phase, correctly on an emergency basis.

ii. The Government should take proper action for detecting the early signs of arsenicosis on a regular basis, of the people of arsenic affected areas.

iii. Provide available equipment and medicine at health centers such that arsenicosis patients can ensure their treatment.

iv. Establish alternate sources of drinking water free from arsenic such as rain water harvesting, damaged wells reconstruction etc. and provide them with these materials at minimum cost.

v. Enhance awareness of the people through massive health education campaign.

vi. More government initiatives should be required for the mitigation of arsenic along with NGOs and also create social awareness.

References

Ahmad S.A., Bandaranayake D. Khan A.W. Hadi S.A. Uddin G. Halim A. 1997. Arsenic contamination in groundwater and arsenicosis in Bangladesh. International Journal of Environmental Health Research. Vol.7, pp. 271-276.

Ahmad S.A., Sayed M.H.S.U., Hadi S.A. Faruquee M.H. Jalil M.A., Ahmed R., Khan A.W. 1999. Arsenicosis in a village in Bangladesh. International Journal of Environmental Health Research. Vol. 9, pp. 187-195.

Bhattacharya P., Chatterjee D., & Jacks G. 1996. Option to Safeguard Groundwater from Arseniferous Aquifers in West Bengal, India. In: Pickford J. et al., Reaching the Unreached-Challenges for the 21st Century, Proceedings of the 22nd WEDC Conference, New Delhi, India, pp. 258-261.

British-Geological Survey. Groundwater Studies for Arsenic Contamination in Bangladesh. Dhaka, Bangladesh: Mott MacDonald Ltd. 1999.

Chakraborti A., Banerjee D., Ghoshal S., Barman P. 1987. Arsenical dermatitis from tube well water in West Bengal. Indian Journal of Medical Research. Vol. 85, pp. 326-334.

Das, D., Samanta, G., Mandal, B.K., 1996. Arsenic in groundwater in six districts of West Bengal, India. Environmental Geo-Chemistry and Health, Vol. 18(1).

Department of Environment (DoE), 1991. Environmental Water Quality Standards for Bangladesh. Dhaka, Bangladesh.

DPHE (Department of Public Health Engineering)/ BGS (British Geological Survey)/ DFID (Department of International Development), 2000. Groundwter Studies of Arsenic Contamination in Bangladesh. Final Report, Dhaka.

Goriar R., Chakraborty K., Pyne R. 1984. Chronic Arsenic Poisoning from Tube Well Water. Journal of the Indian Medical Association. Vol. 82, pp. 34-35.

Guha Mazumder, D.N., Chakraborty A.K., Ghose A., Gupta J.D., Chakraborty D.P., Dey S.B. and Chattopadhyay N. 1988. Chronic Arsenic Toxicity from Drinking Tube Well Water in Rural West Bengal. Bulletin of the World Health Organization, 66(4): 499-506.

Jalil M. A., Ahmed R., Khan M.A., Ahmad A. Faruquee M.H., Sayed M.H., Khan M.H. and Hadi A. 1998. Chronic Arsenicosis: Management by vitamin A, E, C Regimen. Journal of Preventive and Social Medicine. Vol. 17(1), pp.-19-26.

Kadono T., Inaoka T., Murayama N., Ushijima K., Nagano M., Nakamura S., Watanabe C., Ohtsuka R. 2002. Skin manifestations of arsenicosis in two villages of Bangladesh. International Journal of Dermatology. Vol. 41, pp. 841-846.

Khan A.W. 1997. Arsenic contamination of groundwater in Bangladesh- cause, effect and remedy. Paper presented at the training course on: Arsenic problem and de-arsination of water for use in Bangladesh. Organised by ITN, Bangladesh University of Engineering and Technology (BUET), Bangladesh.

Khan A.W. and Ahmad SK. A. 1997. Arsenic in drinking water: Health effects and management. A training manual. Department of Occupational and Public Health, National Institute of Preventive and Social Medicine (NIPSOM), Dhaka.

Momotaj H., Hussain I. 2001. "Effect of Spirulina on Arsenicosis

Patients in Bangladesh". Presentation prepared for 'arsenic in drinking water: An international Conference at Columbia University, New York, November 26-27, 2001.
Rahman Z. 2003. Arsenic victims faces social stigma. Dhaka Courier. Vol. 21, Issue 43, 23 may 2003.
Rahman Z. 2003. Well water now contaminated with arsenic. Dhaka Courier. Vol. 21, Issue-43, 9 May 2003.
Tondel M., Rahman M., Magunuson A., Chowdhry A., Faruquee M.H., Ahmad M.A. 1999. The relationship of arsenic levels in drinking water and prevalence rate of skin lesions in Bangladesh. Environmental Health Perspective. Vol. 9 pp. 187-195.
WHO, 1984. Guidelines for drinking water quality. Geneva.

Table 1. Distribution of Patients by Selected Demographic, Socio-economic and Mass Media Related characteristics

Characteristics	Frequency	Percentage
Age		
≤ 25	70	41.2
25-60	94	55.3
60+	6	3.5
Mean Age	31.77	
Median Age	30.00	
Sex		
Male	84	49.4
Female	86	50.6
3. Marital Status		
Married	118	69.4
Unmarried	42	24.7
Divorce/Widowed	10	5.9
Education		
No education	80	47.1
Primary education	20	11.8
Secondary +	70	41.2
Occupation:		
House wife	69	40.6
Student	26	15.3
Servicemen	27	15.9
Others	48	28.2
Income		
≤ 2000	139	81.8
2000-5000	24	14.1
5000+	7	4.1
Ownership of land		
Own land	75	44.1
No land	95	55.9
Electricity		
Yes	87	51.2
No	83	48.8
Source of drinking water	92	54.1
Tube-well	69	40.6
Well	1	0.6
Bill	6	4.7
Tubewell+well		
Source of cooking water	91	53.5
Tube-well	71	41.8
Well	8	4.7
Others		
Sanitation facility		
Septic tank	39	22.9
High quality hole	91	53.5
Kancha	31	18.3
Open	9	5.3
Listening Radio (Yes/No)	55/115	32.4/67.6
Watching T.V. (Yes/No)	27/143	15.9/84.1
Reading Newspaper (Yes/No)	3/167	1.8/97.6

Table 2. Distribution of Patients' by Arsenicosis Conditions, Place of Treatment and Side-effects.

