ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2012 June 15; 3(6): 110-129

Baishideng Publishing Group
www.wjgnet.com

World Journal of Diabetes

A peer-reviewed, online, open-access journal of diabetes

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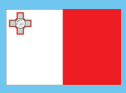

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WJD World Journal of Diabetes

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Monthly Volume 3 Number 6 June 15, 2012

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World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a monthly, open-access, peer-reviewed journal supported by an editorial board of 323 experts in diabetes mellitus research from 38 countries.

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NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
April 15, 2010

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Monthly

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PUBLICATION DATE
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World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/1948-9358office
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doi:10.4239/wjd.v3.i6.110

World J Diabetes 2012 June 15; 3(6): 110-117
ISSN 1948-9358 (online)
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EDITORIAL

Trends in prevalence of diabetes in Asian countries

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Received: March 9, 2012 Revised: June 4, 2012
Accepted: June 10, 2012
Published online: June 15, 2012

Abstract

Diabetes is a major lifestyle disorder, the prevalence of which is increasing globally. Asian countries contribute to more than 60% of the world's diabetic population as the prevalence of diabetes is increasing in these countries. Socio-economic growth and industrialization are rapidly occurring in many of these countries. The urban-rural divide in prevalence is narrowing as urbanization is spreading widely, adversely affecting the lifestyle of populations. Asians have a strong ethnic and genetic predisposition for diabetes and have lower thresholds for the environmental risk factors. As a result, they develop diabetes at a younger age and at a lower body mass index and waist circumference when compared with the Western population. The adverse effect of physical inactivity and fatty food are manifested as the increasing rate of overweightness and obesity, even among children. The health care budgets for the disease management are meager and the health care outcome is far from the optimum. As a result, complications of diabetes are common and the economic burden is very high, especially among the poor strata of the society. National endeavors are urgently needed for early diagnosis, effective management and for primary prevention of diabetes. This editorial aims to highlight the rising trend in prevalence of diabetes in Asia, its causative factors and the urgent need to implement national strategies for primary prevention of type 2 diabetes.

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Key words: Type 2 diabetes; Diabetes in Asia; Prevention of diabetes; Lifestyle changes; Urbanization; Burden of diabetes

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Ramachandran A, Snehalatha C, Samith Shetty A, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3(6): 110-117 Available from: URL: http://www.wjgnet.com/1948-9358/full/v3/i6/110.htm DOI: http://dx.doi.org/10.4239/wjd.v3.i6.110

INTRODUCTION

The prevalence of diabetes, constituted chiefly by type 2 diabetes (T2D), is a global public health threat. The prevalence among adults aged 20-70 years is expected to rise from 285 million in 2010 to 438 million by the year 2030[1]. While T2D poses a huge economic burden to all nations, developing countries bear the highest burden since more than 80% of cases occur in these countries. Prevalence estimates of diabetes and impaired glucose tolerance (IGT) are high for all Asian countries and are expected to increase further in the next two decades[1]. The present trend indicates that more than 60% of the world's diabetic population will be in Asia. This editorial aims to highlight the rising trend in prevalence of diabetes in Asia, its causative factors and the urgent need to implement national strategies for primary prevention of T2D.

Table 1 Prevalence and incidence of type 2 diabetes in South Asia

Country	Year	Diagnosis method	Criteria	Prevalence (%)			Fold increase (%)		
				National	Urban	Rural	National	Urban	Rural
Bangladesh[2,3]	1997	FPG/OGTT	WHO 1985		4.5				
	2005	FPG/OGTT	WHO 1999		8.1	2.3		1.8 (8 yr)	
China									
Mainland[4-6]	1994	FPG/OGTT	WHO 1985	2.5					
	2001	FPG/OGTT	WHO 1985	6.1	6.9	5.6	2.4 (7 yr)		
	2008	OGTT	WHO 1999	9.4	11.4	8.2	3.8 (13 yr)	1.7 (6 yr)	1.5 (6 yr)
Hong Kong[7,8]	1990	OGTT	WHO 1985	4.5					
	1996	FPG/OGTT	ADA 1997/WHO 1998	9.8			2.2 (6 yr)		
Taiwan[28,29]	1987	FPG/OGTT	WHO 1985	4.4			2.2 (8 yr)		
	1996	OGTT	WHO 1985	9.2					
India[9,10]	1989	FPG/WHO	WHO 1985		8.2	2.4		2.3 (16 yr)	3.8 (16 yr)
	2006	OGTT	WHO 1999		18.6	9.2			
Indonesia[11,12]	1981	OGTT	WHO 1980		1.6				
	1995				5.7			3.5 (13 yr)	
South Korea[13]	1997	OGTT	ADA 1997			6.9			
	2003	OGTT	ADA 1997			11.7			1.7 (6 yr)
Malaysia[14,15]	1982		NA		2.1				
	2006	FPG	WHO 1985		11			5.2 (24 yr)	
Nepal[16-18]	1990	FPG	ADA 1997		1.4[1]	0.3			
	1999	FPG	ADA 1997		14.6	2.5		6.81 (17 yr)	8.3 (11 yr)
	2007	NA	NA		9.5[1]				
Pakistan[19]	2006	OGTT	WHO 1985		10.6	7.7			
Philippines[20]	1982	OGTT	≥ 11.0 mmol/L		3.3				
	2002	OGTT	WHO 1999		4.9			1.5 (19 yr)	
Singapore[21-23]	1985	OGTT	WHO 1985	4.7					
	1998	FPG/OGTT	WHO 1985	9					
	2004	FPG/OGTT	WHO 1985	8.2			1.9 (19 yr)		
Sri Lanka[24,25]	1994	OGTT	WHO 1985		5				
	2005	FPG/OGTT	ADA 1997	10.3					
Thailand[26,27]	2000	FPG	≥ 7 mmol/L	6.7					
	2004	FPG	WHO 1985	9.6			1.4 (4 yr)		
Taiwan[28,29]	1987	FPG/OGTT	WHO 1985	4.4			2.2 (8 yr)		
	1996	OGTT	WHO 1985	9.2					
Vietnam[30,31]	1990	FPG	ADA	1.4					
	2001	OGTT	WHO 1985	3.8			2.7 (11 yr)		

[1]Sub urban area, numbers in brackets show the period in which the increase has occurred. **OGTT: Oral glucose tolerance test; ADA: American Diabetes Association; WHO: World Health Organization; FPG: Fasting plasma glucose; NA: Not available.**

CHANGE IN PREVALENCE OF T2D IN SOUTH ASIA

Table 1 shows the changing trends in the prevalence of diabetes in South Asian countries[2-31]. In the past two decades, the prevalence in urban areas has increased remarkably in most countries, the increase being phenomenal in Nepal[16-18] and China[4-6]. The national prevalence has increased by two fold or more within a decade in many countries[6,8,22,29,31]. Rural prevalence has increased considerably in India[9], Nepal[18] and China[6]. India and China have large rural populations and hence the increased prevalence of diabetes in rural areas has contributed to the overall national increase in the prevalence of diabetes in these countries.

