

# ME-JAA

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#### Chief Editor:

Abdulrazak Abyad MD, MPH, AGSF,  
AFCHS  
Email: aabyad@cyberia.net.lb

#### Publisher:

Ms Lesley Pocock  
medi+WORLD International  
572 Burwood Road,  
Hawthorn, Vic Australia 3122  
Phone: +61 (3) 9819 1224:  
Fax: +61 (3) 9819 3269  
Email: lesleypocock@mediworld.com.au

#### Editorial enquiries:

aabyad@cyberia.net.lb

#### Advertising enquiries:

lesleypocock@mediworld.com.au

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## Editorial

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**Author**

**Dr Abdulrazak Abyad**

Chief editor

This issue of the journal discussed various topics from human resources development to child abuse. A paper from Iran looked at Spirituality in Iranian community. The study was carried out to explore spirituality and spiritual coping strategies in institutionalized adolescent girls. The findings of the study provide in-depth understanding of Iranian institutionalized adolescent girls' experiences of spirituality and spiritual strategies in coping with stress which can be useful for nurses and other health care professionals for adolescents specially institutionalized adolescents. The findings can provide a framework for nursing care plans based on teaching spiritual coping strategies to decrease stresses of living in institutes.

A study from Bangladesh looked at mathematical model to marriage migration associated with distance of Comilla district in Bangladesh. In this study an attempt has been given attention to show that the polynomial model is also applicable to the same data set. It is found that marriage migration associated with distance follows polynomial model. To verify the stability of the model, cross validity prediction power is employed to the model.

Hasan M , Uddin T et Khan AR investigated the scenario of human resource development along with its different factors those affect the capacity utilization of the plant as well as dominate the expected production level. The authors used some statistical techniques they have shown that setting up training program can increase the skillness of employees.

A paper from Bangladesh looked at the effect of working status of Bangladeshi women on the decision of age at marriage and fertility in Bangladesh using national representative data from Bangladesh Demographic and Health Survey (BDHS), 2003-2004, allowing for the existence of observed characteristics that affect both age at marriage and fertility.

## Aging May Be The Major Determiner Factor of Excess Weight

**Authors:**

**Mehmet Rami Helvaci\*, Hasan Kaya\*\*, Cahit Ozer\*\*\***

\*Medical Faculty of the Mustafa Kemal University, Antakya, Assistant Professor of Internal Medicine, M.D.

\*\*Medical Faculty of the Mustafa Kemal University, Antakya, Professor of Internal Medicine, M.D.

\*\*\*Medical Faculty of the Mustafa Kemal University, Antakya, Assistant Professor of Family Medicine, M.D.

**Correspondence:**

**Mehmet Rami Helvaci, M.D.**

Hospital of the Mustafa Kemal University

31100, Antakya, Turkey

E-mail: mramihelvaci@hotmail.com

Tel : +903262140649

Fax: +903262148214

### ABSTRACT

**Background:** As a major health problem, prevalence of excess weight is increasing in the world.

**Methods:** Consecutive patients at and above the age of 20 years were taken into the study to permit growth of height in youngsters.

**Results:** The study included 1068 cases (628 females) totally. Due to the small number of cases, 20 cases only, in the ninth decade, they were not included for statistical comparison. There were only 19 (1.7%) cases with underweight and 307 (28.7%) with normal weight, so 69.4% (742) of cases at and above the age of 20 years had excess weight. The prevalence of excess weight was 28.7% in the third but 63.6% in the fourth decades indicating a more than two-fold increase ( $p < 0.001$ ). The prevalence continued to increase, and it was 78.4% in the fifth, 83.1% in the sixth, and 87.0% in the seventh decades. After the seventh decade, it started to decrease, and it was 78.5% in the eighth ( $p < 0.05$ ) and 60.0% in the ninth decades of life.

**Conclusion:** Prevalence of excess weight is increasing by decades particularly in the fourth decade, and this increase turns to a decrease in the eighth decade. So 30th and 70th years of age may be breaking points for weight gaining, and aging may be the main determiner factor for excess weight. Probably decreased physical and mental stresses after the age of 30 years and debility and comorbid disorders induced restrictions after the age of 70 years may be the major causes for the changes.

**Key words:** Aging, excess weight.

### Introduction

As a major health problem, prevalence of excess weight is increasing all over the world since it is a well known entity that excess weight causes a high cost on physical health even in early decades. The foremost physical consequences of excess weight are impaired glucose tolerance or type 2 diabetes mellitus (DM), dyslipidemia, white coat hypertension or hypertension (HT), and coronary heart disease (CHD)(1,2). Persons with excess weight have a higher prevalence of elevated blood pressure (BP) than lean persons, and well-known complications of HT are left ventricular

hypertrophy, CHD, heart failure, chronic renal failure, and stroke(3). Similarly, atherogenic dyslipidemia is commonly seen in cases with excess weight, and it is characterized by increased levels of triglycerides (TG) and/or low density lipoprotein cholesterol (LDL-C), or a decreased level of high density lipoprotein cholesterol (HDL-C) in serum(1). On the other hand, excess weight is accompanied by a large number of coagulation and fibrinolytic abnormalities suggesting that it induces a prothrombotic and proinflammatory state(4).

The slow-rate chronic inflammation is characterized

by lipid-induced injury that initiates invasion of macrophages followed by proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity(5-8). As a supporting evidence of the role of inflammation in atherosclerosis, elevations of serum C-reactive protein (CRP) carry predictive power for the development of major cardiovascular events(9,10). In particular, excess weight is considered as a strong factor for controlling of circulating CRP concentrations because adipose tissue is involved in the regulation of cytokines(11), so individuals with excess weight have elevated levels of CRP(12). Furthermore, excess weight is highly correlated with dietary intake of increased calories and fat, both of which have been linked to several types of cancer including breast, colon, and prostate(13,14). So excess weight is associated with an increased risk of all-cause mortality(15). We tried to understand any effect of aging on excess weight here.

## Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumrupinar University on routine check up patients between August 2006 and March 2007. Consecutive patients at and above the age of 20 years were taken into the study to permit growth of height in youngsters. Their medical histories including smoking habit, HT, DM, dyslipidemia, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), TG, HDL-C, LDL-C, and an electrocardiography was performed. Current daily smokers, at least for a period of last 12-month, and cases with a history of at least five pack-years smoked were accepted as smokers. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by the measurements of the same physician in stead of verbal expressions. Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI of lower than 18.5, normal weight as 18.5-24.9, overweight as 25-29.9, and obesity as a BMI of 30.0 kg/m(2) or greater(1).

Cases with an overnight FPG level > 126 mg/dL on two occasions or already taking antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 100 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level 200 mg/dL or higher is DM(1). Additionally patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations for defining dyslipidemic subgroups(1). Dyslipidemia is diagnosed when LDL-C is 160 or higher and/or TG is 200 or higher and/or HDL-C is lower than 40 mg/dL. Office blood pressure was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hour. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after a 10-minute educa-

tion about proper BP measurement techniques(16).

The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5-minute in the seated position before measurement. An additional 24-hour ambulatory blood pressure monitoring (ABP) was not required due to an equal efficacy of the method with HBP measurement to diagnose HT(17). Eventually, HT is defined as a BP of 135/85 mmHg on HBP measurements(16). A stress electrocardiography was performed in suspected cases, and a coronary angiography was obtained only for the stress electrocardiography positive cases.

Eventually, patients with underweight, normal weight, overweight, and obesity were detected in each decade, and prevalences of them were compared between the decades. Student t-test was used as the method of statistical analysis.

## Results

The study included 1068 cases (628 females and 440 males) totally. Due to the small number of cases, 20 cases only, in the ninth decade, this cases were not included for statistical comparison. There were only 19 (1.7%) cases with underweight and 307 (28.7%) with normal weight, so as a very high prevalence, 69.4% (742) of cases at and above the age of 20 years had excess weight. The prevalence of cases with normal weight was 64.6% in the third decade, and it decreased gradually but significantly until the seventh decade of life ( $p < 0.05$  nearly in all steps), and then it started to increase again and reached up to 30.0% in the ninth decade again (Table 1).

Similarly, the prevalence of obesity was increased gradually but significantly and reached up to 43.7% in the sixth decade ( $p < 0.05$  nearly in all steps), and then initiated to decrease again. In another word, prevalence of excess weight increased from 28.7% in the third to 87.0% in the seventh decade, and then decreased to 78.5% in the eight and 60.0% in the ninth decades of life. On the other hand, prevalences of HT, DM, and CHD continued to increase by aging without any break, whereas prevalence of dyslipidemia decreased in the eight decade parallel to the decreased prevalence of cases with excess weight significantly (Table 2).

## Discussion

Recent studies have revealed that adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin, which are closely related to the development of complications(18,19), so it is important in medical terms to specify the excess weight not only as one of the risk factors, but as 'obesity disease'. For example, the cardiovascular field has recently shown great interest in the role of inflammation in the development of atherosclerosis and numerous recent epidemiological studies have indicated that inflammation plays an important role in the pathogenesis of atherosclerosis and thrombosis(6-8), and obesity is considered a strong factor for controlling of the circulating CRP concen-

**Table 1:** Characteristic features of the study cases

Variables	Third decade		Fourth decade		Fifth decade		Sixth decade		Seventh decade		Eight decade		Ninth decade
Number	181		157		246		249		108		107		20
Prevalence of smoking	11.0% (20)	*	32.4% (51)		28.8% (71)		31.7% (79)		23.1% (25)		23.3% (25)		15.0% (3)
Prevalence of underweight	6.6% (12)	†	1.9% (3)		0.4% (1)		0.0% (0)		0.0% (0)		0.9% (1)		10.0% (2)
Prevalence of normal weight	64.6% (117)	*	34.3% (54)	*	21.1% (52)		16.8% (43)		12.9% (14)	†	20.5% (22)		30.0% (6)
Prevalence of overweight	24.3% (44)	*	42.0% (66)		45.9% (113)	†	39.3% (98)		46.2% (50)		40.1% (43)		25.0% (5)
Prevalence of obesity	4.4% (8)	*	21.6% (34)	*	32.5% (80)	*	43.7% (109)		40.7% (44)		38.3% (41)		35.0% (7)

\*p<0.001 †p<0.05

**Table 2:** Associated diseases of the study cases

Variables	Third decade	Fourth decade	Fifth decade	Sixth decade	Seventh decade	Eight decade	Ninth decade
Prevalence of hypertension	0.0%	5.0%	10.4%	20.4%	31.4%	38.3%	40.0%
Prevalence of diabetes mellitus	0.5%	1.9%	11.7%	21.6%	25.0%	26.1%	10.0%
Prevalence of dyslipidemia	6.6%	26.7%	31.7%	38.9%	39.8%	20.5%	35.0%
Prevalence of coronary heart disease	0.0%	0.0%	3.6%	12.8%	22.2%	24.2%	35.0%

trations because adipose tissue is involved in the regulation of cytokines(11). On the other hand, individuals with excess weight will have an increased circulating blood volume as well as an increased volume of cardiac output, thought to be the result of increased oxygen demand of the extra body tissue. The prolonged increase in circulating blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of HT.

The relationship between the excess weight and HT is also described under the heading of the metabolic syndrome. In addition to the HT, the prevalences of high FPG, high serum total cholesterol, and low HDL-C, and their clustering were all raised with increases in BMI(20). Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with a higher risk of arrhythmias, cardiac failure, or even sudden cardiac death. So the above prospective cohort study showed that the BMI is one of the independent risk factors for stroke and CHD (20). Similarly, the incidences of CHD and stroke, especially ischemic stroke, have increased with an elevated BMI in other studies(21). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increases throughout the range of moderate and severe excess weight both for men and women in all age groups(22).

Similarly, the prevalences HT, DM, and CHD increased gradually and significantly from the third towards ninth decades of life here (p<0.05 nearly in all steps), but interestingly and parallel to the decreased prevalence of excess weight in the eight decade, the prevalence of dyslipidemia decreased after the seventh decade, and it decreased from 39.8% to 20.5% in the eighth decade of life (p<0.001), which may indicate a direct relationship between the dyslipidemia and weight excess.