Characteristics	Frequency	Percentage
Arsenicosis Stage*		
Phase 1	81	47.6
Phase 2	89	52.4
Manifestations		
Melanosis	33	19.4
Keratosis	39	22.9
Melanosis and Keratosis	9	5.3
Melanosis, Keratosis and Hyper-Keratosis	89	52.4
Duration of arsenicosis	112	65.9
≤ 5 years	51	30.0
5-10 years	7	4.1
10 + years		
Treatment place		
NGO	152	89.4
Health complex	2	1.2
Others	16	9.4
Side effects		
Diabetes	24	14.1
Blood pressure	3	1.8
Asthma	19	11.2
Heart disease	1	0.6
Malaria	7	4.1
Jaundice	6	3.5
No	110	64.7

*Phase I: Melanosis, keratosis, and conjunctivitis, Phase II: Leucomelanosis, hyperkeratosis, Phase III: hyperkeratosis with nodule (wart like lesion) in palm and sole, non-pitting edema (Swelling of feet)

Table 3. Distribution of Patients Facing Various Types of Problems.

Characteristics	Frequency	Percentage
Mental problems	168	98.8
Yes	2	1.2
No		
Social problems	4	2.4
Yes	166	97.6
No		
Invitation problems	18	10.59
Yes	152	89.41
No		
Physical problems	74	43.5
Walking	101	59.5
Other problems	70	45.2
No Problem		

Table 4. Distribution of Age, Marital Status and Education by Sex Differentials of Arsenicosis Patients

Various Characteristics	Sex		Total
	Male	Female	
Age			
≤25	39	31	70
25-60	41	53	94
60+	11	26	6
Total	84	86	170
Marital Status			
Married	55	63	118
Unmarried	28	14	42
Divorced/Widowed	1	9	10
Total	84	86	170

Educational Status	27	53	80
No Education	10	10	20
Primary	47	23	70
Secondary+	84	86	170
Total			

Table 5. Distribution of Age and Sex Related to Various Phases of the Arsenicosis.

Character-istics	Phase		Total
	Phase 1	Phase 2	
Age			
≤25	39	31	70
25-60	41	53	94
60+	1	5	6
Total	81	89	170
Sex			
Male	44	40	84
Female	37	49	86
Total	81	89	170

Table 6. Improvement of Arsenicosis by Age and Sex

Character-istics	Improvement			Total
	Complete improve-ment	Partial improve-ment	Un-changed	
Age				
≤25	1	41	28	70
25-60	0	56	38	94
60+	0	4	2	6
Total	1	101	68	170
Sex				
Male	0	59	25	84
Female	1	42	43	86
Total	1	101	68	170

Table 7. Analysis of Variance Test i.e. F Statistics for Testing H_0:ß$_1$=0

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	Test Statistic (F_0)	P-value
Regres-sion	3412.391	1	3412.391	16.786	000
Residual	10164.629	50	203.293		
Total	13577.020	51			

Table 8. Table Shows the Standard Error of Estimates and Intercepts along with t Statistic for Testing H_0:ß$_0$=0, and ß$_1$=0

Predictor	Coefficients	Standard Error	Test Statis-tic t_0	P- Val-ue
Constant	$\hat{\beta}_0$ = -5.486	5.164	-1.062	.293
Population Per square kilometer (measure as population density)	$\hat{\beta}_0$ =.02065	.005	4.097	.000

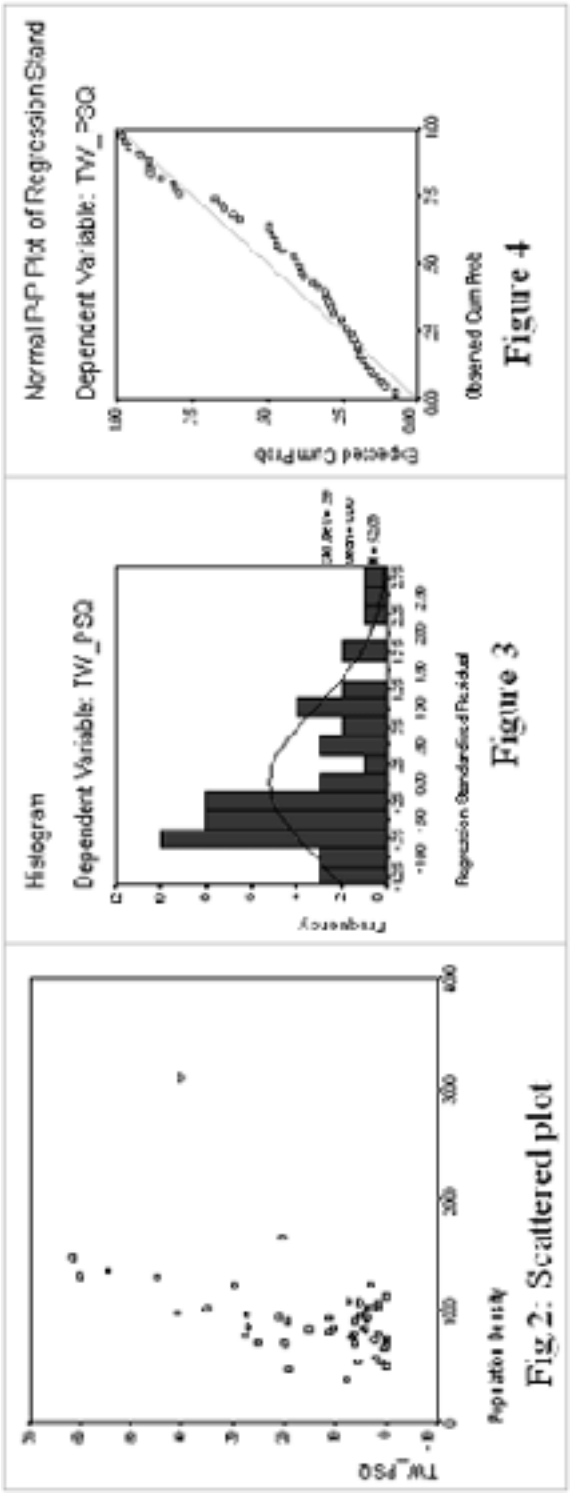

Figure 1 District Wise Percentage Distribution of Tubewells with Arsenic Contaminated Water