The recent improvements seen in health status of people of Singapore in the National Health Survey are commendable[23]. In the past 50 years, the country achieved rapid economic progress and underwent an epidemiological transition from a high prevalence of infectious diseases to a high prevalence of lifestyle-associated chronic non communicable diseases such as diabetes, hypertension (HTN) and cardiovascular risk factors. In 1991, Singapore's Review Committee on National Health Policies reviewed the country's health care services and endorsed policies focusing on health promotion and disease prevention and control of health risk factors, including overweightness and obesity. A series of health promotion measures were initiated in 1992 under the National Healthy Lifestyle Program, focusing on not smoking, being physically active, eating right and managing stress to combat major chronic disease and their risk factors. Health education and disease prevention campaigns made significant achievements in the health status of the people.

With the national initiatives taken to improve the health status of the people, a decrease was seen for the first time in the prevalence of diabetes (from 9% in 1998 to 8.2% in 2004)[23]. A remarkable reduction was seen in other cardiovascular risk factors, such as hypertension, dyslipidemia and smoking. Physical activity levels have

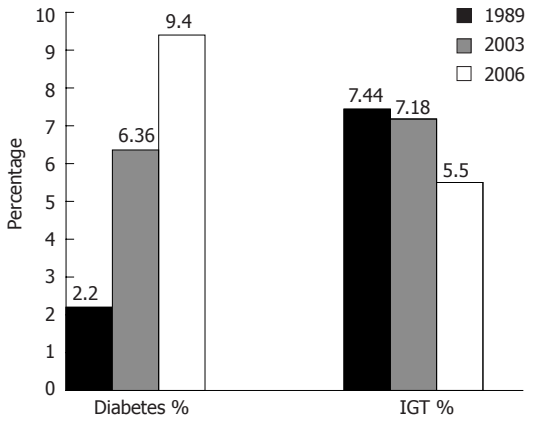

Figure 1 Increasing prevalence of diabetes and impaired glucose tolerance in rural populations in India. IGT: Impaired glucose tolerance.

shown improvement, although much needs to be done to tackle the problem of rising overweightness and obesity.

FACTORS CONTRIBUTING TO THE RAPID INCREASE IN PREVALENCE OF DIABETES IN ASIA

Urbanization and socioeconomic transition

The escalating prevalence of diabetes seen in the last two to three decades can be attributed mostly to the change in lifestyle as a result of rapid socioeconomic growth. The rise in prevalence, therefore, is a result of environmental and behavioral changes and cannot be attributed to altered gene frequencies since the increase has occurred within a few decades. It is estimated that the substantial increase in urbanization will occur in most Asian countries, although the rates are variable among these countries[32]. The highest rates of urbanization (50%) have been in Singapore, Korea, Malaysia, Philippines and Indonesia. China, Pakistan, India and Thailand have intermediate rates (30%) and Bangladesh and Sri Lanka have slow rates of urbanization. The increase in urban population and aging are the main determinants of the global rise in prevalence of diabetes. Urbanization and internal rural to urban migration result in several adverse impacts; physical activity decreases, diet habits shift towards high-energy foods and body mass index (BMI) and upper body adiposity increase considerably.

Socio-economic progress, occurring even in the rural areas of countries such as India and China, have adversely affected the proportion of people affected with lifestyle disorders such as obesity, diabetes, HTN and cardiovascular diseases (CVD). As shown in the recent studies in India[10] and China[6,33], considerable changes have occurred in the living pattern of the rural population, leading to an increase in total prevalence of overweightness and diabetes in these countries. In 1980, less than 1% of Chinese adults had diabetes and in 2008, the prevalence had increased to nearly 10%[6].

The temporal change in the prevalence of diabetes and IGT in rural India over the period of 1989-2006 is shown in Figure 1[10]. Similar trends have been described for Thailand, Malaysia, Bangladesh and Pakistan[34]. A large pool of prediabetic subjects exists even in the rural region, as shown by the high prevalence of IGT. Recent studies in India showed that the conversion rate of IGT to diabetes is high, probably on account of the influence of lifestyle transitions[10,35]. It was noted that the prevalence of IGT decreased from 7.2% in 2003 to 5.5% in 2006, with a concomitant increase in the prevalence of diabetes. In another rural region in India, the crude prevalence of diabetes was 13.2% and prevalence of IGT was 15.9% in 2006[36]. Several other reports also show the rising trend in the prevalence of diabetes in rural regions[37,38].

The natural history of prediabetes is unclear. A review of data from 79 cross sectional studies in South Asian populations showed that diabetes prevalence was rising, whereas IGT prevalence was stable[39]. Possible explanations for this apparent discrepancy are a rapid conversion of IGT to diabetes produced by lifestyle transition or a cohort effect, with improving maternal and infant nutrition in reduced IGT and with a fall in diabetes to follow. More prospective studies are needed to address these hypotheses.

LOW THRESHOLDS FOR CONVENTIONAL RISK FACTORS

Age

Asian populations develop diabetes at a younger age than Western populations[39]. However, racial variations within Asia are evident in the age specific prevalence of diabetes. In the Asian Indian population, prevalence of diabetes peaks at 60-69 years of age, whereas in the Chinese population it peaks at 79-89 years. Indians also have a higher prevalence of IGT at a younger age than the Chinese population. The findings from Pakistan[19] and Sri Lanka[25] are similar to the results from India[10]. The ethnic differences in the prevalence of diabetes and impaired glucose regulation may not be completely explained by the living environment and geographical locations, suggesting a major role for genetic factors as well[40]. It may also be related to an interplay of higher rates of central obesity, insulin resistance, genetic predisposition and/or influence of adverse intrauterine influences present among the Asian Indian population.

Diabetes in the youth

As the prevalence of diabetes increases, the proportion of young people with diabetes also increases. The rapidly increasing prevalence of T2D in the youth is highlighted by studies in the Asian populations in native lands and in migrant countries. China showed an 88% increase in prevalence in 35-44 years age group within a period of 6 years[41]. In southern India, the prevalence of diabetes in

persons under 44 years has increased from 25% of the total prevalence in 2000 to 36% in 2006[10]. Asian people with young onset of diabetes have substantial phenotypic heterogeneity, many with a positive family history, impaired beta cell function, no islet cell autoantibodies and with clustering of cardio metabolic disorders[42,43]. The major cause for the increasing prevalence of T2D in Asian children is the increasing rate of obesity and decreasing rate of physical activity, leading to insulin resistance[44]. Most of the Asian countries are largely rural; hence a sudden change in the lifestyle of the rural people would increase the number of people affected by metabolic disorders.

The rising trend seen in the prevalence of gestational diabetes among Asian women and the increased risk for future diabetes in them may also contribute to the escalating prevalence of diabetes in young people[45].

Anthropometric characteristics

Although the prevalence of obesity and being overweight are relatively lower in Asia compared with Western populations, the recent socioeconomic transition in Asia is resulting in a parallel increase in its prevalence. Among Asians, diabetes occurs at lower BMI levels than in Western populations and small increments in weight triggers glucose intolerance in susceptible subjects[40,46,47]. Analysis of the National Health Interview survey in the United States from 1997 to 2008 showed that Asian Americans had a significantly higher rate for diabetes than the whites throughout the study period[48]. There was a significant upward trend in both groups for diabetes and BMI. However, Asian Americans, especially Asian Indians, had higher odds of developing diabetes, despite having a significantly lower BMI than the white population.