Although the all-known consequences of excess weight on health, its prevalence is increasing in the world with unknown reasons. We saw in this study that the prevalence of excess weight was 28.7% in the third but was 63.6% in the fourth decades indicating a more than two-fold increase in prevalence (p<0.001). The prevalence continued to increase, and it was 78.4% in the fifth, 83.1% in the sixth, and 87.0% in the seventh decades. After the seventh decade, it started to decrease, and it was 78.5% in the eighth (p<0.05) and 60.0% in the ninth decades of life. So 30 and 70 years of age were the breaking points of life for weight gaining. So aging may be the main determiner factor for excess weight. Probably decreased physical and mental stresses after the age of 30 years and debility and comorbid disorders induced restrictions on diet after the age of 70 years may be the major causes for the changes of body weight at these ages.

As a conclusion, although the already known consequences of excess weight on health, nearly three-fourths of cases above the age of 30 years have excess weight, and the prevalence of excess weight is increasing by decades particularly in the fourth decade, and this increase turns to a decrease from the eighth decade of life. So 30th and 70th years of age may be the breaking points of life for weight gaining, and aging may be the main determiner factor for excess weight. Probably decreased physical and mental stresses after the age of 30 years and debility and comorbid disorders induced restrictions after the age of 70 years may be the major causes for the changes of body weight at these ages.

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## Effectiveness of Antifungal Agents in Tissue Conditioners in Treating Candidiasis Over Time

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**Authors:**

**Dr. C.K.W. Chow**

Faculty of Dentistry, University of Toronto  
Faculty of Dentistry,  
University of Toronto,  
124 Edward Street,  
Toronto, Ontario,  
Canada M5G 1G6  
Tel: (416) 979-4574 ext. 3108  
Fax: (416) 979-4936  
email: Clara.chow@utoronto.ca

**Dr. D.W. Matear**

Senior Advisor  
Health Policy and Regulation  
Health Authority Abu Dhabi  
PO Box 5674  
Abu Dhabi, United Arab Emirates  
Tel.: +971 2 419 3612  
Fax.: +971 2 444 4728  
Cell: +971 50 721 6443  
email: dmatear@gahs.ae

**Dr. H.P. Lawrence**

Associate Professor, Faculty of Dentistry,  
University of Toronto  
124 Edward Street  
Toronto, Ontario  
Canada M5G 1G6  
Tel: (416) 979-4908 ext. 4492  
Fax: (416) 979-4936  
email: herenia.lawrence@utoronto.ca

**Helen Grad**

Senior Lecturer, Faculty of Dentistry, University of Toronto  
124 Edward Street  
Toronto, Ontario  
Canada M5G 1G6  
Tel: (416) 979-4901 ext. 4360  
Fax: (416) 979-4963  
email: h\_grad@hotmail.com

### ABSTRACT

*Candida albicans* infection is a primary cause of chronic atrophic candidiasis. Candidiasis is especially prevalent in the institutionalized denture wearers, many of whom have reduced manual dexterity and reduced compliance. In a recent in vitro study<sup>1</sup>, antifungal agents were mixed with tissue conditioners to explore the efficacy of this method of drug delivery.

**Objective:** The present in vitro study is a continuation of the previous experiment, to investigate the effectiveness of the antifungal and tissue conditioner combinations over time.

**Design:** Combinations of nystatin, fluconazole, itraconazole and Coe Soft, FITT were mixed at 5%wt/wt with sterilized saliva. 6mm diameter cores were punched in Sabouraud plates pre-grown with standardized *C. albicans*. Antifungal agents plus tissue conditioner mixtures were injected into each core. Inhibition diameters were measured until a plateau is reached. The cores were then transplanted into a fresh set of pre-grown *C. albicans* plates and the inhibition diameters were measured for 3 days. This step was repeated for a second transfer.

**Results:** Inhibition measurements agreed with results obtained in the previous study<sup>1</sup> that itraconazole groups had significantly better fungicidal properties than nystatin and fluconazole (ANOVA,  $p < 0.05$ ) and confirmed the time of peak effect. The average peak effect of 20.7mm was registered at 2.7 days. The average fungicidal activity of all combinations reduced to a minimal level of 3.2mm at 8.2 days. There was a rise in inhibition diameter following the first transplant; whereas a plateau followed the second transfer. All combinations had inhibition effects that changed significantly (ANOVA,  $p < 0.05$ ) over time.

**Conclusion:** The peak fungicidal activity of antifungal agent and tissue conditioner combinations reached after 3 days suggests that the combinations should be replaced at that time in a clinical trial to follow. If a single combination is placed and not subsequently replaced, it is advisable to remove the tissue conditioner

within 9 days when there is negligible fungicidal effect.

**Keywords:** tissue conditioner, antifungal agents, denture stomatitis, Candidiasis, drug delivery, nystatin, fluconazole, itraconazole.

## Introduction

The prevalence of Chronic Atrophic Candidiasis has been studied extensively, since it is a common and treatable condition especially in the elderly. The prevalence ranges from 11-67% in complete denture wearing populations.<sup>2</sup> Candidiasis is a major problem especially for institutionalized denture wearers, many of whom have reduced manual dexterity, cognitive control, memory loss and reduced compliance. Chronic atrophic candidiasis can be classified as Newton Type I-localized erythematous, Type II-generalized erythematous, and Type III-hyperplastic granular, with severity of inflammation greatest in Type III patients.<sup>3</sup> It may be associated with burning mouth syndrome, xerostomia and immunocompromised diseases. Candidal infection and ill fitting dentures are the primary causes of oral Candidiasis.<sup>4</sup>

Currently, two types of treatment methods are employed to ameliorate the condition, use of topical antifungal agents or use of tissue conditioners within an existing prosthesis. In a recent *in vitro* study<sup>1</sup>, antifungal agents were mixed with tissue conditioners to explore the efficacy of this method of drug delivery. The major advantage of this type of therapy is that it does not rely on patient compliance. Different combinations of tissue conditioners and antifungal agents were mixed at different weight concentrations and fashioned into cores placed in the centre of agar dishes containing cultured *Candida albicans* in the *in vitro* study<sup>1</sup>. The recorded inhibition diameters demonstrated that this method of treatment is efficacious. The most effective combinations were 5%wt/wt itraconazole in Coe Soft and in FITT. Peak fungicidal activity was achieved after 3 days. To what extent the fungicidal effect continues beyond this point, remained unclear. It was important to clarify this point before progressing to the clinical trial stage, as it would help in developing the research methodology. Thus, the present study is a continuation of the previous *in vitro* study<sup>1</sup>, with the objective to investigate the effectiveness of the antifungal and tissue conditioner combinations over time.

## Methods

### *Candida albicans*

Clinical isolates of the yeast *C. albicans* were used as the test organism for antifungal activity.

*C. albicans* ATCC 10231, obtained from Mt. Sinai Hospital, Toronto, was cultured as described by Thomas and Nutt.<sup>5</sup> In brief, yeast was grown on a stock plate at 37°C and incubated for 3 days. 2mm<sup>3</sup> of the stock culture was then transferred and diluted with 2ml saline. 0.2ml of the diluted solution was mixed with 1.8ml of saline. This step was repeated to obtain a 10<sup>-3</sup> solution. The number of cultures per ml of 10<sup>-3</sup> solution was counted with a Petrof-Hausser counter. 1000 organisms per ml was accepted as the standard inoculum concentration.

### Mixing antifungal agents with tissue conditioners

0.1ml of 10<sup>-3</sup> solution was dropped on each sterile Sabouraud agar plate and was spread out using a spreading rod. The plates were incubated at 37°C for 72 hours at humidity of 75%. 6mm diameter holes (cores) were punched in the centre of each 5mm deep agar plate. Nystatin, fluconazole and itraconazole were chosen as the test antifungal agents. These agents are commercially known as Mycostatin<sup>TM</sup> (Bristol-Meyer Squibb), Diflucan<sup>TM</sup> (Pfizer) and Sporanox<sup>TM</sup> (Janssen Ortho), respectively. Nystatin was supplied in a yellowish oral suspension containing 100,000 Units per ml. Fluconazole was supplied in white oral suspension powder and when reconstituted it yields a 10mg per ml solution. However in this study, fluconazole powder for oral suspension was not reconstituted with water. Instead, the powder was used directly from the container. Itraconazole was supplied in a clear yellowish oral suspension which contained 10mg per ml.

The tissue conditioners tested were Coe Soft<sup>TM</sup> (Coe Laboratories) and FITT<sup>TM</sup>(Kerr). These tissue conditioners were mixed according to manufacturer's instructions. Antifungal agents were hand mixed into the tissue conditioners at 5 wt/wt% (i.e. 0.95g base + 0.05g antifungal agent). A disposable syringe was used to inject each antifungal agent and tissue conditioner mixture into the cores. The amount injected and time of injection were recorded for each plate.

Each antifungal and tissue conditioner combination was repeated three times. These combinations include mixtures of nystatin, fluconazole, or itraconazole at 5 wt/wt% with Coe Soft, or Fitt, with sterilized saliva.<sup>1</sup>

The caliper used for the measurement of the inhibition diameter was standardized with a standard error of 0.1mm. Only the largest inhibition diameter reading ("raw data") was taken for each plate. Maximum inhibition diameter was calculated by subtracting the core diameter (6 mm) from the raw data.

### Plate Transfers

Inhibition diameters were recorded until the inhibition diameter had reached a plateau. This was also the stage when the antifungal agents reached their peak activity. The cores were then transplanted into a fresh set of agar plates (also known as Transfer 1 plates). Petrof-Hausser counter was used to ensure that Transfer 1 plates had standardized amount of *C. albicans* pre-grown on it as with the first set of plates. As well, they had a 6mm hole punched in the centre as previously. After the first transfer, the inhibition diameters were recorded daily as before. Three days after the first transfer, the cores were transferred again to a new set of pre-grown *C. albicans* plates (Transfer 2 plates). These Transfer 2 plates were observed for another 3 days to investigate the fungicidal capability of the cores over time. Therefore, the plates were incubated for 11 days in total. Inhibition diameters were measured at hours 15, 24, 39, 48, 72, 135, 159, 183, 207, 231, and 255.

**Statistical Analysis**

One-way ANOVA and the Tukey Studentized range test were used to compare the inhibition diameters at the time of peak and minimal effect. Repeated-measures ANOVA was used to compare the inhibition diameter of different combinations of antifungal agents and tissue conditioners over time. Statistical tests were two-tailed and at the 5% significance level.

**Results**

The statistical tests found significance (ANOVA  $p < 0.05$ ) in inhibition diameter measurements with different antifungal and tissue conditioner combinations.

**Most Effective Combination**

The most effective combinations was itraconazole in Coe Soft (mean inhibition diameter of 17.6mm, Table 1) followed by itraconazole and FITT (17.1mm) but the difference is not significant (ANOVA,  $p < 0.05$ ). They were significantly better (ANOVA,  $p < 0.05$ ) than the fluconazole and nystatin groups at all time points with the exception at 135hr. At this time point, itraconazole in Coe Soft was significantly better (ANOVA,  $p < 0.05$ ) than all groups, whilst itraconazole in FITT was not significantly different (ANOVA,  $p < 0.05$ ) from nystatin in Coe Soft or nystatin in FITT. Fluconazole and nystatin combinations had mean inhibition diameters that ranged from 6.1mm to 7.9mm. Nystatin and FITT had the least mean inhibition diameter and was significantly different from the other combi-

nations (ANOVA,  $p < 0.05$ ) (Table 1).

**Peak Activity**

Average peak activity of all combinations was 20.7mm recorded at 63.5 hours (i.e. 2.7 days) (Table 2). At the peak, both itraconazole groups were significantly better (ANOVA,  $p < 0.05$ ) than all other combinations. Fluconazole in Coe Soft had significantly higher antifungal activity (ANOVA,  $p < 0.05$ ) than fluconazole in FITT and nystatin in Coe Soft. Nystatin in FITT had the least fungicidal activity (Table 2).

**Least Activity**

The least effect of a combination is the inhibition diameter recorded at time of lowest fungicidal activity. In studying the groups daily for 11 days, least effect was registered at approximately 196 hours (i.e. 8.2 days). The average effect at that time was 3.2mm (Table 3). As well, there was no significant difference between FITT and Coe Soft combinations at the time of least effect.

**Transfer #1**

The itraconazole group had higher inhibition results throughout this first transfer period (Figure 1). At the end the first transfer period (183hr), the itraconazole group (10.0mm) and nystatin in FITT (8.0mm) had significantly higher fungicidal activity (ANOVA,  $p < 0.05$ ) than the other groups. There was a rise in inhibition diameter following the first transplant (135-183hr). (Figure 1).