Effect of Depot-Medroxyprogesterone Acetate Injections on Serum Antioxidants Level

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ABSTRACT

Background: The long term use of depot medroxyprogesterone acetate injections (DMPA) may suppress the endogenous estrogen secretion, which leads to changes in plasma lipids which are associated with increased risk of atherosclerosis which may in part, be an inflammatory disease, thus circulating factors that are related to inflammation may be predictors of cardiovascular diseases.
Aim: To evaluate the effect of DMPA on the total antioxidant status, serum malondialdehyde level and other antioxidant markers such as serum uric acid, total serum bilirubin, total serum protein and serum albumin.
Study design: Prospective cohort study.
Study period: 1st January 2006 to 31st March 2007.
Subjects & Methods: A total of 30 healthy married women; their age ranged between 20-35 years, who were attending Al-Batool and Al-Khansa Family Planning Centers in Mosul, Iraq & started (for the first time) to use DMPA injection (150 mg medroxyprogesterone acetate), called "Depo-Provera" as a contraceptive. These women, called DMPA users group, were compared to another 30 healthy married women who did not use any hormonal contraceptives (non users groups). Both groups were followed for one year, during which blood samples were obtained from both groups, before starting to use DMPA, after 6 months and then after 12 months. The sera obtained from the blood samples were used for the estimation of the biochemical studied parameters using commercial kits except serum malondialdehyde which was measured by manually prepared reagents.
Results: Total antioxidant status serum level was significantly elevated after 6 months ($p = 0.023$) and after 12 months ($p = 0.003$), while serum uric acid increased significantly after 12 months of DMPA use ($p = 0.000$), among DMPA users in comparison to non-users and according to the duration of use. The DMPA caused non-significant changes in the serum malondialdehyde level and liver function in respect to the total serum bilirubin, total serum protein and serum albumin levels.
Conclusion: The DMPA injections caused a significant increase in the total antioxidant status & uric acid, but non-significant changes in the liver function.

Key words: Total antioxidants status, malondialdehyde, depot medroxyprogesterone acetate, uric acid, bilirubin, protein.

Introduction

Depot medroxyprogesterone acetate is a long acting progesterone provided as a parenteral contraceptive. It provides a very high level of contraceptive efficacy and it is effective as combined oral contraceptive pills (COCPs). It is usually given within the first 5 days of the menstrual cycle, by intramuscular injection as long acting preparations in a dose of 150 mg to provide contraception for up to 3 months period[1].

Long term use of DMPA injections may cause a reduction of menstrual blood loss, decrease risk of endometrial cancer and suppress the endogenous estrogen secretion; which leads to: reversible reduction in the bone density and changes in plasma lipids which are associated with increased risk of atherosclerosis[2]. Since atherosclerosis may in part, be an inflammatory disease, thus circulating factors that are related to inflammation may be predictors of cardiovascular diseases (CVD) in general population[3].

It is now well established that free radicals and other reactive oxygen species are continuously produced in vivo in the aging, in a wide variety of disease processes in addition to various clinical disorders with inflammatory components such as atherosclerosis[4]. Lipid peroxidation is a chain reaction providing a continuous supply of free radicals, the end product of these reaction are malondialdehyde (MDA), ethane and pentane. The MDA is still widely used in clinical chemistry laboratories to monitor oxidative stress and as an index lipid peroxidation[5].

Female hormones such as e stradiol and estriol, have been reported to have a strong inhibitory action toward lipid peroxidation and in vitro and in vivo antioxidant effects on membrane phospholipids peroxidation[6]. Massafra et

al.,[6] results strongly suggested that when plasma estradiol is restored to physiological levels in amenorrheic patients, it stimulates erythrocyte glutathione peroxidase (GSH-PX) activity while progesterone therapy did not induce significant modifications. Moreover, Massafra et al.,[7] found that there was no effect of progesterone and androgen on erythrocyte antioxidant system. On the other hand Subakir et al.,[8] found that the use of progesterone only contraceptive (Norplant or DMPA) for three months caused a significant increase of lipid peroxide.

Subjects, Materials and Methods

A total of 30 healthy married women, their ages ranged between 20-35 years (mean age ± SD) was 28.36 ± 4.14 years, mean height ± SD was 157.57 ± 3.33 cm and body mass index (BMI) for each womn < 25, who were attending Al-Batool and Al-Khansa Family Planning Centers in Mosul/ Iraq & started (for the first time) to use (DMPA) injection called "Depo-Provera" of Pharmacia NV/SA Puurs-Belgium. Each injection contains 150 mg medroxyprogesterone acetate. These women called DMPA users group, were compared to another 30 healthy married women who did not use any hormonal contraceptives and were drawn from the same population and they were considered to be the non-users groups. Both groups were followed for one year, during which blood samples were obtained from both groups, before starting to use DMPA, after 6 months and then after 12 months.

The sera obtained from the blood samples was used for the estimation of: total antioxidant status (TAS), Serum uric acid, total serum bilirubin (TSB), total serum protein and serum albumin concentrations using commercial kits, while serum malondialdehyde (MDA) concentration was measured by was estimated by method of Buege and Aust[9].