Several studies in Asian populations, particularly in Asian Indians, have highlighted the "metabolically obese" phenotype among normal weight individuals[46-53]. This phenotype, characterized by greater abdominal obesity despite a normal BMI, less muscle mass, higher percentage of body fat and increased propensity for insulin resistance compared with the Western population, renders higher susceptibility for diabetes in Asian populations[49-52].

The association of BMI and diabetes is modified by ethnicity[40]. Ethnicity is associated with several factors, such as genetic constitution, lifestyle, living environment and anthropometric characteristics. Body composition related to fat distribution is a stronger determinant of the metabolic milieu than BMI. The diabetes epidemiology, collaborative analysis of diabetes criteria in Europe/in Asia study group noted that the overall effect of age on the prevalence of diabetes differed considerably between the ethnic groups, even in the subjects with the same BMI[40]. Asian populations are prone to have more intra abdominal fat accumulation and low muscle mass. Asian Indians, in particular, have the above abnormalities which account for the high prevalence of insulin resistance and diabetes at low levels of BMI. A study by our group showed that the risk of diabetes increases progressively from a BMI of $\geqslant$ 23 kg/m^2 among Indians[54]. BMI in $\geqslant$ of 23 kg/m^2 is also considered overweight for most Asian populations[55].

Smoking and alcohol use

The risk of diabetes is shown to be higher by 45% in smokers than among non smokers[56]. Smoking increases the risk of central obesity and insulin resistance[57] and nicotine exposure has several other deleterious effects. Asian countries such as China and India continue to produce and consume tobacco products and hence face a huge public health problem.

The increasing use of alcohol in Asian countries, especially among the middle class and rural population, also increases the risk for diabetes and other metabolic diseases.

Genetic susceptibility

Prevalence of T2D is high among Asian populations, particularly so in Asian Indians, by virtue of a high genetic susceptibility and enhanced interaction with environmental triggers. Exposure to a high fat diet and lower levels of physical activity are the common factors which trigger the gene-environmental interaction.

Both the thrifty genotype and thrifty phenotype hypotheses appear to have etiological roles in development of diabetes in Asian populations. While the thrifty genotype hypothesis points to a mismatch between the ancestral genes and modern environment, the thrifty phenotype hypothesis postulates a mismatch between intrauterine and adult life environments[58]. The selective presence of "thrifty genotypes"has been considered to be advantageous in certain populations during evolutionary selection by repeated famine and feast cycles. However, these genes have rendered them highly predisposed to obesity and diabetes during the modern of era of continuous feasting[59]. The "thrift phenotype" hypothesis postulates that intrauterine malnutrition leads to metabolic and structural changes in the beta cells that are beneficial for early survival, but increases the risk of T2D and other chronic disorders in adulthood[60]. Rapid weight gain occurring in childhood due to a nutritionally rich environment enhances the risk of these adult diseases. A recent collaborative study of prospective data from large numbers of individuals in 5 low and middle income countries, including India, showed that lower birth weight is a risk factor for glucose intolerance[61]. Higher than expected weight gain between 48 mo and adolescent/adult is also a risk factor for glucose intolerance.

The combination of gestational diabetes, *in utero* nutritional imbalance, childhood obesity and over nutrition in adulthood will continue to fuel the epidemic in Asian countries undergoing rapid nutritional transitions[58].

DIABETIC COMPLICATIONS

Asian diabetic patients have a high risk of developing long term diabetic complications because they develop

the disease earlier. The association between vascular complications and poor glycemic control is well known[62,63]. The health care outcome among diabetic patients in many Asian countries is far from optimum.

Diabetes is associated with debilitating micro and macro vascular complications. As Asian populations develop diabetes at a young age, they live long enough to develop the complications too, resulting in high rates of morbidity and early mortality[1]. The risk of CVD increases by 3-4 fold in a diabetic person. More than 75% of all mortality among diabetic persons occurs from cardiovascular disease[64]. The UK Prospective Diabetes Study (UKPDS) showed that every 1% increase in HbA1c was associated with 12% increase in heart failure[64]. In diabetic subjects, several stronger risk factors other than the classic risk factors exist, such as elevated small, dense low-density lipoprotein (LDL) cholesterol or oxidized LDL, which confer a higher risk in diabetic than in non-diabetic individuals with elevated LDL. The process of atherogenesis in diabetes is complex and consists of interrelated multiple factors. The chronic hyperglycemia activates the mechanisms related to atherogenesis. The cardiovascular pathology is related to a combination of both micro and macrovascular dysfunction[64]. The epidemiology of diabetes intervention and complications study[65] in type 1 diabetes and the extended UKPDS study[66] have shown definite cardiovascular benefit with lowering of blood glucose levels.

Few population based data on prevalence of diabetic complications are available from developing countries. However, it is been estimated that nearly 30% of type 2 diabetic patients in Asian countries have retinopathy. The prevalence of diabetic end stage renal disease is also higher than among the white populations. The prevalence of neuropathy and foot complications are also high among the Asian patients[46,47].

COST OF DIABETES

The young age at onset not only increases the health care burden of treating large numbers of people with diabetes, but also increases the morbidity and premature mortality due to diabetic complications. The rate of complications increases proportionally with the duration of diabetes.

The cost of diabetes care is high and increasing worldwide. The economic burden is very high, especially in developing countries, and more so in the lower economic groups, who spend 25%-34% of their income on diabetes care[67,68]. The cost of care increases substantially when complications occur or when admission to hospital, surgery or insulin treatment is needed.

Studies from developed western countries and developing countries in Asia have shown similar results with respect to the quality of diabetes care and the glycemic outcome among the diabetic population[67,69]. Less than 30% of the patients achieve the desired glycemic goals[69].

PRIMARY PREVENTION

In most Asian countries, the medical challenge posed by the burden of diabetes is huge. It is unmatched by the budget allocations for health care. Primary prevention is important to reduce the burden of diabetes faced by patients, families and society at large. Several prospective randomized clinical trials have shown that primary prevention of T2D is possible by lifestyle intervention or by the use of pharmacological agents such as metformin[70]. The Chinese Da-Qing study[71] and the Indian Diabetes Prevention Programs[72] have shown the benefits of lifestyle modification focused on improved physical activity and healthy diet habits to prevent or at least delay the onset of diabetes in high risk subjects. Lifestyle intervention can have a sustained 43% reduction in the incidence of diabetes over a 20 year period[73].

Prevention of obesity and diabetes will be cost effective as it will prevent not only the development of diabetes but can also prevent the occurrence of complications.

The serious epidemic nature of diabetes has been recognized by the United Nations and it recommends member countries to develop national policies to combat the disease. In several Asian countries, governments have initiated national programs for the prevention and control of non-communicable diseases[74]. The health care programs implemented by Singapore have been effective and fruitful[23].

CONCLUSION

The health care and societal burden of diabetes is alarming in many Asian countries, particularly in China and India. In addition to the rising number of people with the disease and its complications, the younger age at which the disease develops and the escalating occurrence of T2D in children and adolescents are of significant concern. Rapid rates of urbanization, modernization, readily available fast foods and sedentary habits have altered the lifestyle of the population, more so among the youth. The health consequences are devastating in Asian populations due to a strong genetic predisposition to metabolic diseases like diabetes and CVD. Current lifestyle parameters perhaps accelerate the clinical expression of the disease at a very young age itself.

Primary prevention of diabetes is possible by modifying risk factors such as obesity and insulin resistance[70-74]. National programs promoting healthy lifestyle among the population, starting from a young age, should be given priority in the health care agenda.