**Table 1:** Mean Inhibition Diameter by Repeated Measures ANOVA

TREATMENT GROUP	Mean (mm)	95% Confidence Interval (mm)
Itraconazole + Coe Soft	17.6A*	17.1-18.1
Itraconazole + FITT	17.1A	16.6-17.6
Fluconazole + Coe Soft	7.9B	7.4-8.3
Fluconazole + FITT	7.6B	7.1-8.0
Nystatin + Coe Soft	7.4B	6.9-7.8
Nystatin + FITT	6.1C	5.6-6.6

\*Means with the same letter are not significantly different according to the Tukey test.

**Table 2:** Time and Inhibition Diameter at Peak Effect

Treatment Group	Peak Inhibition Diameter (mm)	95% Confidence Interval (mm)	Peak time(hr)	95% Confidence Interval (hr)
Itraconazole + Coe Soft	32.7A*	31.2-34.1	64A	29.6-98.4
Itraconazole + FITT	31.3A	29.9-32.8	61A	13.7-108.3
Fluconazole + Coe Soft	19.7B	18.5-21.1	64A	29.6-98.4
Fluconazole + FITT	16.0C	13.5-18.2	48A	48.0-48.0
Nystatin + Coe Soft	14.3C	12.9-15.8	72A	72.0-72.0
Nystatin + FITT	6.1C	8.9-11.8	72A	72.0-72.0
Average of Combinations	20.7	16.4-25.1	63.5	57.3-69.7

\*Means with the same letter are not significantly different according to the Tukey test.

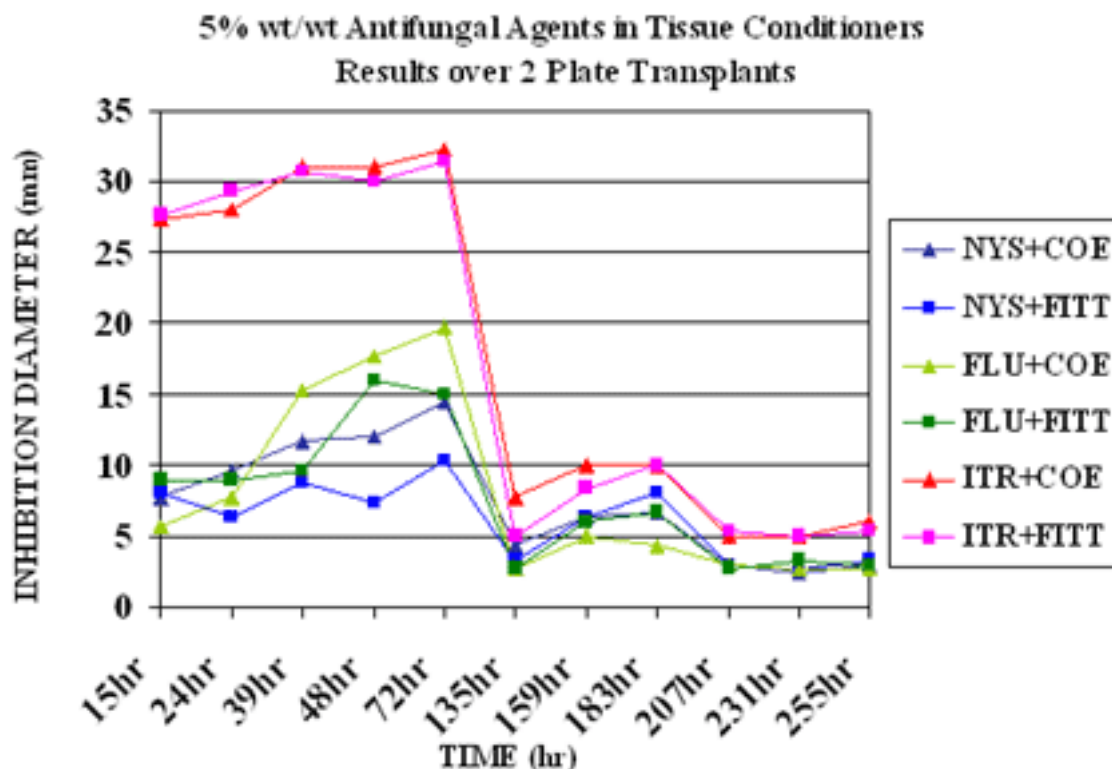
**Table 3:** Time and Inhibition Diameter at Minimum Effect

Treatment Group	Minimum Inhibition Diameter (mm)	95% Confidence Interval (mm)	Time to Reach Minimum Effect (hr)	95% Confidence Interval (hr)
Itraconazole + Coe Soft	4.7A*	3.2-6.1	215A	180.6-249.4
Itraconazole + FITT	4.7A	3.2-6.1	159A	55.74-262.3
Nystatin + FITT	2.7B	1.2-4.1	191A	66.9-315.1
Fluconazole + FITT	2.3B	0.9-3.8	159A	55.7-262.3
Fluconazole + Coe Soft	2.3B	0.9-3.8	231A	171.4-290.6
Nystatin + Coe Soft	2.3B	0.9-3.8	223A	188.6-257.4
Average of Combinations	3.2	2.6-3.8	196	175.8-216.9

\*Means with the same letter are not significantly different according to the Tukey test.

**Fig. 1** Inhibition diameters of combinations of the antifungal agents and tissue conditioners: at 5%wt/wt with saliva.

Mean inhibition diameter ranged from 2.3mm at 231 hours for nystatin in Coe Soft to 32.3mm at 72 hours for itraconazole in Coe Soft. Itraconazole had greater fungicidal activity than fluconazole and nystatin. Optimal inhibition was achieved at approximately 63.5 hours followed by a drop. There is a slight rise after the first transplant (135-183 hours) and a plateau after the second transplant (207-255 hours).



**Transfer #2**

In contrast to transfer 1, there was no slight rise in inhibition activity; rather there was an immediate plateau (Figure 1). For instance, itraconazole in FITT had inhibition diameter of 5.3mm, 5.0mm, 5.3mm at 207hr, 231hr and 255hr, respectively. The itraconazole group had the highest inhibition results (6mm for itraconazole in Coe Soft at 255hr). Similar to the itraconazole group, fluconazole in FITT was also significantly better (ANOVA,  $p < 0.05$ ) than the other groups at 231 hours.

**Interaction between antifungal activity and time**

As shown from the time versus inhibition diameter figure (Figure 1), all combinations exhibited different fungicidal activity at different times (ANOVA,  $p < 0.05$ ). For example, fluconazole in Coe Soft showed some inhibitory effect before 72 hours,

although not as high as itraconazole, but exhibited the lowest effect of all combinations after the plates were transferred.

**Discussion**

In the previous study<sup>1</sup>, the most effective antifungal agent and tissue conditioner combination and the optimum concentration were found. All treatment group combinations had greater fungicidal activity than negative controls (i.e. tissue conditioner only) and comparable inhibition diameters to positive controls (i.e. antifungal agents alone). The peak fungicidal activity was also noted.<sup>1</sup> However, there was a need to explore the long term effectiveness of the mixtures, which has not previously been investigated by other studies.

The purpose of the current study was to examine the timing of peak activity and subsequent effects by means of transferring cores to fresh agar plates so that an initial protocol may be derived for a pilot study. In the preceding study<sup>1</sup>, continued fungicidal activity could not be explored due to lack of fresh *C. albicans* in the area immediate to the core.

The plate transfer technique allowed the exhibition of continued fungicidal activity by means of having fresh *C. albicans* around the core. The kinetic flow characteristics of the antifungal are then controlled for, because any new activity can be readily measured. The rationale for adding sterilized saliva to the cores was to serve as a standard protocol for a controlled comparison of the antifungals used. 5% wt/wt was tested as it was the best concentration of antifungal agents in tissue conditioner found in the previous study<sup>1</sup>.

Comparing the combinations at this percentage enabled contrast of effectiveness of antifungal agent mixed in the base; as oppose to only comparing effectiveness of antifungals agents alone.

Oral suspensions of the antifungal agents were selected as in the previous study. The observation period totaled 11 days. The core was first transferred after a peak in antifungal activity was registered.

In concurrence with the previous *in vitro* study<sup>1</sup>, itraconazole combinations had significantly higher antifungal activity than fluconazole and nystatin groups. The most effective combination was itraconazole in Coe Soft with a mean time adjusted inhibition diameter of 17.6mm (Table 1).

FITT combinations reached the peak faster than combinations with Coe Soft, but the difference in time was not significant. The average peak of all combinations was reached at 63.5 hours. There was a rise in inhibition diameter throughout the period following the first transfer. Conversely, there was no obvious rise in inhibition results after the second transfer. These results reflect continual antifungal activity up to approximately two days after the first transfer followed by a plateau after the second transfer. The mean least effect of all combinations was 3.2mm and the mean time of least effect was recorded at 196 hours, followed by a plateau (Table 3, Figure 1). This mean inhibition diameter result was similar to results obtained by testing the negative control (tissue conditioners only) of 3.1mm in the previous *in vitro* study<sup>1</sup>. The fungicidal activity declined in the second transfer and this trend demonstrated a loss of fungicidal activity after 9 days.

### Conclusion and Recommendation of a Pilot Study

Inhibition diameters recorded in this study, confirmed that itraconazole groups had significantly higher fungicidal properties than fluconazole or nystatin. The peak effect was achieved after approximately 3 days. Both of these findings agreed with results of the previous study<sup>1</sup>.

From the plateau of antifungal activity observed after the second transfer, it can be concluded that antifungal agent and tissue conditioner cores were effective up to 9 days after placement. Consequently, it is ideal to replace the antifungal agent

and tissue conditioner combinations after 3 days when the peak activity has been reached. It is also advisable to remove the tissue conditioner within 9 days after which there is little fungicidal effect, if a single combination is placed and not replaced subsequently.

The *in vitro* results recorded in this study further support the efficacy of mixing antifungal agents into tissue conditioners as a method of drug delivery. The tissue conditioner method of drug delivery has the advantages of being cheaper than conventional therapy and can simultaneously relieve candidal infection and traumatized denture bearing tissues. In addition, it is not dependent on patient cooperation, which is most beneficial in the institutionalized setting.

The results of this study will be incorporated into a clinical protocol in a pilot study to evaluate the effectiveness of this modality of drug delivery.

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## Bone Mass Density In Diabetic Women: Is There A Detrimental Effect?

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**Author:**

*Khalda Al-Zaabi \**

*Hanan E. Badr\*\**

*Suad Mahussain\**

*Masoud Mohammad\**

*Naheel Al - Nafisi\**

*Department of Nuclear Medicine, Al-Amiri Hospital, Kuwait\**

*Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait \*\**

*Department of Family Health, High Institute of Public Health, Alexandria University, Egypt \*\**

**Correspondence:**

**Hanan El-Sayed Badr**

Department of Community Medicine and Behavioral Sciences

Faculty of Medicine, Kuwait University

P.O. Box 24923 Safat

13110 Kuwait

### ABSTRACT

**Objective:** The aim of this study was to assess bone mass density (BMD) values in diabetic female patients and to determine the prevalence of osteoporosis among them.

**Methods:** A convenience sample of 210 Kuwaiti females with type 2 diabetes mellitus, aged 40-79 years were selected after excluding those with current or previous histories of any condition that can alter the BMD values. An age matched group of 655 non-diabetic healthy Kuwaiti women were selected after confirming the same exclusion criteria and they represented the control group. Bone mass measurements were performed by dual-energy X-ray absorptiometry (DXA) machine at the lumbar spine (L2-L4) and femur (neck and total hip). Body size measurements and lifestyle issues were asked about.

**Results:** There were no significant differences of the BMD values or the prevalence of osteoporosis between the diabetic and the non-diabetic women. On multivariate analysis, weight showed a dominant significant constructive effect in both groups. In the non diabetic group each kg of body weight had a change of 0.6%, 0.5% and 0.7% of the spine femur neck and total hip BMD respectively. In the diabetic group, each kg of body weight showed a significant change by 0.2% and 0.3% in the femur region (neck and total hip respectively) only.

**Conclusion:** Women with type 2 DM showed no significant difference either in BMD values or osteoporosis prevalence from non-diabetic women. The aggravating factors of BMD were more apparent among the diabetic women than the non-diabetic group and vice versa.