Quality Control: Two types of quality control were done:

1. External quality control: This was the only available with the TAS Kit (Randox, Cat NO.: NX 2331). This control serum was human in origin.
2. Internal Quality Control: Steps of Work: Pool of different sera was collected and divided into aliquots of 0.5 ml, transferred into small plastic tubes and kept frozen at -20°C. To determine the precision, within batch and between batches, replicates of analysis were carried out for different biochemical parameters.

The results of external quality control: These are shown in Table (1).

The result of Internal Quality Control within batch precision and between batch precision were compared with others as shown in Table (2).

The numbers between brackets represent within batch CV while the preceding value represents in between batch CV. ** The TAS, CV was compared with a local study done in Mosul by Al-Hamdani[11] who found the in between batch and within batch CV of TAS equal to 4.5% and 5.9% respectively.

Standard statistical methods were used to determine the mean, standard deviation (SD) and the range. Paired t-test was used to compare the results of various biochemical parameters among DMPA users and non-users. ANOVA Test (analysis of variance) was used to identify the variation in the different variables in relation to the duration of DMPA users group. All values quoted as the mean ± SD and a P-value of < 0.05 was considered to be statistically significant.

Table 1 Distribution of Patients by Selected Demographic, Socio-economic and Mass Media Related characteristics

Target values (mmol/l)	Range (mmol/l)	Mean Measured (mmol/l)
1.10	0.825 - 1.38	1.67

Table 2 Distribution of Patients' by Arsenicosis Conditions, Place of Treatment and Side-effects.

Parameters	Measured CV*	Desirable Precision			
		Cotlove	Young	Barnett	Tanks
Uric acid	6.92%(7.5)%	9.7	6.6	8.5	10.0
TAS	4.89%(6.3%)	Unavailable**			

Results

The (mean ± SD) age of the DMPA users was 28.36 ± 4.14 years, while the (mean ± SD) age of the non-users was 27.40 ± 4.71 years. There was no significant difference between mean ± SD height of the DMPA users (157.57 ± 3.33 cm.), and the mean ± SD height of the non users (159.30 ± 3.25 cm.), p= 0.056.

Table (3) demonstrates that the use of DMPA injection causes a significant increase in serum TAS among DMPA users in comparison with the non-users after 6 and 12 months. But there was a non-significant difference in the mean TAS of the DMPA users and non-users at the baseline time (0 month). ANOVA analysis among the DMPA users group indicated a significant (F=5.99, p=0.007) increase in the mean serum TAS (mainly after 12 months) according to the duration of DMPA injections use.

Table (4) illustrates that although there was an increase in the mean serum uric acid after 6 and 12 months among DMPA users in comparison with DMPA non-users, but only the increase after 12 months was significant. Also there was a non-significant difference in the mean serum uric acid of DMPA users and non users at baseline time. ANOVA analysis among the DMPA users group revealed a significant (F=7.79, p=0.002) increase in the mean serum uric acid (more after 12 months) among DMPA users according to the duration of DMPA injections use.

There were non significant changes in the serum MDA, total serum bilirubin total serum protein and mean serum albumin level among DMPA users in comparison to the non-users after 6 and 12 months. ANOVA analysis of the DMPA users group indicated that there were non-significant changes in the serum MDA, mean TSB, total serum protein and mean serum albumin level among DMPA users in relation to the duration of DMPA injections usage.**Table 3** Distribution of Patients Facing Various Types of Problems.

Period of use (Months)	(Mean ± SD) Serum TAS (mmol/l)		P-value
	DMPA Users (n=30)	Non Users (n=30)	
0 Month	1.807 ± 0.80 a	1.660 ± 0.579	0.604
6 Months	2.261 ± 0.44 a	1.659 ± 0.579	0.023
12 Months	2.689 ± 0.38 b	1.662 ± 0.579	0.003

Table 4 Distribution of Age, Marital Status and Education by Sex Differentials of Arsenicosis Patients

Period of use (Months)	(Mean ± SD) Serum Uric Acid (mmol/l)		P-value
	DMPA Users (n=30)	Non Users (n=30)	
0 Month	0.166 ± 0.06 a	0.251 ± 0.239	0.317
6 Months	0.195 ± 0.38 a	0.260 ± 0.063	0.505
12 Months	0.260 ± 0.06 b	0.15 ± 0.05	0.000

Discussion

The present study demonstrated that DMPA injection causes a significant increase in TAS level after 6 and 12 months of usage with a significant variation in relation to the duration of DMPA injections. To the best of THE author's knowledge no previous study has been done to assess TAS level in the DMPA injection user women and the role of progestins in antioxidant defense is still unknown. One study done by Bertrand et al.,[12], found that serum TAS level is higher in postmenopausal women after hormonal replacement therapy.

Capel et al.,[13] suggested that sex steroid may have an antioxidant activity that is mediated by an increase in erythrocyte antioxidant markers like erythrocyte (Glutathione peroxidase (GSH-PX), catalase (CAT) and superoxide dismutase (SOD)) activities progressively with duration of use which is in agreement with the present study in this point.

It is found that the physiological ovarian steroidal production during the menstrual cycle may have an important role in regulating erythrocyte GSH-PX activity but no effect of progesterone and androgen on erythrocyte antioxidant system was documented[7], and it was strongly suggested that when plasma estradiol is restored to physiological levels in amenorrheic patients, it stimulates erythrocyte GSH-PX activity while progesterone therapy did not induce significant modifications[6]. Moreover Bednarek-Tupikowska et al.,[14] found that medroxyprogesterone acetate did not influence the antioxidant action of estradiol in the postmenopausal women on hormone replacement therapy.

Malondialdehyde plasma concentrations were evaluated as an index of lipid peroxidation and peroxidative tissue injury. Determination of MDA has been used in several human studies to establish the involvement of lipid peroxidation in various disease processes[4]. Several methods have been developed to evaluate MDA in biological sample, nevertheless MDA often assayed with thiobarbituric acid (TBA) assay, which was used in this study. This method is of particular interest because of its procedural simplicity and nanomolar sensitivity[15].