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S- Editor Wu X **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/1948-9358office
wjd@wjgnet.com
doi:10.4239/wjd.v3.i6.118

World J Diabetes 2012 June 15; 3(6): 118-122
ISSN 1948-9358 (online)
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BRIEF ARTICLE

Sitagliptin counteracts seasonal fluctuation of glycemic control

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Received: January 6, 2012 Revised: May 11, 2012
Accepted: June 10, 2012
Published online: June 15, 2012

Abstract

AIM: To assess the effect of sitagliptin therapy on seasonal fluctuation of glycemic control in Japanese type 2 diabetic patients.

METHODS: Participating patients (age: 29-80 years) had been treated with conventional oral antidiabetic agents and/or diet and exercise therapy for over 6 mo. From December 2009, 35 patients were additionally prescribed oral sitagliptin starting from 50 mg once daily, while 19 patients taking α-glucosidase inhibitors were switched to sitagliptin. Twenty-four patients who refused sitagliptin formed the control group. Changes of mean monthly hemoglobin A_{1c} (HbA_{1c}) during the "winter holiday season" were compared between groups using Student's *t*-test (2008-2009 *vs* 2009-2010). Statistical significance was accepted at $P < 0.05$. Multivariate analysis was performed to assess whether sitagliptin use was associated with deterioration or improvement of glycemic control.

RESULTS: Both add-on sitagliptin and switching from α-glucosidase inhibitors to sitagliptin prevented the seasonal deterioration of glycemic control and tended to improve HbA_{1c}. Multivariate analysis revealed that both adding and switching to sitagliptin were negatively correlated with deterioration of glycemic control. In 44 patients who continued sitagliptin therapy for another year, elevation of HbA_{1c} was suppressed without adverse effects.

CONCLUSION: Sitagliptin is a suitable oral agent for preventing deterioration of glycemic control during the winter holiday season.

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Key words: Type 2 diabetes mellitus; Dipeptidyl-peptidase 4 inhibitors; Sitagliptin; Seasonal variation; Hemoglobin A_{1c}

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Matsuhashi T, Sano M, Fukuda K, Kohsaka S, Suzuki Y. Sitagliptin counteracts seasonal fluctuation of glycemic control. *World J Diabetes* 2012; 3(6): 118-122 Available from: URL: http://www.wjgnet.com/1948-9358/full/v3/i6/118.htm DOI: http://dx.doi.org/10.4239/wjd.v3.i6.118

INTRODUCTION

In Japan, glycemic control typically deteriorates during the New Year winter holiday season[1-3], since diabetic patients (like other Japanese) celebrate with a high calorie diet and alcohol. In 2009, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin was approved as the first

incretin enhancer for use in Japan[4-11]. Although it has been suggested that seasonal fluctuations of hemoglobin A1c (HbA1c) are noted in patients with type 2 diabetes, no reports have been published concerning the efficacy of antidiabetic agents for such fluctuations. Because the hypoglycemic effect of sitagliptin (a DPP-4 inhibitor) becomes stronger with an increase of the blood glucose level, it has the potential to inhibit seasonal HbA1c fluctuations[12-14]. To evaluate the effect of sitagliptin on seasonal fluctuation of glycemic control, we studied patients with relatively good blood glycemic control over 2 years while on treatment with conventional oral antidiabetic agents and/or diet and exercise.

Table 1 Baseline characteristics

	Add-on group (n = 35)	Switching group (n = 19)	Control group (n = 24)	P value
Age (yr)	64.66 ± 10.63	55.84 ± 12.96	63.04 ± 8.85	0.171
Gender				
Male	28	15	18	0.897
Female	7	4	6	
Disease duration (yr)	11.98 ± 9.66	10.00 ± 11.22	8.31 ± 8.25	0.797
Body mass index (kg/m^2)	24.28 ± 3.49	23.94 ± 3.69	25.20 ± 3.27	0.536
Using sulfonylureas	16	12	13	0.463

MATERIALS AND METHODS

Patients with type 2 diabetes aged 29-80 years were enrolled. Type 2 diabetes was diagnosed from clinical criteria according to the Japan Diabetes Society guidelines. They were all patients periodically attending our hospital. They were prescribed adequate diet/exercise therapy by specialists and nutritionists and received other appropriate treatment depending on their condition. There were no differences of baseline treatment between the sitagliptin and control groups. Exclusion criteria were type 1 diabetes, treatment with insulin or steroids, and poor glycemic control (HbA1c ≥ 10%). Each patient provided informed consent for monthly blood tests and the study was approved by the ethics committee of our institution. Patients receiving DPP-4 inhibitors or glucagon-like peptide-1 receptor agonists were also excluded.

Sitagliptin was released in December 2009 as the first DPP-4 inhibitor to be approved in Japan. Because this clinical study was started simultaneously with its release, patients who had already received DPP-4 inhibitor therapy were not enrolled. There is a rule in Japan that patients receiving a new drug should be examined every 2 wk for 1 year after release of the drug, so subjects were assigned to the sitagliptin and control groups solely based on whether they could attend hospital at fortnightly intervals or not. Because basal treatment was identical and there were no differences of other baseline characteristics between the two groups, the subjects were considered to be comparable. Laboratory data from 2008-2009 before the start of this study were used for baseline values. From December 2009, 35 patients were additionally prescribed oral sitagliptin starting from 50 mg once daily (add-on group), while 19 patients taking α-glucosidase inhibitors were switched to sitagliptin (switching group). Twenty-four patients who refused sitagliptin formed the control group. Throughout the 2 year observation period, the doses of oral diabetic agents other than sitagliptin were not changed. To test baseline characteristics, analysis of variance was employed for age, disease duration and body mass index, while the χ^2 test was performed for sex and use of sulfonylureas. Changes of mean monthly HbA1c during the "winter holiday season" were compared between groups using Student's t-test (2008-2009 *vs* 2009-2010) and statistical significance was accepted at $P < 0.05$. Multivariate analysis was performed to assess whether sitagliptin use was associated with deterioration or improvement of glycemic control.

RESULTS

There were no significant differences of baseline characteristics among the three groups (Table 1). When this study was started, the 54 subjects had already been treated for at least 1 year at our hospital and had a good relationship with their physicians. There were no differences of patient education between the sitagliptin group attending hospital every 2 wk and the control group attending every 4 wk because compliance with diet/exercise therapy was adequate in both groups. Since the subjects were assigned to the treated and control groups solely based on their ability to attend the hospital, there was no bias of baseline characteristics between the two groups, making it appropriate to compare the two groups in this study. From December 2008 to February 2009, the mean change of HbA1c was + 0.19% (6.51% ± 0.13% *vs* 6.72% ± 0.14%, $P < 0.001$) in the add-on group and + 0.23% (6.40% ± 0.13% *vs* 6.63% ± 0.16%, $P = 0.002$) in the control group (Figure 1). Thus, both groups showed an increase while on conventional antidiabetic therapy. From December 2009 to February 2010, the mean change of HbA1c was -0.08% (6.60% ± 0.14% *vs* 6.52% ± 0.15%, $P = 0.19$) in the add-on group and 0.22% (6.33% ± 0.12% *vs* 6.55% ± 0.14%, $P = 0.005$) in the control group. Seasonal deterioration of HbA1c was prevented in the add-on group (0.19% *vs* -0.08%). In the switching group, the mean change of HbA1c from December 2008 to February 2009 was 0.33% (6.55% ± 0.23% to 6.88% ± 0.25%, $P < 0.001$), while the mean change from December 2009 to February 2010 was 0.13% (6.48% ± 0.19% to 6.61% ± 0.18%, $P = 0.013$). Thus, deterioration of HbA1c was less marked (0.33% *vs* 0.13%). There were no changes of body weight in any group.