**Key words:** Bone Mineral Density, Diabetes Mellitus, Osteoporosis.

### Introduction

Osteoporosis is a bone disorder that is characterized by low bone mass, increased bone fragility and consequently increased fracture risk. It usually remains asymptomatic and does not become clinically evident until there is a fracture. The World Health Organization (WHO) defines osteoporosis in terms of bone density measurements of postmenopausal white females compared to young adult mean<sup>(2)</sup>. Although white

women are most often affected, women of all races and all ethnic groups are susceptible to osteoporosis and fractures. As the population growth and aging increases all over the world, osteoporosis is becoming an important public health problem with its great significant economic and social impact. Therefore it is important to identify population at increased risk of developing osteoporosis<sup>(2)</sup>.

## Material and Methods

### Materials:

The study was carried out at the department of nuclear medicine in Amiri Hospital, Kuwait. We recruited 210 Kuwaiti females known to have type 2 DM referred from different primary care centers to the nuclear medicine department from March 2002 till October 2005.

We excluded females with one or more of the following conditions that may modify the BMD picture such as chronic diseases of the liver, kidney, heart, malabsorption syndrome, cancer or history of chemotherapy or radiation therapy; endocrine problems such as prolonged secondary amenorrhea, hyperthyroidism, hyperparathyroidism; connective tissue diseases like rheumatoid arthritis; history of oophorectomy or hysterectomy before menopause; females taking drugs known to alter bone metabolism were also excluded for example steroids, bisphosphonates, hormone replacement therapy, estrogen receptor modulators, anticonvulsants, thyroxin, calcium and vitamin D.

Non-diabetic age-matched Kuwaiti females who pursued the above mentioned exclusion criteria were invited within the same period of the study to volunteer as a control group. The total number of the eligible control sample was 655 healthy Kuwaiti females.

### Methods:

All diabetic and non-diabetic females were asked to complete an anonymous structured questionnaire during their visits after obtaining their verbal consent. This questionnaire was designed to include some personal and reproductive data like age, age of menarche, age of menopause, parity and duration of lactation. Complete medical and drug history, life style habits such as smoking, daily consumption of caffeine, daily dairy intake and practicing physical exercise were also asked about. Diabetic women were inquired about the duration of diabetes, and modality of anti-diabetic treatment.

BMD was measured at the lumbar spine (L2-L4) and the dual proximal femur (neck and total femur) using dual-energy X-ray absorptiometry (DXA) machine which is a GE Lunar-Prodigy densitometer (GE Medical Systems, Madison, WI, USA) provided with enCore™ 2004 software (version 8.10.027). Daily quality assurance measurement was done using spine phantom to ensure the precision of the machine. The in vivo precision of error measurements, expressed as coefficient of variation, were 1.5% for the lumbar spine, 2% for the femur neck and 1.8% for the total femur. This was assessed by duplicate measurements on 30 patients' representative of our clinic patient's population with repositioning the patients after each scan.

Standard positioning was used for anterior-posterior scan of the lumbar and the dual proximal femur. The BMD was expressed as g/cm<sup>2</sup> and standard deviations (SD) from the young adult normal mean (T-score) and from the age-matched mean adjusted to body weight (Z-score). These values were compared to the Middle East Reference Population supplied by the

manufacturer. Using the World Health Organization (WHO) criteria for defining osteoporosis when the T-score values is at or less than -2.5 SD, osteopenia when the T-score values between -1 SD and -2.5 SD and normal when T-score is at or above -1 SD (2,36).

### Data analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) version 13. Mean and standard deviation (SD) were calculated for different continuous variables. Student-t test, chi square test, Univariate analysis of variance and Z test to compare between two proportions were used to examine the statistical differences between diabetics and non-diabetics. Univariate and multiple linear regression analysis were used to determine the predictors for the change in BMD separately in diabetics and non-diabetics. The level of significance was  $p < 0.05$  and Confidence Interval (CI) was 95%.

### Results

The study involved 210 diabetic women and 655 non diabetic women in the age range of 40-79 years with a significantly different mean age of about 59 and 55 years respectively as shown in table 1. Obesity was significantly higher among the diabetic group. The mean BMI of both groups were 33 and 30 respectively, where 30.5% of diabetics and 37.9% of non diabetics were overweight (BMI= 25-29.9) and 65.7% and 48.9% respectively were obese (BMI  $\geq$  30). The daily consumption of caffeine and dairy products were significantly less likely to be consumed among diabetic women than non diabetic women.

On the other hand, the later group practiced exercise significantly more than the former group. Regarding parity and lactation, the table illustrated that diabetic women had significantly more pregnancies than non diabetic women (about 6 and 4 pregnancies respectively) but with a significant shorter duration of lactation (7 and 9 months respectively). In the diabetic women, the mean duration of the DM was  $11.99 \pm 8.6$  years with a range of 0.1-40 years. Oral hypoglycemic medications were the line of treatment of most of them (65.2%) while insulin injection was experienced by 16.2%. The rest of the diabetic sample (18.6%) was following both lines of treatment. The majority of diabetic and non-diabetic women reached menopause (86.4% and 82.7% respectively).

The mean spine and femoral region (neck and total hip) BMD in different decades were illustrated in table 2. There was no significant difference between the two groups regarding BMD values in different areas and age groups.

Although the prevalence of spine, femoral neck, and total hip osteoporosis was higher among the diabetic women than the non diabetic group but this difference was not statistically significant as shown in table 3.

The influence of age, height, weight and lifestyle factors on BMD was investigated by univariate and multiple regression analysis separately among diabetics and non diabetic women. The results of multiple regression significant influencing factors were illustrated in table 4. Age was a dominant significant injurious factor in all regions (spine, femur neck and total hip)

in both groups. There was an annual decrease ranged from 0.7% - 0.9% of BMD in diabetic women and 0.6% & 0.8% in non diabetic females.

Weight showed a dominant significant constructive effect in the non diabetic group as each kg of body weight had a change of 0.6% of the spine BMD, 0.5% of neck BMD and 0.7% of total hip BMD. In the diabetic group, each kg of body weight showed a significant change by 0.2% and 0.3% in the femur region (neck and total hip respectively) only.

Height showed a significant influence only in the femur neck BMD of the diabetic group where each cm of body height has 0.3% change of femur neck BMD. On the level of univariate analysis, height showed significant influence in spine BMD and total hip BMD in diabetic women ( $\beta$  0.004,  $p=0.05$ , CI: 0.000 – 0.008 and  $\beta$  0.004,  $p=0.04$ , CI: 0.000 – 0.008 respectively). In the non diabetic group it confirmed also significant effect in spine BMD ( $\beta$  0.005,  $p<0.0001$ , CI: 0.003 – 0.007), femur neck BMD ( $\beta$  0.005,  $p<0.0001$ , CI: 0.003 – 0.006) and total hip BMD ( $\beta$  0.003,  $p=0.002$ , CI: 0.001 – 0.005) but its effect was masked when other variables entered the equation of the multivariate analysis.

Table 4 also pointed out the detrimental effect of parity on spine BMD of both groups. Each pregnancy decreased the spine BMD by 1% among diabetics and 1.5% in the other group. On the other hand, lactation drew attention to its negative effect on spine BMD among diabetics only where each month of lactation decreased spine BMD by 0.4%. On the level of univariate analysis, the harmful effect of parity and lactation were obvious in the diabetic women on the femur neck

BMD ( $\beta$  -0.01,  $p=0.002$ , CI: -0.002 to -0.004 and  $\beta$  -0.005,  $p=0.001$ , CI: -0.008 to -0.002 respectively). Also they showed the same pattern in the total hip BMD ( $\beta$  -0.01,  $p=0.006$ , CI: -0.017 to -0.003 and  $\beta$  -0.006,  $p=0.001$ , CI: -0.009 to -0.002 respectively). In the non diabetic group, lactation showed no effect on BMD in all regions on the level of univariate or multivariate analysis. Parity illustrated its injurious outcome on the neck BMD in the univariate analysis only ( $\beta$  -0.007,  $p=0.013$ , CI: -0.012 to -0.001) but its effect disappeared in the multivariate analysis.

The duration of illness with diabetes mellitus called attention to its border line significant negative effect barely on the spine BMD just on the level of univariate analysis ( $\beta$  -0.002,  $p=0.05$ , CI: -0.005 to 0.000).

In the non diabetic women, the influence of daily consumption of dairy products demonstrated its positive effect on the femur region BMD (neck:  $\beta$  0.054  $p=0.01$ , CI: 0.013 - 0.096 and total hip:  $\beta$  0.049,  $p=0.035$ , CI: 0.003 - 0.094) in the univariate analysis. Practicing exercise also showed a significant constructive effect on the neck BMD merely in the univariate analysis ( $\beta$  0.037,  $p=0.032$ , CI: 0.003 - 0.071). But their supremacy was masked by the influence of other more prevailing factors when entered the multivariate analysis model. These factors showed no significant effect in the diabetic women in both levels of univariate or multivariate analysis.

Smoking and caffeine consumption showed no significant effect on BMD in any area in both groups of women either in univariate or multivariate analysis.

**Table 1.** General characteristics of the diabetic and non-diabetic females included in the study.

Variables	Diabetic women n=210	Non-diabetic women n=655	p
Age			
Mean (SD)	58.7 (8.6)	54.8 (7.8)	<0.0001 <sup>a</sup>
BMI	33.3 (6.7)	29.7 (4.2)	<0.0001 <sup>a</sup>
Smoking (yes %)	3.3	1.5	NS <sup>b</sup>
Using caffeine (yes %):	75.5	66.9	<0.05 <sup>b</sup>
Mean (SD) cups/day	1.6 (1.6)	2.1 (1.4)	<0.01 <sup>a</sup>
Dairy products (yes %):	82.9	84.2	NS <sup>b</sup>
Mean (SD) cups/day	1.3 (0.9)	1.6 (0.9)	<0.0001 <sup>a</sup>
Exercise (yes %):	16.7	28.4	<0.01 <sup>b</sup>
< one hour/wk	80.0	27.6	<0.0001 <sup>b</sup>
≥ one hour/wk	20.0	72.4	
Parity			
Mean (SD)	5.7 (3.0)	4.3 (2.8)	<0.0001 <sup>a</sup>
Lactation (yes %):	76.2	68.3	<0.05 <sup>b</sup>
Mean months (SD)	6.7 (6.7)	8.8 (10.4)	<0.05 <sup>a</sup>

<sup>a</sup> Student-t test

<sup>b</sup> Chi square test

NS: not significant ( $p>0.05$ )

## Discussion

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing person to an increased risk of fracture<sup>(1)</sup>. The clinical relevance of osteoporosis related to type 2 DM is less acknowledged. Until now no consensus has been reached on osteoporosis risk in people with type 2 DM due to inconsistent findings among researchers. They have

reported lower, equal and greater bone mass in type 2 diabetics relative to non-diabetics subjects<sup>(7, 9-33)</sup>.

The present study showed that BMD values of women with type 2 DM were not significantly dissimilar to the control healthy women in all measured regions (spine, femur neck, and total hip). In addition the prevalence of osteoporosis among women with type 2 DM was not significantly different from

**Table 2.** Mean (SD) of BMD in different body areas in diabetic (n=210) and non diabetic women (n=655) according to age.

Variables	40-49	50-59	60-69	70-79	Total
Spine					
Diabetics	1.248 (0.16)	1.118 (0.15)	1.027 (0.18)	0.977 (0.15)	1.087 (0.18)
Non diabetics	1.165 (0.16)	1.105 (0.16)	0.973 (0.16)	0.941 (0.15)	1.086 (0.18)
Neck					
Diabetics	0.980 (0.12)	0.933 (0.14)	0.847 (0.12)	0.726 (0.13)	0.885 (0.15)
Non diabetics	0.958 (0.12)	0.931 (0.13)	0.811 (0.11)	0.721 (0.10)	0.902 (0.14)
Total femur					
Diabetics	1.047 (0.12)	1.043 (0.15)	0.932 (0.13)	0.797 (0.14)	0.976 (0.16)
Non diabetics	1.015 (0.13)	1.005 (0.14)	0.893 (0.12)	0.812 (0.13)	0.974 (0.15)

No significant difference was found between diabetic and non diabetic women regarding BMD in different body areas in all age groups by univariate analysis of variance.

**Table 3.** Prevalence of osteoporosis in different body areas in diabetics and non diabetics

Variables	Diabetics n=210 n(%)	Non diabetics n=655 n(%)	p
Spine	18 (8.6)	44 (6.7)	NS
Neck	10 (4.8)	17 (2.6)	NS
Total femur	5 (2.4)	8 (1.2)	NS

NS: not significant (p>0.05) by using Z test to compare between two proportions.