The present study showed non-significant changes in the mean MDA level in the users group in comparison to the non-users and in relation to the prospective pretreatment level. This is in contrast to the study of Subakir et al.,[8] which found that the use of progesterone only contraceptive (Norplant or DMPA) for three months causes significant increase of blood concentration of lipid peroxide and significant decrease blood concentration of vitamin E. They concluded that in progesterone only contraceptive users, higher lipid peroxide and lower vitamin E concentration may cause endometrial cell damage and decrease the endometrial angiogenic response and suggested that vitamin E supplementation may counteract these unwanted side effects.

Uric acid is the end product of purine metabolism in man and it had been considered to be a metabolically inert end product without any physiological value. However, this compound has proven recently to be a selective potent antioxidant capable especially of reaction with hydroxyl radicals and hypochlorous acid[16]. In the present study, it was found that there is a significant increase in serum uric acid level after 12 months of DMPA use and a significant increase from perspective pre treatment level. In contrast to this study, it is found that hormonal replacement therapy containing medroxyprogesterone acetate did not change serum albumin and uric acid levels. Moreover medroxyprogesterone acetate did not influence the antioxidant action of estradiol[17].

Jacobs,[18] has reported that urate contributed to 35-60% of the total peroxyl radical trapping antioxidant activity in healthy subjects. Although it is difficult to assess the actual importance of any antioxidant in vivo, a significant positive correlation between serum uric acid and TAS ($r = 0.8$, $p = < 0.001$) was observed in a study done by AL-Hamdani[11] in Mosul city in Iraq, who compared TAS in type 1 and type 2 diabetic patients, and he suggested that TAS is influenced by serum uric acid levels and the decreased serum uric acid in diabetes might have an implication in diminishing the overall antioxidant capacity. In the present study a statistically non-significant correlation between TAS and uric acid ($r = 0.107$, $p = 0.964$) of DMPA users after 12 months was

found.

The present study showed that the use of DMPA injections for one year caused little but non-significant changes in the liver function in the view of TSB and serum albumin level, in spite of there being significant decrease in total serum protein after 12 months of DMPA injections usage in comparison to non-users. This was not of clinical importance since comparison of changes with their respective pre-treatment values was not statistically significant. This is in agreement with the study of Tagy, et al.,[19] , who found that the use of DMPA injections, causes a non significant change in liver function tests, and is safe and can be prescribed in cases with compensated bilharzial hepatic fibrosis with normal function.

Another study[20] on the metabolic effects of longterm use of DMPA injections, found only higher significant levels of plasma insulin, alkaline phosphatase and morning cortisol levels, but found no significant differences for other tests (including total serum bilirubin) and suggested some effects of DMPA injection on carbohydrate metabolism and liver function in long term users. In the study of Fajumi[21] on 13 serum proteins of 50 Nigerian women who received DMPA injections over a period of 18 months and 40 women as controls. The significant alterations were observed in the serum proteins that are notably synthesized by the liver, an observation consistent with the influences which gonadal hormones exert on the metabolic activities of this organ.

For many years, bile pigment (bilirubin) was considered to be only a toxic waste product formed during heme catabolism. Recent evidence, however, suggest that bilirubin acts as a potent physiologic antioxidant that may provide important protection against atherosclerosis, coronary artery diseases and inflammation and it was noted there is an inverse relationship between the presence of cardiovascular diseases and the circulating total bilirubin[22].

Conclusion

Well-organized anti-smoking programs are needed in schools health and universities in Qatar. One third of the high school students at their graduation from high school are already regular smokers as concluded from this study. This percentage is liable to increase as they begin to work and advance their academic carrier, but this percentage can be decreased if effective measures are undertaken at an early stage of school life.

References

1. Laurance DR, Bennett PN and Brown MJ. Hypothalamic pituitary and sex hormones. In: Clinical Pharmacology, 9th ed. Laurance DR, Bennett PN, Brown MJ editors. Churchill Livingstone , London 2003. pp 709-733.
2. Greenberg GM, Apgar BS. Family planning and contraception. In: family Medicine. Principles and Practice. 6th ed. Taylor RB, Dard AK, Fields SA, Philips DM, Scherger J E, editors. Springer-Verlag, USA 2003. pp 859-866.
3. Danesh J, Wheeler JG, Hirschfield GM et al., C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. The New Eng J Med 2004; 350: 1387-1397.
4. Halliwell B, Gutteridge JMC, and Gross CE. Free radicals antioxidants and human disease" where are we use now ? J lab Clin Med 1992; 119; 598-620.
5. Janero DR. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. Free Radic Biol Med 1990; 9(6): 515-540.
6. Massafra C, Buonocore G, Gioia D, Sargentini I, Farina G. Effects of estradiol and medroxyprogesterone-acetate treatment on erythrocyte antioxidant enzyme activities and malondialdehydle plasma levels in amenorrheic women. The J Clin Endocrin Metab 1997; 82(1): 173-175.
7. Massafra C, Gioia D, De-Felice. Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle. J Endocrinal 2000; 167(3): 447-452.
8. Subakir SB, Abdul Madjid O, Sabariah S, Affandi B. Oxidative stress, vitamin E and progestin breakthrough bleeding. Hum Reprod 2000: 15(3); 18-23.
9. Buege JA, Aust SD. Microsomal lipid peroxidation. In: Methods in Enzymology. Biomembranes. Part C: Biological oxidations Microsomal, Cytochrome P-450, and other hemoprotein systems. Fleischer S, Packer L editors. San Francisco London 1978; 52: 302-306.
10. Varly H, GowenLock AH, Bell M. Practical Clinical Biochemistry. William Heinemann Medical Books Ltd. London, UK 1980. pp 355-357.
11. Al-Hamdani RY. Total antioxidants and serum uric acid in diabetic patients. Ann Coll Med Mosul 2003; 29(1): 40-44.
12. Bertrand P, Starck M, Herbeth B, Vincent-Viry M, Schiele F, Siest G. Serum total antioxidant status is higher in post menopausal women and after estrogen replacement therapy. Clin Chem Lab Med 2002; 40(8): 850-852.
13. Capel ID, Jenner M, Williams DC, Donaldson D, Nath A. The effect of prolonged oral contraceptive steroid use on erythrocyte glutathione peroxidase activity. J Steroid Biochem 1981; 14: 729-732.
14. Bednarek-Tupikowska G, Tupikowski K, Bidzinska B et al., Serum lipid peroxide and total antioxidant status in postmenopausal women on hormone replacement therapy. Gynecol Endocrinol 2004; 19(2): 57-63.
15. Albro PW, Corbett JT, Schroeder JL. Application of the thiobarbiturate assay to the measurement of lipid peroxidation products in microsormes. J Bioch Biophys Methods 1986; 13: 185-194.
16. Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med 1993; 14: 615-631.
17. Bednarek-Tupikowska G, Tupikowski K, Bidzinska B, et al., Serum lipid peroxidase and total antioxidant status in postmenopausal women on hormonal replacement therapy. Gynaecol Endocrinol 2004; 19(2): 57-63.
18. Jacob RA. The integrated antioxidant system. Nut. Res 1995; 15: 755-766.
19. Tagy AH, Saker ME, Moussa AA, Kolgah A. The effect of low-dose combined oral contraceptive pills versus injectable contraceptive (Depo provera) on liver function tests of women with compensated bilharzial liver fibrosis. Contraception 2001; 64(3): 173-176.
20. Virutamasen P, Wongsrichanalai C, Tangkeo P, Nitichai Y, Rienprayoon D. Metabolic effects of depot-medroxyprogesterone acetate in long-term users: a cross-sectional study. Int J Gynecol Obstet 1986; 24(4): 291-296.
21. Fajumi JO. The effects of Depo-Provera on serum protein levels in Nigerian women. J Steroid Biochem 1984; 20(2): 581-583.
22. Schwertner HA, Jackson WG, Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary artery disease. Clin Chem 1994; 40:18-23.