Multivariate analysis showed that both adding sitagliptin and switching to sitagliptin were negatively correlated with deterioration of glycemic control (defined as an increase of HbA1c by > 0.1%) after adjustment for age, gender, duration of antidiabetic therapy and body

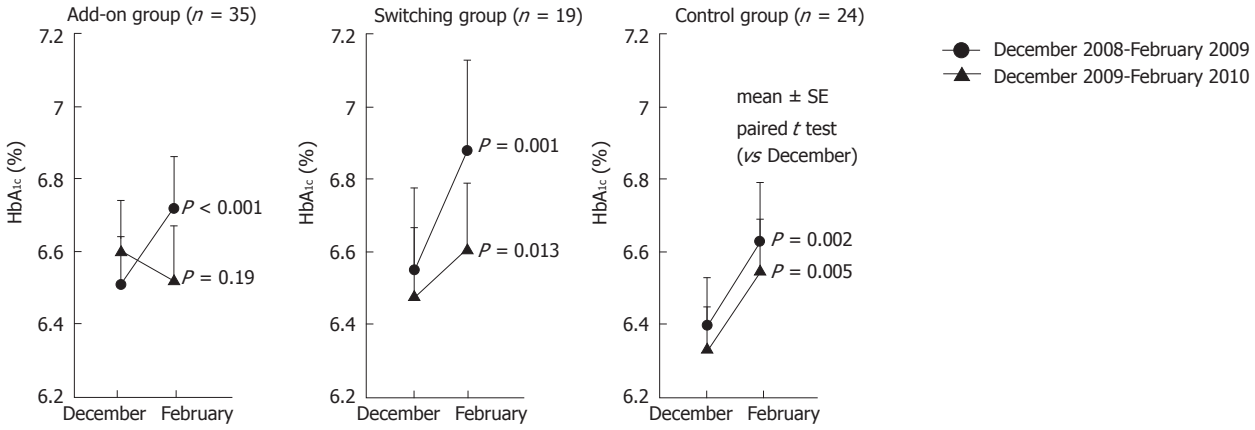

Figure 1 Changes of mean hemoglobin A1c during the winter holiday season. Circles are from December 2008 to February 2009 and triangles are from December 2009 to February 2010. Data are the mean ± SE. HbA1c: Hemoglobin A1c.

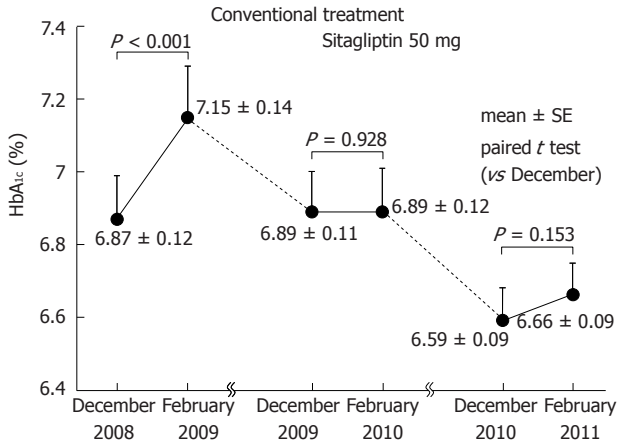

Figure 2 Changes of mean hemoglobin A1c in 44 patients during one year before and after initiation of sitagliptin therapy. Data are the mean ± SE. HbA1c: Hemoglobin A1c.

mass index [odds ratio (OR): 0.07, 95% confidence interval (CI): 0.02-0.31, and $P = 0.007$ for adding sitagliptin; OR: 0.20, 95% CI: 0.04-0.94, and $P = 0.041$ for switching to sitagliptin]. Sitagliptin treatment was also significantly correlated with a decrease of HbA1c by > 0.1% (OR: 9.85, 95% CI: 2.75-35.1, and $P < 0.001$ for adding; OR: 4.71, 95% CI: 1.11-19.8, and $P = 0.034$ for switching).

We also followed 44 patients who continued to receive sitagliptin for another year without any changes in dosages of concomitant drugs for another year (Figure 2). As occurred during the first year of sitagliptin treatment, elevation of HbA1c in February was suppressed in the second year. No adverse events or changes of weight were observed.

DISCUSSION

In Japanese patients, the effect of overeating around New Year is usually reflected by elevation of monthly HbA1c values between December and February. Although we focused on type 2 diabetic patients with good glycemic control for 2 years, HbA1c levels still increased significantly during the winter holiday season, suggesting that conventional oral antidiabetic therapy cannot prevent seasonal deterioration of glycemic control. However, the present study showed that add-on therapy with sitagliptin prevented seasonal deterioration of glycemic control and tended to improve HbA1c despite the increased calorie intake and decrease of physical activity during the New Year holiday period.

In 44 patients who continued sitagliptin therapy for an additional year, elevation of HbA1c was also suppressed in the second year, demonstrating the characteristics of incretin therapy, which exerts a stronger hypoglycemic effect when blood glucose levels are high. Our results suggest that sitagliptin, which has been reported to suppress diurnal variation of blood glucose levels, may also suppress seasonal variation and is a suitable oral agent for preventing deterioration of glycemic control during the winter holiday season in Japanese patients with type 2 diabetes.

Although this was a relatively small study, the results are considered to be reliable because: (1) all of the patients who visited our hospital during a one month period (December) were enrolled, except for those who met the exclusion criteria; and (2) patients assigned to the control group were selected solely on the basis that they could not attend the hospital fortnightly and all participating patients received similar basal treatment (including diet).

According to Takao *et al*[15] who investigated glycemic control over 10 years in Japanese type 2 diabetic patients, there was a correlation between the change of blood glucose and progression of diabetic retinopathy. In addition, Wadén *et al*[16] reported that HbA1c variability could not only predict incident microalbuminuria and progression of renal disease, but also cardiovascular events in type 1 diabetes patients. Bouchi *et al*[17] recently reported that there is a relationship between blood glucose changes and cardiovascular events in Japanese patients with type 2 diabetes. Thus, the importance of good glycemic control has continued to attract attention. There is a possibility that cardiovascular events can be prevented by regulating blood glucose excursion. Because previous reports

concerning cardiovascular events in Japanese type 2 diabetic patients have not clarified this issue, whether blood glucose excursion is related to cardiovascular events remains to be determined[18]. HbA_{1c} elevation during the winter holiday season was also attenuated by switching from α-glucosidase inhibitors to sitagliptin (HbA_{1c} increased by 0.33% before switching *vs* 0.13% after switching). This 0.2% difference of HbA_{1c} over 2 mo between α-glucosidase inhibitor therapy and sitagliptin is clinically important.

It is too early to draw definite conclusions from our study without placebo control. Further investigations are needed to confirm whether better glycemic control by using sitagliptin with or without other oral hypoglycemic agents can improve pre-existing atheroma and thus prevent major cardiovascular events[19-26].