**Table 4.** Multiple regression analysis of significant factors associated with BMD in different body areas in diabetics and non diabetics

Variables	Diabetics (n=210)		Non diabetics (n=655)	
	β	CI	β	CI
Spine				
Age	-0.007	-0.010 to -0.004 <sup>a</sup>	-0.006	-0.010 to -0.003 <sup>b</sup>
Weight			0.006	0.003-0.009 <sup>a</sup>
Parity	-0.010	-0.018 to -.002 <sup>c</sup>	-0.015	-0.028 to -0.003 <sup>c</sup>
Lactation	-0.004	-0.007 to 0.000 <sup>c</sup>		
Neck				
Age	-0.008	-0.011 to -0.006 <sup>a</sup>	-0.008	-0.011 to -0.005 <sup>a</sup>
Weight	0.002	0.001-0.003 <sup>b</sup>	0.005	0.002-0.007 <sup>a</sup>
Height	0.003	0.000-0.006 <sup>c</sup>		
Total femur				
Age	-0.009	-0.011 to -0.006 <sup>a</sup>	-0.008	-0.011 to -0.004 <sup>a</sup>
Weight	0.003	0.002-0.004 <sup>a</sup>	0.007	0.004--0.009 <sup>a</sup>

a p<0.0001, b p<0.01, c p<0.05

- Predictors of diabetics were age, height, weight, smoking, consuming caffeine, consuming dairy products, practicing exercise, parity, lactation, duration of disease, type of treatment.
- Predictors of non diabetics were age, height, weight, smoking, consuming caffeine, consuming dairy products, practicing exercise, parity and lactation.

the healthy control group. No significant differences were found between the two groups even when further adjustments were made for other possible confounders. Our results confirm the findings of previous studies that reported similar BMD in type 2 DM to healthy subjects<sup>(7, 24-26)</sup>. Touminen J et al. examined the BMD of only proximal femur with DXA machine of 68 type 2 diabetic females on insulin treatment and found out that the BMD levels of the diabetic women did not differ significantly from the control group<sup>(7)</sup>. Also Sosa M et al. reached

for the same findings in 46 type 2 diabetic females where the lumbar spine BMD values were measured by DXA and QCT techniques<sup>(26)</sup>. Wakasugi M et al found same results on 78 diabetic patients (40 females and 37 males) by measuring the lumbar spine by DXA machine<sup>(25)</sup>. Weinstock RS et al showed also similar findings on 28 type 2 diabetic females by using dual photon absorptiometry<sup>(24)</sup>.

On the other hand, this study' findings contradicted earlier

observations of higher and lower BMD in type 2 DM patients reported by other investigators<sup>(9-23, 27-33)</sup>. These discrepancies may be explained by methodological differences or by using the old non-sensitive techniques used to measure bone density such dual photon absorptiometry. For example Isaia G et al used dual photon absorptiometry of the lumbar spine and found that the bone mineral content (BMC) was lower in 40 type 2 diabetic women on dietary and/or oral treatment than the age-matched non-diabetic women<sup>(27)</sup>. Also Gregorio F et al, reported reduced BMC in 60 well-controlled and 50 poorly controlled type 2 diabetic patients on oral hypoglycemic drugs as compared to 50 healthy controls<sup>(27)</sup>. Furthermore Guven M et al observed that the BMD values of the lumbar spine and the femur region were also lower in 100 type 2 diabetic patients (57 females and 43 males) than the control group by using DXA machine<sup>(30)</sup>. Al-Maatouq et al assessed the BMD of lumbar spine and femur neck using DXA machine of 104 postmenopausal type 2 diabetic women and found lower BMD values of the diabetic women as compared to the controlled group<sup>(31)</sup>.

Several researchers however had reported higher bone mass in type 2 diabetic patients relative to non-diabetic control subjects<sup>(9-23)</sup>. For example Kao WH et al found that type 2 diabetic Mexican-American women in 600 subjects from 34 families have higher BMD at the hip and spine compared to their non-diabetic counterparts<sup>(17)</sup>. Schwartz AV et al also reported high BMD values in 657 women with type 2 DM; 101 of them were on insulin treatment. Hanley DA et al found higher BMD at the lumbar, femur neck and trochanter regions in 347 females and 182 males with type 2DM<sup>(13)</sup>. Dennison EM et al reported high BMD at the spine and proximal femur in newly diagnosed diabetic subjects consisting of 444 females and 465 males<sup>(14)</sup>. van Daele PL et al also demonstrated increased BMD at the lumbar spine and proximal femur in 243 men and 335 women with non-insulin-dependant DM<sup>(11)</sup>. Sahin G et al found significantly higher levels of BMD at the lumbar and femoral regions in the diabetic postmenopausal females compared to the control group<sup>(19)</sup>. Rakie V et al reported high BMD at the forearm, total hip and femoral neck regions in 194 patients with type 2 DM women vs. control subjects<sup>(23)</sup>. Kwon DJ et al found that the BMD at the lumbar vertebrae was slightly higher in 185 diabetic females as compared to control group<sup>(29)</sup>. Gredhem P et al reported high BMD values at the lumbar and femur neck in 74 women with type 2 DM<sup>(16)</sup>.

Another output of this study was that obesity was significantly higher among diabetic females. Type 2 DM is generally associated with obesity, which is considered one of the risk factors for the development of this disease<sup>(37)</sup>. Increased body weight has been associated with an increased bone mass in both normal and diabetic individuals and may account for the relative protection seen in patients with type 2 DM<sup>(38)</sup>. A higher body weight may influence BMD through a variety of mechanisms, including higher mechanical loading on weight-bearing bones, estrogen synthesis in adipose tissue, higher levels of sex hormones and their precursors, and lower bone turnover<sup>(39)</sup>. In several studies a significant relationship was found between BMD and BMI in type 2 diabetic population<sup>(30, 18)</sup>.

On the other hand, although obesity was prevalent more among diabetic women than non-diabetics, but its protective

effect was apparent and noticeable among the non-diabetics than diabetics (it was almost 3 times in non-diabetics) as indicated by the multivariate analysis.

Another point was the diabetes status, as the univariate analysis illustrated negative effect of the duration of diabetes on BMD but this was masked in the multivariate analysis. This is in congruence of the study results of Wakasugi M et al who reported that BMD in 78 diabetic subjects was inversely correlated with age and duration of the diabetes<sup>(25)</sup>. These might be explained by presence of suggested detrimental role of type 2 DM as a known catabolic status on several body parts that are capable of including bone metabolism. The existence of other confounders (e.g. obesity) might disguise the real picture of BMD.

Our findings showed that age, parity, lactation and duration of the disease had significant negative effect on spine BMD in type 2 diabetic patients. This is in concordance with Kwon et al who showed also that age, duration of diabetes and duration of menopause among the risk factors for decreased BMD in 185 females with type 2 DM<sup>(29)</sup>. In addition Guven M et al also found that age, duration of diabetes and sex were additional risk factors for developing of bone loss in 100 diabetic subjects<sup>(30)</sup>. However, Weinstock RS et al did not find any significant relation between duration of diabetes and BMD in 28 diabetic females<sup>(24)</sup>.

## Conclusion

Women with type 2 DM showed no significant difference either in BMD values or osteoporosis prevalence from non-diabetic women. The aggravating factors of BMD were more apparent among the diabetic women than the non-diabetic group and vice versa. Further studies are recommended on larger scale to unravel the ambiguous results of different studies regarding the actual consequence of type 2 DM on bone metabolism and BMD values.

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## Review of what's new in Alzheimer's disease?

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**Dr Nehal Shams. B.Sc(USA). MB. MRCP(UK). DME. DGM**  
Consultant Geriatrician and Physician.  
Portiuncula Hospital. Rep.of Ireland

The latest worldwide estimate of Alzheimer's disease prevalence shows that 26.6 million people were living with the disease in 2006. The researchers predict that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, at which time 1 in 85 persons worldwide will be living with the disease. More than 40 percent of those cases will be in late stages, requiring a high level of care. The pace, to find a cure for this disease is rapid and exhausting. The following gives a summary of what may be available to the patient and physicians in the near future.

### In Diagnosis

The need for early diagnosis is vital for prevention. It is estimated that build-up of A-beta and tau, begins 15 years before symptoms begin. When symptoms begin, more than 50% of cell loss has occurred.

Geert De Meyer, Ph.D., of Innogenetics (Belgium) and colleagues are testing an assay, to detect and measure the concentrations of various forms of A $\beta$  (b-amyloid) in blood. In recent trials a single blood sample from each individual was taken and measured, using the new assay for concentrations of beta amyloid forms including A $\beta$ 1-42, A $\beta$ 1-40, and other A $\beta$  forms.

The researchers found that persons at risk for developing Alzheimer's according to their clinical/CSF biomarker profiles had significantly different A $\beta$  levels in their blood compared with those whose clinical/CSF biomarker profiles did not show risk of Alzheimer's. According to the scientists, approximately 60 percent of the patients tested could be classified by the test as having either a clearly enhanced or a decreased risk for progression to Alzheimer's.

Cerebrospinal fluid (CSF) measurement of total tau is not a specific indicator for AD because tau can be elevated after stroke and in Creutzfeldt-Jacob disease. However, the level of phosphorylated tau or p-tau is a specific indicator for AD because p-tau specifically reflects the phosphorylation state of tau in the formation of tangles in AD. Even total tau can be useful in the differential diagnosis of AD from these conditions. Because A-beta42 (but not A-beta40) in the CSF is lowered in AD and p-tau is elevated, the p-tau181/Abeta42 ratio can be used as a diagnostic marker.

### In Radiology

The Brazilian researchers compared the FDG PET brain glucose metabolism with Tc-99m ethylcysteinate dimer (ECD) single-photon emission computed tomography (SPECT) brain

regional cortical blood flow in patients with Alzheimer dementia. This study showed that similar functional cerebral regions are involved on PET and SPECT in Alzheimer's disease, although PET seemed to be more powerful in depicting the extent and severity of the functional impairments.

There has also been a growing interest in imaging beta-amyloid deposits directly with PET in Alzheimer dementia. An Australian study evaluated the relationship between amyloid burden as assessed by Pittsburgh Compound-B (PIB) PET and cognitive decline in predominantly normal elderly population (age 73  $\pm$  6 years). These investigators observed that subjects with declining cognition were more likely to show cortical PIB retention than in stable subjects, suggesting that amyloid deposition is not a part of normal aging and likely represents preclinical Alzheimer's disease. The researchers from the University of Pennsylvania compared the amyloid imaging agents [F-18]3'-F-PIB and [C-11]PIB in patients with Alzheimer's disease and in healthy subjects. The F-18-labeled compound showed uptake and retention characteristics similar to those of C-11-labeled compound in the more important cortical brain regions with SUV in the range of 3.1 to 4.5.

### In Treatment of the future

#### An anti-amyloid compound

Tramiprosate binds to amyloid beta protein and interferes with its ability to build plaque. Tramiprosate is an orally administered amyloid beta antagonist that is currently in Phase III clinical trials to assess its safety, efficacy and disease modifying effects in patients with mild to moderate Alzheimer's. Tramiprosate has been shown to protect against A $\beta$ -induced cytotoxicity in neuronal and organohippocampal cultures, decrease amyloid burden in transgenic mice, reduce CSF A $\beta$  levels in AD patients and be generally well tolerated in humans.

#### Brain Cell Death Inhibitor

Dimebon is a novel oral small molecule shown to be well tolerated and improve cognition, function, behaviour, and global impression of change. Preclinically, dimebon has demonstrated cognition and memory-enhancing properties and protected neurons in the cerebellum cell culture against the neurotoxic action of  $\gamma$ -amyloid fragment. In vitro, Dimebon displayed Ca<sup>2+</sup>-blocking properties and pronounced anticholinesterase activity for butyrylcholine esterase and acetylcholine esterase. It also exhibited strong anti-NMDA activity in the prevention of NMDA-induced seizures in mice. The improvement at the end of 12 months was more than at the end of 6 months which

suggests that Dimebon didn't just stabilize the patients' condition, it improved it over time. The one-year data confirmed the durability of the treatment and safety profile.

### **Immunotherapy**

Immunization of AD patients with synthetic A $\beta$ 42 (AN1792) was studied in an immunotherapeutic clinical trial that was discontinued following reports of encephalitis. A one-year follow-up showed that AN1792 antibody responders showed improvements on some cognitive measures and a decrease in brain volume compared to placebo.

The study assessed efficacy and safety profiles 4.5 years after immunization with AN1792. Compared to the placebo group, the antibody responders showed significant favourable results in the ability to look after themselves and pursue leisure activities. After the first year, brain volume changes in antibody responders and placebo patients were similar. No additional cases of encephalitis were observed.