Overview of Thyroid Tuberculosis

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ABSTRACT

Thyroid tuberculosis is rare, with an incidence of 0.1-0.4 % in histological specimens[1,2], but during autopsy this disease is found more often in about 2 to 7% of cases[3,4]. Diagnosis can be very challenging, since it may mimic other thyroid disorders[5]. In this article we discuss various aspects of thyroid tuberculosis.

Overview

The first case of tuberculous of the thyroid was reported by Lebert in 1862 in a patient with disseminated tuberculosis[6]. In1893, Burns described the first case of tuberculous thyroiditis which was diagnosed in a middle aged woman with a rapidly enlarging goiter, with cervical lymphadenopathy but no evidence of pulmonary tuberculosis[6]. In 1894, Schwartz reported the first successful drainage of tuberculous thyroid abscess[6]. Subsequently, in the last two decades more cases have been reported[2,5,7-18]

Thyroid tuberculosis is a rare disease with an incidence of 0.1-0.4% upon histological examination of the thyroid gland[1, 2], but when an autopsy is done, the incidence increases up to 2-7% of cases[3,4]. The reason for the disease to be rare is unknown, however, there are many hypotheses that might explain the rarity of this disease; which are

1. Presence of bactericidal thyroid colloid[1,5,19],
2. extremely high blood flow volume and excessive iodine in the thyroid[1,5,19],
3. Enhanced destruction of tubercle bacilli by increased physiologic activity of phagocytes in patients with hyperthyroidism[1,5,19],
4. Oxygenation of the thyroid tissue[20].

It can be part of generalized miliary spread to the thyroid gland, in which about seven percent of miliary tuberculosis involves the thyroid gland[10], and this spread from miliary tuberculosis to thyroid gland does not seem to cause a clinical thyroid disease[21]. It can present as a localized swelling mimicking carcinoma[6,9,10,11,12,19,22,23,24], common thyroid nodule[6,25], thyroiditis[17], acute abscess[26,27], and diffuse goiter[5,21,28]. Certain tissues are relatively resistant to tuberculous infection, so it is rare to find tubercules in thyroid, pancreas, heart and striated muscle[29].

The thyroid gland can also be involved by blood-borne or it can be introduced by direct extension from the larynx and cervical lymph nodes[10]. Diabetes mellitus, old age, malnutrition and AIDS can play a role in the occurrence of thyroid tuberculosis[20].

Most of the affected cases are middle age women[11,13,21]. Clinically, the patient might be complaining of thyroid nodule[6,25], or pressure symptoms like dyspnea[21], dysphagia[5,18], and recurrent laryngeal nerve palsy[7,30]. Local findings might mimic carcinoma[6,9,10,11,12,19,22,23,24]. Lymphadenopathy in the cervical region has been reported[2,5,11,12,13]. Signs of TB elsewhere in the body are rarely found [2,5,9,13,28]. The duration of symptoms in thyroid tuberculosis varies from 2 weeks to one year[31].

The diagnosis is rarely made clinically[32]. Most of the cases are diagnosed either post-operatively or at autopsy[13]. To diagnose Tuberculous of the thyroid gland Seed[33] required 3 conditions to be met and they are: a necrotic or abscessed gland, AFB within the thyroid gland, and the demonstration of a definitive tuberculous focus outside the thyroid gland. If the first two criteria are met, the third criterion is not essential[34]. The bacteriologic and histological testing is usually diagnostic[34].

Thyroid tests are usually normal[35], though myxedema[27] and hyperthyroidism[5,15,21] have been reported.

To establish the diagnosis, fine needle aspiration cytology (FNAC) has been used[2,5,11,12,13,16]. Epithelioid granuloma and necrosis, with or without Langhan's giant cells and lymphocytes are seen in the FNAC specimen[13]. If cytology from FNAC is negative, then cervical lymph nodes sampling may provide evidence of TB[2,5].

Ultrasound evaluation of subacute granulomatous thyroiditis shows moderate enlargement of the thyroid gland, with multiple small hypoechoic areas[36]. Contrast enhanced CT scan for patients with tuberculous involvement of the thyroid gland, may show a characteristic necrotic center and peripheral enhancement of cold abscess[37,38,39]. CT or MRI scan can help to detect the signs of compression caused by an abscess from

tuberculous thyroiditis[32].