COMMENTS

Background

Epidemiological studies have suggested that seasonal fluctuations of hemoglobin A_{1c} (HbA_{1c}) are noted in patients with type 2 diabetes, but no reports have been published concerning the efficacy of antidiabetic agents for such HbA_{1c} fluctuations.

Research frontiers

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was the first incretin enhancer approved in Japan (in 2009). This drug causes few side effects when regulating blood glucose levels but the effect of sitagliptin therapy on seasonal fluctuation of glycemic control in Japanese type 2 diabetic patients is unknown.

Innovations and breakthroughs

This is the first study to demonstrate that add-on therapy with sitagliptin can prevent seasonal deterioration of glycemic control and even improve HbA_{1c} levels despite the increased calorie intake and decrease of physical activity during the New Year holiday period.

Applications

In Japan, glycemic control typically deteriorates during the New Year winter holiday season, since Japanese people (including diabetic patients) celebrate with a high calorie diet and alcohol. By understanding and utilizing the response to sitagliptin demonstrated in the present study, treatment can be tailored to better manage the seasonal deterioration of glycemic control, which is unfavorable for patients with type 2 diabetes.

Terminology

DPP-4 inhibitors, of which sitagliptin was the first to be released in Japan, inhibit the enzyme DPP-4 and are used to treat type 2 diabetes. Inhibition of DPP-4 enhances the activity of incretins that play an important role in regulating insulin secretion and blood glucose.

Peer review

This is an interesting study that suggests the beneficial effects of sitagliptin during the winter holiday period in Japanese diabetic patients. The authors report that HbA_{1c} was significantly reduced during the holiday period in diabetic patients switching to sitagliptin or using it as add-on therapy compared with control patients.

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S- Editor Wu X **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/1948-9358office
wjd@wjgnet.com
doi:10.4239/wjd.v3.i6.123

World J Diabetes 2012 June 15; 3(6): 123-129
ISSN 1948-9358 (online)
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BRIEF ARTICLE

Association between psychological distress and gastrointestinal symptoms in diabetes mellitus

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Supported by The Qatar Diabetic Association and Qatar National Research Fund- QNRF NPRP 30-6-7-38
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Received: April 8, 2012 Revised: May 27, 2012
Accepted: June 10, 2012
Published online: June 15, 2012

Abstract

AIM: To examine the possible association between gastrointestinal symptoms and anxiety and depression in type 2 diabetes mellitus (T2DM).

METHODS: The study was a matched case-control study based on a face to face interview with designed diagnostic screening questionnaires for gastrointestinal (GI) symptoms and T2DM, Patient Health Questionnaire (PHQ-9) for depression and General Anxiety Disorders (GAD-7) for anxiety. The questionnaire consisted of questions about symptoms and signs of anxiety and depression disorders. Also, socio-demographic characteristics, life style habits and the family history of patients were collected. It was carried out from June 2010 to May 2011 among Qatari and other Arab nationals over 20 years of age at Primary Health Care Centers of the Supreme Council of Health, Qatar, including patients with diabetes mellitus and healthy subjects over 20 years of age.

RESULTS: In the studied sample, most of the studied T2DM patients with GI symptoms (39.3%) and healthy subjects (33.3%) were in the age group 45-54 years ($P < 0.001$). The prevalence of severe depression (9.5% *vs* 4.4%, $P < 0.001$) and anxiety (26.3% *vs* 13.7%, $P < 0.001$) was significantly higher in T2DM patients with GI symptoms than in general population. Obesity (35.7% *vs* 31.2%) and being overweight (47.9% *vs* 42.8%) were significantly higher in T2DM patients with GI symptoms than in healthy subjects ($P = 0.001$). Mental health severity score was higher in T2DM patients with GI symptoms than in healthy subjects; depression (8.2 ± 3.7 *vs* 6.0 ± 3.6) and anxiety (7.6 ± 3.3 *vs* 6.0 ± 3.7). The most significant GI symptom which was considerably different from controls was early satiety [odds ratio (OR) = 10.8, $P = 0.009$] in depressed T2DM patients and loose/watery stools (OR = 2.79, $P = 0.029$) for severe anxiety. Anxiety was observed more than depression in T2DM patients with GI symptoms.

CONCLUSION: Gastrointestinal symptoms were significantly associated with depression and anxiety in T2DM patients, especially anxiety disorders.

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Key words: Gastrointestinal; Type 2 diabetes mellitus; Distress; Depression; Anxiety; Qatar

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Bener A, Ghuloum S, Al-Hamaq AOAA, Dafeeah EE. Association between psychological distress and gastrointestinal symptoms in diabetes mellitus. *World J Diabetes* 2012; 3(6): 123-129 Available from: URL: http://www.wjgnet.com/1948-9358/full/v3/i6/123.htm DOI: http://dx.doi.org/10.4239/wjd.v3.i6.123

INTRODUCTION

Gastrointestinal (GI) diseases are common worldwide. Although GI symptoms are very common in the general population, recent studies reported that GI complaints are commonly reported by diabetic patients, when compared with non-diabetic controls[1]. GI disturbances commonly include symptoms of stomach pain, heart burn, diarrhea, constipation, nausea and vomiting. Koch *et al*[2] indicated that complications involving the GI tract occur frequently and represent a major cause of morbidity in diabetes mellitus (DM). Although GI symptoms are not life threatening, the majority of those affected will cause significant burden to the health care system as well as reduced quality of life[3]. A study in Germany documented that GI symptoms were more frequent in patients with DM compared with controls[4]. Previous studies by Bener *et al*[5,6] stated that DM is becoming increasingly common because of the epidemic of obesity and sedentary lifestyles in the Qatar. A more recent study[7] revealed that the prevalence rate of GI disorders is high in the general community and there is a significant association with psychological disorders. But, no study has yet been conducted in Qatar to determine the prevalence of GI symptoms among the diabetic population. It is important to investigate the prevalence of GI symptoms in the diabetic population because GI symptoms affect quality of life adversely and represent a substantial cause of morbidity in patients with diabetes.

In general, GI symptoms are influenced by psychological factors such as depression and anxiety. Talley *et al*[8] indicated that diabetic patients with anxiety and depression had a two fold higher prevalence of GI symptoms. Moreover, a case-control study[9] in Qatar of the prevalence of psychological distress in diabetic patients showed that depression and anxiety were severe in diabetes, which is two fold higher than in non-diabetics. The three studies revealing the high prevalence of GI symptoms in general community and its association with psychological disorders and the severity of depression and anxiety in diabetics initiated the authors to examine whether these GI symptoms are more frequent in diabetic patients and to assess the association of GI symptoms with the psychological disorders. Investigation of a possible association between psychological distress and GI symptoms in diabetics has been extremely limited. The combination of psychological disorders and diabetes is common and especially harmful because it has a strong impact on psychosocial as well as medical outcomes in patients with diabetes[10]. Also, the gastrointestinal disturbances in diabetes may result from psychiatric morbidity.

In the Middle East region, we have found no studies examining the prevalence of GI symptoms and its association with psychological disorders in the diabetic population. This is the first study in Qatar investigating the prevalence of GI symptoms among the type 2 diabetes mellitus (T2DM) patients, as well as their psychosocial impact.