### **Anti - Diabetic**

A treatment for type 2 diabetes, rosiglitazone, has been studied for the treatment of Alzheimer's disease. Researchers studied the effect of an extended release form of rosiglitazone (XR) on Alzheimer's patients for 72 weeks. This was a follow up open label extension (48 weeks) to a randomised 24-week controlled trial. The results of the 24 week randomised controlled study suggested that rosiglitazone may help some Alzheimer's patients depending on their APOE genotype. Patients that were "APOE e4-negative" did benefit from the treatment, and showed some improvement. But patients who were "APOE e4-positive" either did not improve or continued to decline.

### **Huperzine**

A new type of ChEI (cholinesterase inhibitor), known as ZT-1, transforms nonenzymatically into its active compound, huperzine A (Hup A). Hup A is a reversible, potent and selective acetyl cholinesterase inhibitor extracted and isolated from the Chinese medicinal herb *Huperzia serrata*. Hup A has been used in China to treat disorders such as memory loss, schizophrenia and hypertension, and following a series of clinical trials carried out in China, it has been approved for use in the treatment of AD.] Hup A is licensed as a dietary supplement to enhance cognition.

Hup A has demonstrated memory-enhancing effects in a broad range of behavioural animal models. Clinical trials have revealed that Hup A produced significant improvements in memory deficiencies in aged patients and in patients with AD. The results from a 12 week, double-blind, randomised and placebo-controlled clinical trial with 202 patients diagnosed with possible or probable AD confirmed the efficacy of Hup A on cognition and function. After treatment with Hup A at a dose of 400  $\mu$ g/day, patient outcomes as measured by the MMSE, ADAS-Cog, Clinical Dementia Rating and ADL improved significantly at week 6 and further improved at week 12. Only mild adverse events were recorded.

### **Secretory phospholipase A<sub>2</sub>-IIA (sPLA<sub>2</sub>-IIA)**

Is an inflammatory protein known to play a role in the pathogenesis of many inflammatory diseases. Although this enzyme has also been implicated in the pathogenesis of neurodegenera-

tive diseases, there has not been a direct demonstration of its expression in diseased human brain. THE sPLA<sub>2</sub>-IIA-immunoreactive astrocytes present in AD hippocampus and inferior temporal gyrus (ITG). In ITG, the majority of sPLA<sub>2</sub>-IIA-positive astrocytes were associated with amyloid  $\beta$  (A $\beta$ )-containing plaques. Studies with human astrocytes in culture demonstrated the ability of oligomeric A $\beta$  and interleukin-1 $\beta$  (IL-1 $\beta$ ) to induce sPLA<sub>2</sub>-IIA mRNA expression, indicating that this gene is among those induced by inflammatory cytokines. Since exogenous sPLA<sub>2</sub>-IIA has been shown to cause neuronal injury, understanding the mechanism(s) and physiological consequences of sPLA<sub>2</sub>-IIA up regulation in AD brain may facilitate the development of novel therapeutic strategies to inhibit the inflammatory responses and to retard the progression of the disease.

### **Gamma Secretase inhibitor**

A phase-II trial of a gamma-secretase inhibitor (LY450139) is currently being studied as a potential disease-modifying treatment for Alzheimer's the molecule inhibits the gamma-secretase enzyme which contributes to the formation of A $\beta$  (b amyloid). Patients with Alzheimer's were given 100 mg or 140 mg each day for six to 12 weeks.

Eric Siemers, M.D. and colleagues conducted this study to assess the safety and tolerability of LY450139 as well as its effect on A $\beta$  levels in blood and CSF.

Fifty-one participants with mild to moderate Alzheimer's were randomised; 43 completed the study. A $\beta$ 1-40 concentrations in blood were reduced by 58.2 percent for the 100 mg group and by 64.6 percent for the 140 mg group. According to the researchers, a number of side effects were reported, but they were generally mild in severity and the drug was generally well tolerated. Safety assessments showed 38.9 percent complained of mild fatigue or sleepiness, compared to 13.3 percent in the placebo group. There were three adverse event gastrointestinal related discontinuations. There was a mean prolongation of "QTcF interval" of 16.8 msec (corrected for baseline values) on electrocardiograms in the 140 mg group.

### **Statins**

Amyloid B is 39-43 amino acid residues long and is derived in part from the transmembrane region of the amyloid-precursor protein (APP). The initial pathophysiological role of A $\beta$  is widely agreed on.] A mounting body of experimental in vitro and in vivo data indicate that brain cholesterol homeostasis is coupled with brain amyloid metabolism, although the mechanism is not known. However, the causative role of cholesterol in the pathogenic cascade of excessive A $\beta$  deposition in the brain of AD patients is not proven. Cell culture studies demonstrate that membrane cholesterol controls the direction of the processing of the APP. Under similar experimental conditions, reduced A $\beta$  levels were found to increase  $\gamma$ -secretase activity. Suggesting that membrane cholesterol variations are coupled with activity shifting of APP-cleaving secretases.

### **Mediterranean Diet**

Some physicians are beginning to recommend this (MeDi) diet for the prevention of Alzheimer's disease in view of the two recent trials. There have been no major clinical trials and other groups have not replicated same results. On the other hand, considering the positive results of two studies, and taking into account that the [Mediterranean] diet has been shown to be

beneficial for many other diseases, it would make sense for patients to adopt it as early as possible.

### Anti-inflammatory (NSAID)

The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), had been running for 3 years when it was stopped, having randomised 2400 participants over the age of 70, after discovering, that both celebrex and naproxen appeared to increase the risk of cardiovascular (CV) events and stroke by 50% compared with patients on placebo. Researchers and physicians now feel that it was done in haste and results have been encouraging.

### Vascular Risks

There is growing evidence that factors that increase the risk of vascular events like heart attack or stroke also increase the risk of cognitive decline. Results of recent trials, showed that patients whose vascular risk factors were treated appeared to decline at a slower rate and that it took them three years to decline as much as untreated patients.

### Conclusion

Many treatment models have shown a promising reduction of disease but no disease-modifying drug has yet been approved for use. Although that day may not be far away. Dietary factors, such as the MeDi, regular exercise, and reduction in vascular events, seem to modify the disease course and may help to prevent or delay AD.

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## Quality of life in elderly people in Kashan, Iran

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**Author**

Vahid Nejati<sup>1</sup>; Peymaneh Shirinbayan<sup>2</sup>; Ahmadali Akbari Kamrani, MD<sup>3</sup>; Mahshid Foroughan, MD<sup>4</sup>; Parisa Taheri, MD<sup>5</sup>; Mehrdad Sheikhvatan, MD<sup>6</sup>

1) Neuroscientist, Rehabilitation and well-being college, Tehran, Iran

2) Master of Psychometry, Rehabilitation and well-being college, Tehran, Iran

3) Assistant Professor of internal medicine, Rehabilitation and well-being college, Tehran, Iran

4) Psychologist, Rehabilitation and well-being college, Tehran, Iran

5) Specialist of Geriatric Medicine, Rehabilitation and well-being college, Tehran, Iran

6) Researcher, Medical Sciences/ University of Tehran, Tehran, Iran.

**Correspondence:**

**Vahid Nejati**

P.O.Box: 13185-1678,

Tehran, Iran

Tel: +9821 66439463

Fax: +98 021 66919206

Email: swt\_f@yahoo.com

### ABSTRACT

The objective of this article was to identify determinants of quality of life and investigate their association with physical and social functions, physical and emotional roles, and physical and mental health among older people in Kashan, Iran. In a cross-sectional study 389 elderly persons (aged  $\geq 60$  years) was selected randomly from 120 zones of Kashan. The structured interview consisted of 36 questions including sub-questions related to different aspects of life by using on SF-36 health survey. The mean age of participants was  $69.8 \pm 7.74$  years. Illiteracy rate in men and women were 31.2% and 8.5% ( $P < 0.0001$ ), whereas marriage rates were 87.6% and 87.1% ( $P = 125$ ), respectively. The mean score of aspects of physical function ( $P < 0.0001$ ), general health perception ( $P < 0.0001$ ), physical role ( $P < 0.0001$ ), vitality ( $P = 0.0007$ ), mental health ( $P = 0.003$ ), and bodily pain ( $P < 0.0001$ ) in men was higher than in females, whereas social function ( $P = 0.844$ ) and emotional role ( $P = 0.397$ ) were similar between the two genders. Illiteracy is common in elderly people, and quality of life in men was higher than women in all aspects.

**Keywords:** Quality of life, Old age, SF-36 health survey

### Introduction

Quality of life is a universally desired patient outcome that is essential to human health<sup>[1]</sup>. Quality of life is a subjective and multidimensional concept that is increasingly being recognized as a useful outcome in health and social care research. The World Health Organization Quality of Life group defined quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. The subjective nature of quality of life purports that it can be conceptualized differently by different groups of people. Age, gender, health status, and cultural factors are some of the important factors that influence their conceptualization<sup>[2]</sup>. The term quality of life is of a more recent origin.

Social scientists started to use it in the 1970s and since then there has been a growing interest in quality of life issues in medicine, nursing and other health care areas. There are various explanations for this growing interest. One has to do with the growing number of elderly people in society. Higher age often brings about health problems and a decrease in functional capacity. This means that we have a growing number of people living with chronic diseases, health problems and decreasing capacity. For these patients the goal of health care cannot be freedom from disease. What we can do is to help the patients to live as good a life as possible despite their illnesses and decreasing capacities<sup>[3]</sup>.

There are several previous studies about quality of life in elderly people in different societies. However, a few studies

about quality of life in this group in Iran were done. In order to obtain a detailed and organized program like other countries in the world and many of the East-Mediterranean countries (EMRO) have proposed their seniors' health national program. It was necessary for Iran to perform an epidemiological survey to determine seniors' social and physical health, setting priorities for social and physical health needs, assess the amount of services needed for them and to adopt national policies on caring for this age group.

The objective of this article was to identify determinants of quality of life and investigate their association with physical and social functions, physical and emotional roles, and Physical and Mental health among older people in Kashan, a city in Iran located in the center of this country. The estimated 2006 population of Kashan City is 301864 and of that 51.2% of the population is male.

## Materials and Methods

### Study population:

A cross-sectional study of 389 elderly persons (aged  $\geq 60$  years) was selected randomly from 120 zones of Kashan city. Data for this study were collected between April 2005 and April 2006. The sample was restricted to people living in non-institutional settings (e.g. their own homes or houses for elderly people). The study site has been described as a typical Iranian agricultural community and as being similar to most of rural Iran in terms of ethnicity, culture, and language. Individuals who agreed to participate met with the researcher or research assistant who explained the purpose of the study and obtained informed consent.

### Data collection:

Because elderly people in institutions usually have more health problems and lower functional capacity than elderly people living in their own homes, they might have difficulties in completing a long interview. The researchers sent a letter to the informants, describing the purpose of the study, and then contacted them by telephone to set a date for the interview. Ethical committees in Kashan University of medical sciences have approved this study. The structured interview consisted of 36 questions including sub-questions related to different aspects of life: age, sex, marital status, literacy (ability to read and write), physical function, knowledge of general health perceptions, physical role, social function, emotional role, vitality, mental health, and bodily pain. Questions were based on SF-36 health survey. SF-36 is a generic questionnaire for the measurement of quality of life, and covers 8 dimensions of health status and 2 summary areas, one physical and one mental<sup>[4]</sup>. The scores are in the range of 0 to 100 (a higher score indicating a better health status). The questionnaire has been trans-

lated and validated in an Iranian population<sup>[5]</sup>. The reason for choosing previously tested instruments was to guarantee initial validity and reliability.

Components of each question of quality aspects were categorized into five steps according to categorized scales: The scores on the summed quality of life questions could range from 0 to 100 (mean = 50): very good (80-100), good (60-79), moderate (40-59), poor (20-39), and very poor (0-19).

### Statistical analysis:

Results were reported as the mean  $\pm$  standard deviation (SD) for quantitative variables and percentages for categorical variables. Categorical variables between the groups were compared using Pearson's  $\chi^2$ -test and Fisher's exact test. Differences in mean scores with regard to aspects of quality of life were tested by non-parametric one-way analysis of variance, the Mann-Whitney U-test. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed by using SPSS version 13 and SAS version 9.1 for windows.