Regarding treatment, (though most of the reported cases had surgery[35,40], the principle treatment is with antituberculous medication[9,20], and treatment of tuberculous thyroiditis should not differ from the other forms of the disease, and it involves the administration of two or three effective antituberculous (isonized, pyrazinamide, rifampicin, ethambutol), and it should be given for at least six months[14]. If the patient was diagnosed pre-operatively, the antituberculous drugs should be given before and after surgery[41]. If there is tuberculous abscess, then drainage is sufficient and surgery is rarely required[20]. Repeated puncture drainage and anti-TB medication are the least invasive modes of treatment[42].

Conclusion

Tuberculosis of the thyroid gland is a very rare disease. It can mimic thyroid carcinoma. Fine needle aspiration cytology can help in making the diagnosis. The mainstay of treating tuberculous thyroiditis is the use of antituberculous medications.

References

1. Rankin FW, Graham AS. Tuberculosis of the thyroid gland. Ann Surg 1932:96:625.
2. Das DK, Pant CS, Chachra KL, et al. Fine needle aspiration cytology diagnosis of tuberculous thyroiditis. A report of eight cases. Acta cytol 1992:36:517.
3. Sanehi S, Chandrashekhar D, Chaudhary N, et al. Primary thyroid tuberculosis. Indian J. Otolaryngol. Head Neck Surg. (April-June 2007) 59, 154-156.
4. Simkus A. Thyroid tuberculosis. Medicina (2004) Vol. 40, No. 3 - http//medicina.kmu.lt.
5. Khan EM, Haque I, Pandey R, et al. Tuberculosis of the thyroid gland: A clinicopathological profile of four cases and review of literature. Aut N Z J Surg 1993:63:807.
6. Balasarkar D, Dhareswar J, Satoskar RR, Awsare N, Mahey R, Kumar V. Primary Thyroid Tuberculosis. Available from: URL: http://www.bhj.org/journal/1999_4102_apr99/ CASE333.HTM.
7. Emery P. Tuberculous abscess of the thyroid with recurrent laryngeal nerve palsy: case report and review of literature. J Laryngol Otol 1980:94:553-8.
8. Tan KK. Tuberculosis of the thyroid gland- a review. Ann acad Med Singapore 1993:22:580-2.
9. Lioté HA Spaulding C, Bazelly B, Milleron BJ, Akoun GM. Thyroid tuberculosis associated with mediastinal lymphadenitis. Tubercle 1987;68:229-31.
10. Magboo ML, Clark OH. Primary tuberculous thyroid abscess mimicking carcinoma diagnosed by fine needle aspiration biopsy. West J Med 1990;153:6579.
11. Takami H, kozakai M. Tuberculous thyroiditis: report of a case with review of the literature. Endocr J 1994; 41:743-7.
12. Winkler S, Wiesinger E, Graninger W. Extrapulmonary tuberculosis with paravertebral abscess formation and thyroid involvement. Infection 1994; 22:4202.
13. Mondal A, Patra DK. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculosis of the thyroid gland: a study of 18 cases. J Laryngol Otol 1995;109:36-8.
14. Orlandi F, Fiorini S, Gonzaatto I, Saggiorato E, Piavano G, Angeli A, et al. Tubercular involvement of the thyroid gland: a report of two cases. Hor Res 1999:52:291-4.
15. Kapoor VK, Subramani K, Das SK, Mukhopadhyay AK, Cattopadhyay TK. Tuberculosis of the thyroid gland with thyrotoxicosis. Postgrad Med J 1985; 61:339-40.
16. Garg SK, Ganapathy V, Bandhopadhya PK, Gupta SK, Dash RJ. Pyrexia of unknown origin as a rare presentation of tuberculous thyroiditis. Indian J Chest All Sci 1987; 29:52-5.
17. Sachs MK, Dikinson G, Amazon K. Tuberculous adenitis of the thyroid mimicking subacute thyroiditis. Am J Med 1988; 85:573-5.
18. Allan R, O'Flynn W, Clarke SEM. Tuberculosis of the thyroid bed presenting as recurrent medullary thyroid carcinoma. Tubercle 1990; 71: 301-2.
19. Bahadur P, Bhatnagar BNS, Aurora AL, et al. Tuberculous abscess of thyroid gland. Indian Journal of Tuberculosis 1983; 30:33.
20. El Malki HO, El Absi M, Mohsine R, et al. La Tuberculose de la thyroide. Diagnostic et traitement. Ann Chir 2002; 127:385-387.
21. Coller FA, Huggins CB. Tuberculosis of the thyroid gland. Ann Surg 1926; 84: 804-20.
22. Crompton GK, Cameron SJ. Tuberculosis of the thyroid gland mimicking carcinoma. Tubercle 1969; 50:61-4.
23. Pramar H, Hasmi M, Rajput A, Patankar T, Castillo M. Acute tuberculous abscess of the thyroid gland. Australasian Radiology 2002; 46(2):186.
24. Unnikrishman AG, Koshy GR, Rajaratnam S, Seshadri MS, Sarada V. Suppurative neck abscess due to tuberculous thyroiditis. J Assoc Physicians India 2002; 50:610-1.
25. Svahn A, Petrini B, Skedinger M. A lump in the thyroid gland can be tuberculosis. Lakartidningen 1991; 88 (8):625.
26. Goldfarb H, Schifrin D, Graig FA. Thyroiditis caused by tuberculous abscess of the thyroid gland. Am J Med 1965; 38:82-8.
27. Johnson AG, Phillips ME, Thomas RJS. Acute tuberculous abscess of the thyroid gland. Br J Surg 1973; 60:668-9.
28. Barnes B, Weatherstone R. Tuberculosis of the thyroid : two case reports. Br J Dis Chest 1979; 73:187-91.
29. Corton R.S., Kumar V., Robbins S.L. In Robbins Pathological basis of disease, 5th edition, 1994. W.B. Saunders Company U.S., pp 326 and 82.
30. Bilgin G, Hasanoglu A, Cakir B, et al. Tuberculosis of the thyroid with vocal cord paralysis: a report of a case. Kocatepe Tip Dergisi 2005 (May); 6:67-69.
31. Pandit AA, Joshi AS, Ogale SB, Sheode JH. Tuberculosis of thyroid gland. Ind J Tub 1997; 44:205-7.
32. Tas A, Yagiz R, Karasalihoglu A. Thyroid gland tunerculosis with endolaryngeal extension: a case with laryngotracheal dyspnoea. The J of Laryngol Otol 2005 (Jan); 119, pp. 54-56.
33. Seed L. Tuberculosis of the thyroid gland. In: Goldburg's clinical tunerculosis. 2nd ed. Philadelphia : F.A. Davis; 1939.
34. Chung SY, Oh KK, Chang HS. Sonographic findings of tuberculous thyroiditis in a patient with Behcet's syndrome. J Clin Ultrasound; 2002 (Mar/Apr):30:3: 184- 88.
35. Al-Mulhim AA, Zakaria HM, Abdelhadi MS, et al. Thyroid tuberculosis mimicking carcinoma: report of two cases. Surg Today 2002; 32:1064-67.
36. Gritzmann N, Koischwitz D, Rettenbacher T. Sonography of the thyroid and parathyroid glands. Radiol Clin North Am 2000; 38:1131.
37. Kang BC, Lee SW, Shim SS, et al. US and CT findings of tuberculosis of the thyroid : three case reports. Clin Imaging 2000; 24:283.
38. Kim YJ, Kim DJ, Sung KJ, et al. Tuberculous abscess of the thyroid gland : a case report of CT demonstration. Journal of the Korean Radiological Society 1996; 34:201.
39. Moon WK, Han MH, Chang KH, et al. CT and MR imaging of head and neck tuberculosis. Radiographics 1997; 17:391.
40. 40- Oklah A, Al-kaisi N. Thyroid tuberculosis : a case report. JRMS 2005(June); 12 (2): 60-62.
41. Berger SA, Zonzein J, Vllamena P, Mittman N. Infectious diseases of the thyroid gland. Rev Infect Dis 1983; 5:108-122.
42. Intarasupht N, Hunsapinyo K, Rajatanavin R. Treatment of tuberculous thyroiditis with repeated puncture drainage and antituberculous medications. Intern Med J Thai 2003; 19: 48-51.