MATERIALS AND METHODS

This is a matched case-control study performed at the primary health care centers. The survey was conducted among the population residing in the Qatar from June 2010 to May 2011. Primary health care centers are frequented by all levels of the general population as a gateway to specialized care. The study was approved by the Hamad General Hospital, Hamad Medical Corporation. All human studies have been approved by the Research Ethics Committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

T2DM is a major chronic disease with high morbidity and mortality in Qatar[9-11] and it is considered to be on the verge of an emerging diabetes epidemic. The power calculation was actually based on a reported prevalence rate of T2DM of 16.7%[6], allowing an error of 5%, level of significance (type-1 error) of 1% and with 95% confidence limits. It was computed that 453 cases and 453 controls as a sample size were needed to achieve the objective of our study. Of the 22 primary health care centers available, we selected 12 health centers at random. Of these, 9 were located in urban and three in semi-urban areas of Qatar. Finally, subjects were selected systematically 1-in-2 using a systematic sampling procedure. Each participant was provided with brief information about the study and was assured of strict confidentiality. The study excluded patients who were under 20 and over 65 years, patients with any cognitive or physical impairment and who refused to give consent to take part in the study.

Selection of T2DM subjects

The diagnosis of diabetes mellitus and impaired glucose tolerance was based on the criteria by the American Diabetes Association[12]. Subjects reporting a history of DM and currently taking oral medications for diabetes were considered to have DM. DM was defined according to the World Health Organization Expert Committee group[13], i.e. fasting venous blood glucose concentration $\geqslant$ 7.0 mmol/L and/or 2 h post-glucose meter and an oral glucose tolerance test (OGTT) venous blood glucose concentration $\geqslant$ 11.1 mmol/L. In all subjects, fasting blood glucose determined by OGTT was conducted only if blood sugar was < 7 mmol/L. For the OGTT, subjects were requested to drink, within the space of 5 min, 75 g anhydrous glucose dissolved in 250 mL water. Samples were processed within 30 min of collection and the above laboratory tests were measured. A total number of 625 T2DM patients aged over 20 years were selected sys-

tematically 1-in-2 using a systematic sampling procedure of the Primary Health Care (PHC) centers and 453 cases agreed to participate in the study, with a response rate of 72.5%.

Selection of controls

Control subjects aged over 20 years were identified from the community as healthy if their venous blood glucose values were < 6.1 mmol/L and if they had never taken any diabetic medication. This group involved a random sample of 646 healthy subjects who visited the PHC centers for any reason other than acute or chronic disease. Of the 646 healthy subjects approached, 453 controls responded to our questionnaire, with a response rate of 70.1%. The healthy subjects were selected in a way to match the age and the gender of cases to give a good representative sample of the studied population.

The data were collected through validated self-administered questionnaires with the help of qualified nurses. The questionnaire had three sections. The first part included socio-demographic details, medical and family history, and dietary habits of patients. The second part included the most prevalent GI symptoms in primary care, like esophageal symptoms, upper dysmotility symptoms, constipation and diarrhea.

Depression was assessed with the eight-item depression module of the Patient Health Questionnaire (PHQ-9)[14]. Patients were asked to answer the questions by grading them from 0 to 3; with 0 for "not at all", 1 for "several days", 2 for "more than half of days" and 3 for "nearly every day". Anxiety was assessed with the General Anxiety Disorders (GAD-7)[15]. Patients were asked to answer the questions by grading them from 0 to 3; with 0 for "not at all", 1 for "several days", 2 for "more than half the days", and 3 for "nearly every day". PHQ-9 ⩾ 15 represent severe symptoms of depression and GAD ⩾ 11 represent severe symptoms of anxiety disorders. We used cut-off scores of ⩾ 15 on PHQ-9 and cut-off score of ⩾ 11 on GAD-7 because this threshold reflects severe levels of depression and anxiety. Content validity, face validity and reliability of the questionnaire were tested using 100 children. These tests demonstrated a high level of validity and high degree of repeatability (kappa = 0.86).

Student-*t* test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by non-parametric Mann-Whitney test. χ^2 and Fisher's exact test were performed to test for differences in proportions of categorical variables between two or more groups. Stepwise logistic regression analysis was used to predict potential confounders and order the importance of risk factors (determinant) for diabetic factors associated with GI symptoms. The level $P < 0.05$ was considered as the cut-off value for significance.

RESULTS

Table 1 shows the socio-demographic characteristics of the studied T2DM patients with GI symptoms and healthy subjects. Most of the studied T2DM patients with GI symptoms (39.3%) and healthy subjects (33.3%) were in the age group 45-54 years ($P < 0.001$). The prevalence of severe depression (9.5% *vs* 4.4%, $P < 0.001$) and anxiety (26.3% *vs* 13.7%, $P < 0.001$) was significantly higher in T2DM patients with gastrointestinal symptoms compared to healthy subjects. Mental health severity score was higher in T2DM patients with GI symptoms than in healthy subjects; depression (8.2 ± 3.7 *vs* 6.0 ± 3.6) and anxiety (7.6 ± 3.3 *vs* 6.0 ± 3.7). A significant difference was observed in the age group between T2DM with GI symptoms and non-diabetic subjects ($P < 0.001$). Most of the studied subjects were married (83.9%), with secondary education (32.7%) and sedentary/professional jobs (30.4%).

Table 2 shows the lifestyle habits and family history of studied T2DM patients with GI symptoms and healthy subjects. Obesity (35.7% *vs* 31.2%) and being overweight (47.9% *vs* 42.8%) were significantly higher in T2DM patients with GI symptoms compared to healthy subjects ($P = 0.001$). Compared with healthy subjects, physical activity was significantly less frequent in T2DM patients with GI symptoms (64.9% *vs* 43.9%, $P < 0.001$) and smoking was also higher in T2DM patients (30% *vs* 13.9 %, $P = 0.001$).

Table 3 presents the comparison of gastrointestinal symptoms between studied T2DM patients with GI symptoms and healthy subjects with severe anxiety and depression. The depression and anxiety were more prevalent in T2DM patients with most of the GI symptoms compared to healthy subjects. Compared to healthy subjects, the diabetic patients were more depressed with a significant difference with anal blockage (46.5% *vs* 20%, $P = 0.050$), heartburn (41.9% *vs* 15%, $P = 0.046$), < 3 bowels/wk (51.2% *vs* 20%, $P = 0.028$), > 3 bowels/d (48.8% *vs* 20%, $P = 0.050$), early satiety (41.9% *vs* 5%, $P = 0.003$) and fecal incontinence (37.2% *vs* 5%, $P = 0.007$). The diabetic patients were significantly more anxious with GI symptoms of anal blockage (53.3% *vs* 35.5%, $P = 0.026$), heartburn (34.6% *vs* 17.7%; $P = 0.019$), loose/watery stools (26.2% *vs* 11.3%, $P = 0.021$) and postprandial illness (26.2% *vs* 12.9%, $P = 0.042$).