## Results

### Demographic characteristics:

The age of our study population ranged from 60 to 120 years with the mean age of  $69.8 \pm 7.74$  years (Figure 1). Demographic characteristics of cases in two genders were summarized in Table 1. Male to Female ratio was 1.08. There were no significant differences in the mean age ( $P=0.465$ ) and marriage condition ( $P=0.125$ ) between the two genders, but illiteracy was more frequent in women ( $P<0.0001$ ). Literacy was found in 31.2% of men and only 8.5% of women, whereas only 1.4% of men and 0.5% of women had a postgraduate degree.

### Aspects of quality of life:

Scores of different aspects of quality of life in the two genders are shown in Table 2. With the exception of emotional role, very good scores predominated in the male elderly group. Also, comparison of mean scores between the two genders showed that these scores were higher in men in aspects of physical function, general health perception, physical role, vitality, mental health, and bodily pain (Table 3).

## Discussion

Public health policies in most countries are concerned with how to keep older people living independently with a qualitatively good life in the community as long as possible. However, knowledge about what may characterize those seemingly 'healthy' older people is sparse<sup>[6]</sup>.

**Table1.** Demographic characteristics of elderly population

Characteristics	Female (n= 187)	Male (n=202)	P value
Mean age (Mean $\pm$ SD)	68.49 $\pm$ 7.19	70.12 $\pm$ 7.22	0.465
Literacy * (%)	8.5	31.2	<0.0001
Marriage (%)	87.1	87.6	0.125
* Ability to read and write			

**Table2.** Scores of different aspects of quality of life in two genders

Aspect	Very poor (0-19)	Poor (20-39)	Moderate (40-59)	Good (60-79)	Very good (80-100)
Physical function: -Male	0	2.5	35.7	40.8	30.1
-Female	0	12.4	61.6	20.7	5.1
General health perception: -Male	30.1	2.5	30.7	0	30.6
-Female	6.7	9.8	51.8	0	31.6
Physical role: -Male	5.1	9.6	58.6	0	26.5
-Female	1.5	15.5	67.3	1.5	14.5
Social function: -Male	63.7	1.5	12.2	0	22.9
-Female	60.1	0.5	7.2	0	32.1
Emotional role: -Male	13.2	2.5	30.1	0	52.0
-Female	19.1	2.0	27.4	0	51.2
Vitality: -Male	25	2.5	32.1	0	40.3
-Female	12.4	3.1	43.0	0	46.6
Mental health: -Male	81.6	0	5.1	0	9.1
-Female	76.6	0	3.1	0	20.2
Very low	Low	Moderate	High	Very high	
Bodily pain: -Male	27.5	5.6	16.8	0	44.8
-Female	9.8	8.8	31.0	0	50.2

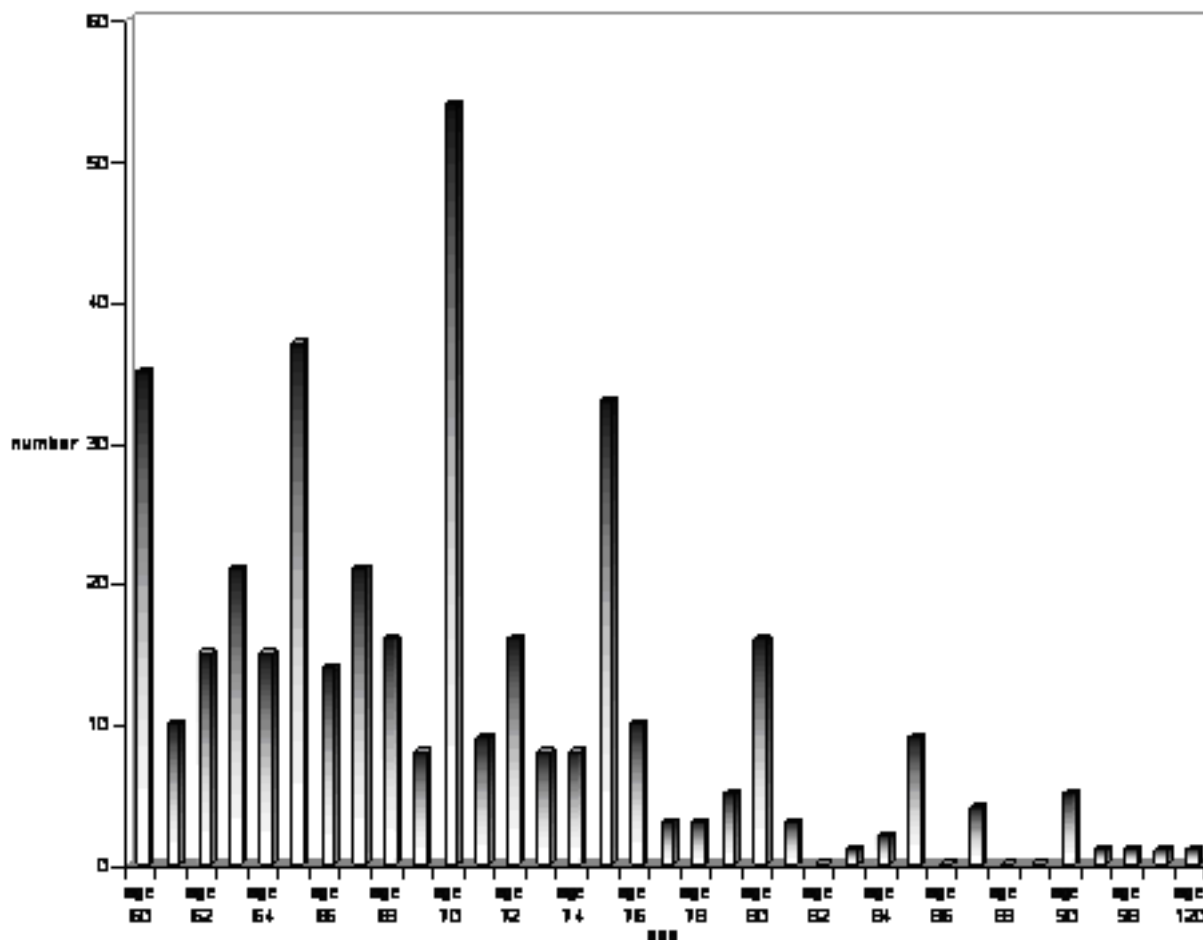
**Table3.** Comparison of quality of life means scores in elderly men and women

P value	Female (n=187)	Male (n=202)	Aspect
<0.0001	57.01±13.82	66.6±18.35	Physical function
<0.0001	55.59±14.89	65.72±17.31	General health perception
<0.0001	47.54±12.07	54.56±12.68	Physical role
0.844	78.03±17.50	78.40±19.30	Social function
0.397	61.21±12.68	62.38±14.41	Emotional role
0.0007	59.70±15.72	65.76±19.02	Vitality
0.003	91.43±16.67	97.36±22.78	Mental health
<0.0001	57.22±15.79	66.10±20.61	Bodily pain

**Table 4.** Comparison of quality of life means scores in Kashan and other cities

Aspects	Kashan (Mean±SD)	Tehran (Mean±SD)	Zahedan (Mean±SD)	Canada (Mean±SD)	Lebanon (Mean±SD)	Turkey (Mean±SD)
Physical function	59.07±17.69	58.3±25.5	42.7±21.9	75.9±20.5	81.3±22.8	58.9±27.6
General health perception	60.71±16.92	50.1±20.1	38.6±15.6	73.3±18.3	66.3±22.9	50.2±20.1
Physical role	51.05±12.85	38.8±39.8	36.8±33.0	68.6±35.0	63.6±43.6	54.3±42.4
Social function	78.22±18.40	59.6±28.1	43.9±16.0	63.3±20.0	68.8±29.6	71.3±24.9
Emotional role	61.08±14.05	50.0±43.6	45.0±24.7	82.1±34.2	53.0±43.3	60.9±20.4
Vitality	62.73±17.69	54.6±18.8	46.7±19.4	64.9±18.5	60.8±22.5	42.5±21.7
Mental health	94.42±21.47	63.2±17.4	42.6±18.9	79.6±14.0	62.8±22.5	58.8±45.7
Bodily pain	61.70±18.89	58.3±28.5	37.8±19.3	72.3±24.1	68.9±30.6	59.5±28.1

**Figure 1**



According to the latest census taken in 1996 in Iran, the elderly population aged 60 and older was 6.6% of the whole population and the Census Bureau predicts that the elderly age dominance will be more significant from the year 2030 on. In this regard the elderly population aged over 60 will be 8.5 million in 2020 and five years later in 2025 this will reach up to 10.5 million<sup>[7]</sup>.

In our study, illiteracy was found in 68.8% of elderly males and 91.5% of elderly females in Kashan, whereas marriage rate in elderly males and females were 87.6% and 87.1%, respectively. In another study, it was found that overall illiteracy rate

in Iran was very high among the elderly. 79% of urban females and 95% of rural females were illiterate, on the other hand 50.7% of urban males and 71.5% of rural males were illiterate. Also, marriage rate in males was two times more than females, so that 37-42% of females had a husband while 86-89% of males had a wife. The reason for this is that men may marry for a second time following loss of their wives while females remain widowed<sup>[7]</sup>.

In this article, we also compared our results about quality of life in selected elderly people in Kashan city with two other cities in Iran; Tehran<sup>[8]</sup> and Zahedan<sup>[9]</sup> and four cities in other

countries; Toronto in Canada<sup>[10]</sup>, south cities in Lebanon<sup>[11]</sup>, and Samsun in Turkey<sup>[12]</sup>.

Results of this comparison are summarized in Table 4. We found that the mean scores of quality of life in all aspects in Kashan were higher than the capital of Iran (Tehran). Physical role score in this city was more than the other two cities in Iran. Also, physical role score was less and social function and mental health was more than other countries. These results showed that several factors can influence the quality of life in elderly populations in different societies. Functional capacity, perceived health, good housing conditions, an active life style, and good social relationships were some of the factors that explained life satisfaction and subjective quality of life<sup>[13-16]</sup>. Low economic status is another determinant affecting quality of life. Social capital was discussed as an important aspect of successful aging<sup>[17]</sup>.

In summary, although extremely wealthy in terms of tourism potentials, the city remains largely undeveloped. Illiteracy is common in the elderly population, and quality of life in men was higher than women in all aspects.

### Acknowledgement

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## Modeling and Forecasting of $l_2$ (Survivors at Age 2) Values for Male and Female Population of Bangladesh: Regression Model Approach

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**Author**

**Md. Rafiqul Islam**

**Correspondence:**

**Dr. Md. Rafiqul Islam**

Associate Professor and Chairman Dept. of Population Science and Human Resource Development,  
University of Rajshahi Bangladesh.

E-mail: rafique\_pops@yahoo.com

### ABSTRACT

The purpose of the present study is to build up statistical models to  $l_2$  (number of survivors at age 2) values for male and female population of Bangladesh. For this, the secondary data of  $l_2$  values for male and female population of Bangladesh have been taken from various sources. To check up the soundness of the model, the model validation technique, cross-validity prediction power (CVPP), is applied. It is seen that simple linear regression model is fitted to  $l_2$  values for male and female population of Bangladesh. Then, these are forecasted during 2008–2031 using these fitted time trend statistical models.

**Keywords:**  $l_2$  (Survivors at Age 2) Values for male and female Population of Bangladesh Modeling- Cross- validity prediction power (CVPP) F-test

### Introduction

Modeling in Demography in the Asian region, in particular, in Bangladesh has hardly ever been used. For representing data in the up to date hi-tech era, statistical models are very sophisticated and pragmatic devices. The statistical model is very much significant and imperative in differentiating necessary and unnecessary characteristics in the midst of a variety of socio-economic and demographic phenomena. Modeling is in fact essentially an endeavor to find out the functional interaction and their vibrant behaviors surrounded by the various components, not only in demographic but also in socio-economic analysis. Last but not least, a model is very important for the estimation of population projections and estimations. Normally, one can depict a number of figures for the demographic parameters as well as socio-economic indicators but, in the perception of Bangladesh, very few of us comprehend which types of functional or mathematical shapes are more appropriate for the parameters and social indicators. In this study,  $l_2$  is defined as the number of survivors at age 2 in the  $l_x$  function of a life table in life table analysis.  $l_2$  is very important and needed for the linking to adult mortality to attain a complete  $l_x$  function

or column of a life table that is employed in the application of Orphanhood method, Widowhood method and other indirect methods for the estimation of demographic parameters of Bangladesh.