Pulmonary Mycobacterium Kansasii Infection in a Cardiac Transplant Recipient with Invasive Pulmonary Aspergillosis

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Case Report

Infection is one of the major clinical determinates of survival among solid organ transplant recipients. Nontuberculous Mycobacterial (NTM) infections have been previously reported to occur in a handful of cardiac transplant patients, but none of whom had underlying pulmonary aspergillus. We report the first case of such an infection in a cardiac allograft recipient with invasive pulmonary aspergillosis.

A seventy one year old man who had undergone cardiac transplantation in January 2000 because of alcoholic cardiomyopathy, developed dyspnea, nonproductive cough and generalized weakness in January 2004. He denied associated fever, chills, rash, arthralgia or myalgia. His postransplantation course was complicated by right lower lobe nodule secondary to aspergillosis on August 2000. He was treated with Amphotericin B and maintained on lifelong prophylaxis with Itraconazole. His current immunouppressive regimen includes prednisone 10 mg po daily, cellcept 250 mg po daily and prograf 1.5 mg po bid. His examination was essentially unchanged from his prior evaluations and notable for hepatomegaly and intentional tremor. His laboratory testings were unremarkable except for a chest x-ray that showed new multifocal nodular opacities in both lung fields as compared to that done in December 2003. The patient was placed in respiratory isolation, started on Voriconazole intravenously, as well as oral isonizide, rifampin, ethambutol and pyrazinamide. Chest CT scan confirmed the presence of bilateral nodules. He underwent bronchoscopy that showed yellowish nodules in the upper airway bronchi and transbronchial biopsies stained positive for acid fast. The bronchoalveolar lavage fluid smear was acid fast positive and the DNA probe showed mycobacterium Kansasii . During therapy, the patient had elevated liver transaminases so rifampin was stopped and his antimicrobial course changed to isoniazid, ethambutol, clarithromycin. A one-month follow-up CT scan of the chest revealed significant decrease in the size of nodules.

NTM infection is extremely rare in cardiac transplant patients- only 23 cases have been identified worldwide(1, 2). Unfortunately, the exact incidence, predisposing factors and the optimal therapeutic regimens are unknown. Our case, similar to most of the reported cases, occurred late after transplant, responded favorably to antimicrobial therapy, and did not seem to affect long-term survival. However, unlike others, our patient had a history of invasive pulmonary aspergillosis more than three years ago. This raises the question of whether Aspergillus fumigatus is a predisposing factor for subsequent NTM infection among solid transplant recipients.

Simpson et al. reported an association between norcardiosis and future development of NTM among cardiac transplant patients(3). The mechanism behinds this potential association is unclear but may be a reflection of poor immune response system in this subset of patients. NTM should be considered as a potential pathogen of infection in the late post-transplantation period especially if the recipients have prior history of norcardiosis and possibly aspergillus infection.

References

1. Patel R, Roberts GD, Keating MR et al. Infections due to Nontuberculous Mycobacteria in kidney, heart and liver transplant recipients. Clin Infect Dis. 1994 Aug;19(2):263-73.
2. Novick RJ, Moreno-Cabral CE, Stinson EB et al. Nontuberculous mycobacterial infections in heart transplant recipients: A seventeen-year experience. J Heart Transplant. 1990 Jul;9(4):357-63.
3. Simpson GL, Raffin TA, Remongton JS. Association of prior norcardiosis and subsequent occurrence of nontuberculous mycobacteriosis in a defined immunosuppressed population. J Infect Dis. 1982 Aug;146(2):211-9.