Ali (1994) found that the relationship of total separation rates and separation rates due to death, with their age variable and found a semi-log function of the type . In Islam et al (2003), it was reported that age distribution, age specific death rates (ASDRs) and the number of persons surviving at an exact age  $x$  ( $l_x$ ) for male population of Bangladesh in 1991 follow a modified negative exponential model, 4<sup>th</sup> degree polynomial model and 3<sup>rd</sup> degree polynomial model, respectively. Islam (2005) observed that age structure, ASDRs and  $l_x$  for female population of Bangladesh follow a modified negative exponential model, 4<sup>th</sup> degree polynomial model and biquadratic polynomial model respectively. It was set up that the values of a life table for the male population followed a four parameters 3<sup>rd</sup> degree polynomial model, i. e. cubic polynomial model (Islam, 2006).

Therefore, the fundamental aims and objectives of this study are as follows:

- i) to build up time trend statistical models to  $I_2$  values for male and female population of Bangladesh and,
- ii) then to forecast these values employing these fitted statistical regression models for 2008-2031.

## Data and Methodology

### Data Sources

To fulfill the objectives mentioned above the secondary data on  $I_2$  values for male and female population of Bangladesh have been taken from (Islam, 2003, 2006, 2007 and 2007). These have been utilized as raw materials in the current study that are shown in Table 1.

### Data Smoothing

It is observed that there is some kind of unpredicted distortions in the data aggregate if it is placed on a graph paper. Therefore, before going to fit the models to this data, an adjustment is needed to relieve these unpredicted distortions. So, these are smoothed using the Package Minitab Release 12.1 by the latest smoothing technique "4253H, twice" (Velleman, 1980). Afterward, the smoothed data are used to fit statistical models and these are shown in Table 1.

### Regression Model Fitting

Using the scattered plot of  $I_2$  values for male and female population of Bangladesh, it appears that these are linearly distributed. Therefore, a statistical model, that is, a simple linear regression model is considered and the structure of the model is

$$y_t = a_0 + a_1 t + u$$

where,  $t$  represents time (years);  $y_t$  represents  $I_2$  values;  $a_0, a_1$  are unknown parameters and  $u$  is the stochastic disturbance term of the model.

Note that these models are fitted using the software STATISTICA.

### Model Validation Technique

To test out the validity or legitimacy of these models, the CVPP,  $\rho_{cv}^2$ , is applied. The mathematical formulation for CVPP is given as

$$\rho_{cv}^2 = 1 - \frac{(n-1)(n-2)(n+1)}{n(n-k-1)(n-k-2)} (1 - R^2)$$

; where,  $n$  is the number of classes,  $k$  is the number of regressors in the model and the cross-validated  $R$  is the correlation between observed and predicted values of the dependent variables (Stevens, 1996). The shrinkage of the model is the positive value of  $(\rho_{cv}^2 - R^2)$ ; where  $\rho_{cv}^2$  is CVPP and  $R^2$  is the coefficient of determination of the

fitted model. As well, 1-shrinkage is the stability of  $R^2$  of the model. The estimated CVPP analogous to their  $R^2$  and information on model fittings are summarized in Table 2. It is noted that CVPP was also employed by Islam (2003 and 2005), Islam et al (2003 and 2005) and Khan and Ali (2004) as the model justification method.

To find out the overall measure of significance level of the fitted models as well as the significance of  $R^2$ , the F-test is employed in this information. The F-test is specified by

$$F = \frac{R^2 / (1-l)}{(1-R^2) / (n-l)}$$

with  $(1-l, n-l)$  degrees of freedom (d.f.); where  $l$  = the number of parameters is to be estimated in the fitted model,  $n$  is the number of cases and  $R^2$  is the coefficient of determination of the model (Gujarati, 1998).

## Results and Discussion

The statistical models, that is, simple linear regression model is assumed to fit to  $I_2$  values for male and female population of Bangladesh and the fitted time trend models are in the following:

$$y_t = -5.2775 + 0.00308t \text{ for male ... (1)}$$

t-stats (-12.2147) (14.1946)

$$y_t = -4.60916 + 0.00275t \text{ for female ... (2)}$$

t-stats (-9.72565) (11.53224)

The information on model fittings and estimated CVPP,  $\rho_{cv}^2$ , analogous to their  $R^2$  of these models is shown in Table 2. From this table it appears that the fitted models (1) - (2) are highly cross-validated and their shrinkages are 0.0173 and 0.0259 respectively. These imply that the fitted models (1) - (2) will be stable more than 95% and 93% respectively. Moreover, it is found that the parameters of the fitted models (1) - (2) are highly statistically significant with significant of variance explained. The stability for  $R^2$  of these models is more than 98% and 97% respectively.

The calculated values of F statistic for the models (1) - (2) are 201.53 with (1, 5) d.f. and 133.01 with (1, 5) d.f. respectively whereas the analogous tabulated values are only 16.3 for (1) - (2) models at 1% level of significance. Therefore, from these statistics it is seen that these models and their analogous  $R^2$  are highly statistically significant. Hence, the fits of these models are well.

It should be mentioned here for information that others

**Table 1** Observed, Predicted and Residual of  $I_2$  Values for Male and Female Population of Bangladesh During 1961-2007

Year	Male				Female			
	Observed	Smoothed	Predicted	Residual	Observed	Smoothed	Predicted	Residual
1961	0.77813	0.778130	0.76803	0.01011	0.78989	0.789890	0.778273	0.01162
1974	0.77067	0.793406	0.80810	-0.0147	0.77815	0.802052	0.813988	-0.01194
1981	0.81750	0.826434	0.82968	-0.0032	0.82571	0.828114	0.833219	-0.00511
1991	0.87999	0.867742	0.86051	0.00723	0.86339	0.861243	0.860692	0.00055
2005	0.90280	0.896771	0.90367	-0.0069	0.89020	0.888750	0.899154	-0.01040
2006	0.90862	0.909496	0.90676	0.00274	0.91015	0.906124	0.901901	0.00422
2007	0.91161	0.914609	0.90984	0.00477	0.91282	0.915702	0.904648	0.01105

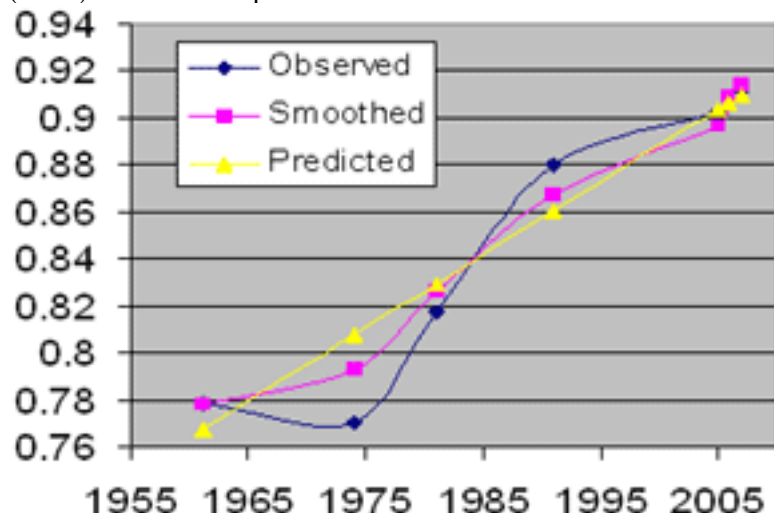
**Table 2** Information on Model Fittings

Model	n	k	R <sup>2</sup>	$\rho_{\sigma}^2$	Shrinkage	Parameters	Significant Probability (p)
(i)	7	2	0.97579	0.958497	0.0173	a0 a1	0.0001 0.00003
(ii)	7	2	0.96377	0.937891	0.0259	a0 a1	0.00020 0.00009

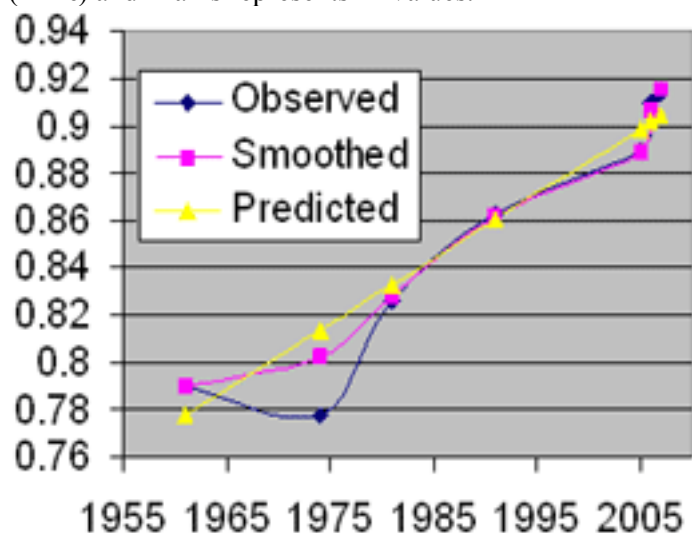
**Table 3** Forecasted  $I_2$  Values for Male and Female Population of Bangladesh During 2008-2031

Year	Male	Female
2008	0.90714	0.91284
2009	0.91022	0.91559
2010	0.91330	0.91834
2011	0.91638	0.92109
2012	0.91946	0.92384
2013	0.92254	0.92659
2014	0.92562	0.92934
2015	0.92870	0.93209
2016	0.93178	0.93484
2017	0.93486	0.93759
2018	0.93794	0.94034
2019	0.94102	0.94309
2020	0.94410	0.94584
2021	0.94718	0.94859
2022	0.95026	0.95134
2023	0.95334	0.95409
2024	0.95642	0.95684
2025	0.95950	0.95959
2026	0.96258	0.96234
2027	0.96566	0.96509
2028	0.96874	0.96784
2029	0.97182	0.97059
2030	0.97490	0.97334
2031	0.97798	0.97609

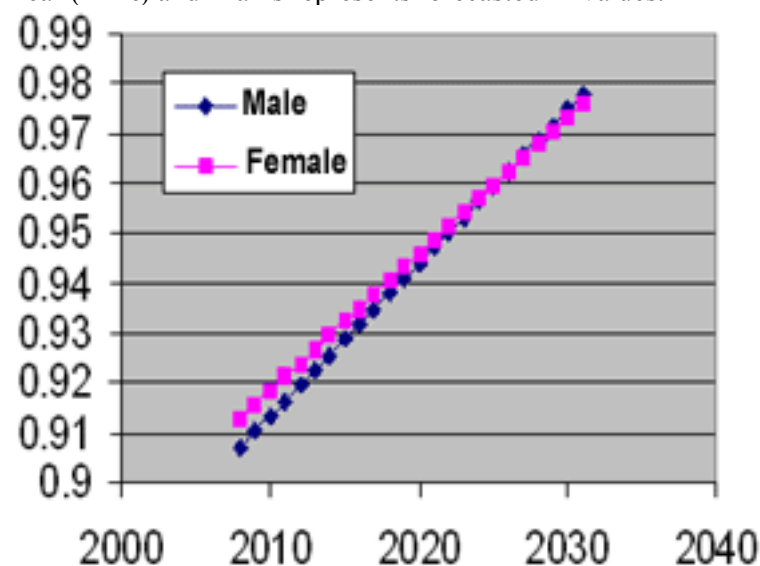
**Figure 1** Observed, Smoothed and Predicted I2 Values for Male Population of Bangladesh. X axis represents Year (Time) and Y axis represents I2 Values.



**Figure 2** Observed, Smoothed and Predicted I2 Values for Female Population of Bangladesh. X axis represents Year (Time) and Y axis represents I2 Values.



**Figure 3** Forecasted I2 Values for Male and Female Population of Bangladesh During 2008-2031. X axis represents Year (Time) and Y axis represents forecasted I2 Values.



models such as exponential, logistic, quadratic, cubic, biquadratic were also applied to fit model to these data but those are not fit well due to shrinkage and proportion of variance explained.

Thereafter, the forecasted values are estimated using these fitted time trend regression models that are presented in Table 3. It is found from the Table 3 that  $I_2$  values are increasing, i.e., upward trend due to time during the forecasted period 2008-2031.

## Conclusion

In this study it is found that  $I_2$  values for male and female population of Bangladesh follow a simple linear regression model. Then these are forecasted using these statistical models during 2008–2031. These might be used as predicted  $I_2$  values for male and female population of Bangladesh for 2008–2031 for further higher study as these may be used in the application of Orphanhood method, Widowhood method and other indirect techniques for the estimation of demographic parameters for the forecasted period 2008–2031.

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