Table 4 shows the extracted odd ratios and confidence intervals of GI symptoms on anxiety and depression with diabetic patients *vs* healthy subjects. The diabetic patients with severe anxiety were significantly more different from the healthy subjects in loose/watery stools (OR = 2.79, $P = 0.029$), heartburn (OR = 2.45, $P = 0.022$), postprandial fullness (OR = 2.39, $P = 0.042$), anal blockage (OR = 2.07 $P = 0.026$) and dysphasia (OR = 1.98; $P < 0.001$). Similarly, diabetic depressed patients were also significantly different from non-diabetic subjects in early satiety (OR = 10.8; $P = 0.009$), fecal incontinence (OR =8.89; $P = 0.024$), heartburn (OR = 5.04; $P = 0.036$), < 3 bowels/wk (OR = 4.54; $P = 0.038$), > 3 bowels/d (OR = 4.14; $P = 0.043$) and anal blockage (OR = 3.77; $P = 0.05$).

Figure 1 reveals the distribution of severe levels of depression and anxiety in diabetic patients with GI symptoms. The prevalence of anxiety was observed more in

Table 1 Socio-demographic characteristics of the diabetic subjects with gastrointestinal symptoms and controls *n* (%)

Variables	Total *n* = 906	Diabetic with GI *n* = 453	Healthy subjects *n* = 453	*P* value
Age (mean ± SD)	46.9 ± 10.3	49.0 ± 9.9	44.8 ± 10.2	< 0.001
Age group (yr)				
< 35	121 (13.4)	37 (8.2)	84 (18.5)	
35-44	225 (24.8)	101 (22.3)	124 (27.4)	< 0.001
45-54	329 (36.3)	178 (39.3)	151 (33.3)	
⩾ 55	231 (25.5)	137 (30.2)	94 (20.8)	
Gender				
Male	544 (60.0)	278 (61.4)	266 (58.7)	0.456
Female	362 (40.0)	175 (38.6)	187 (41.3)	
Nationality				
Qatari	423 (46.7)	200 (44.2)	223 (49.2)	0.143
Non-Qatari	483 (53.3)	253 (55.8)	230 (50.8)	
Marital status				
Single	146 (16.1)	62 (13.7)	84 (18.5)	0.058
Married	760 (83.9)	391 (86.3)	369 (81.5)	
Educational level				
Illiterate	56 (6.2)	32 (7.1)	24 (5.3)	
Primary	114 (12.6)	63 (13.9)	51 (11.3)	
Intermediate	182 (20.1)	96 (21.2)	86 (19.0)	0.329
Secondary	296 (32.7)	139 (30.7)	157 (34.7)	
University	258 (28.5)	123 (27.2)	135 (29.8)	
Occupation				
Not working/housewife	275 (30.4)	132 (29.1)	143 (31.6)	
Sedentary/professional	275 (30.4)	138 (30.5)	137 (30.2)	
Clerk/manual	187 (20.6)	90 (19.9)	97 (21.4)	0.564
Businessman	106 (11.7)	56 (12.4)	50 (11.0)	
Army/police/security	63 (7.0)	37 (8.2)	26 (5.7)	
Household income[1]				
< 5000	71 (7.8)	38 (8.4)	33 (7.3)	
5000 – 9999	303 (33.4)	147 (32.5)	156 (34.4)	0.227
10 000 – 15 000	328 (36.2)	176 (38.9)	152 (33.6)	
> 15 000	204 (22.6)	92 (20.3)	112 (24.7)	
Mental health severity				
PHQ-9 depression (0–24) mean ± SD (95% CI)	7.1 ± 3.8	8.2 ± 3.7 (7.9-8.6)	6.0 ± 3.7 (5.7-6.4)	< 0.001
GAD-7 anxiety (0-21) mean ± SD (95% CI)	6.8 ± 3.6	7.6 ± 3.3 (7.3-7.9)	6.0 ± 3.7 (5.7-6.4)	< 0.001
Comorbidity				
Severe depression (PHQ⩾ 15)	59 (6.5)	43 (9.5)	20 (4.4)	< 0.001
Severe anxiety (GAD7⩾ 11)	169 (18.6)	107 (23.6)	62 (13.7)	< 0.001
Frequency of GI symptoms (at least two or more symptoms)	389 (42.9)	264 (58.3)	217 (47.9)	0.002

[1]$ 1 US Dollars = 3.65 Qatar Riyals; GI: Gastrointestinal; PHQ: Patient health questionnaire; GAD: General anxiety disorders.

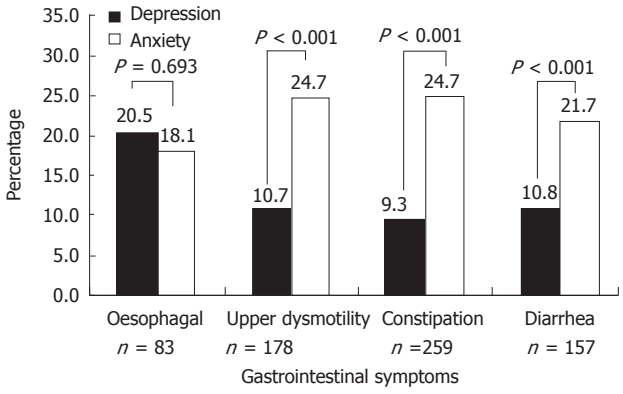

Figure 1 Distribution of severe levels of depression and anxiety in diabetic patients with gastrointestinal symptoms (*n* = 453).

diabetic patients with GI symptoms; upper dysmotility (24.7% *vs* 10.7%, $P < 0.001$), constipation (24.7% *vs* 9.3%, $P < 0.001$) and diarrhea (21.7% *vs* 10.8%, $P < 0.001$), while depression was higher in esophageal symptoms (20.5% *vs* 18.1%).

DISCUSSION

Gastrointestinal symptoms are reportedly common in diabetic patients and symptoms are also frequent in individuals without DM. Therefore, this study determined whether these GI symptoms are more frequent in the diabetic population of Qatar and also assessed the association between GI disorders and psychological distress. The potential association between GI symptoms and psychological distress in diabetes has not been studied in this region. It is important to assess the effect of GI symptoms on the psychological profile for individual symptoms in diabetic patients because the co-occurrences of psychological disorders and gastrointestinal symptoms

Table 2 Lifestyle habits and family history of diabetic patients with gastrointestinal symptoms and healthy subjects (*n* = 906) *n* (%)

Variables	Diabetic with GI *n* = 453	Healthy subjects *n* = 453	*P* value
BMI (kg/m^2)			
Normal (< 25)	74 (16.3)	118 (26.0)	
Overweight (25-30)	217 (47.9)	194 (42.8)	0.001
Obese (> 30)	162 (35.7)	141 (31.2)	
Physical activity			
Yes[1]	159 (35.1)	254 (56.1)	< 0.001
No	294 (64.9)	199 (43.9)	
Smoking (Cigarette/sheesha)			
Yes	136 (30.0)	63 (13.9)	0.001
No	317 (70.0)	390 (86.1)	
Dietary habits[2]			
Type of food			
Arabic	408 (90.1)	402 (88.7)	0.590
Indian/Pakistani	59 (13.0)	87 (19.2)	0.014
Western	24 (5.3)	34 (7.5)	0.222
Type of oil			
Vegetable oil	302 (66.7)	299 (66.0)	0.833
Olive oil	248 (54.7)	181 (40.0)	< 0.001
Animal fat/butter	104 (23.0)	92 (20.3)	0.334
Pattern of daily food			
Vegetable	327 (72.2)	242 (53.4)	< 0.001
Fruit	221 (48.8)	144 (31.8)	< 0.001
Red meat	206 (45.5)	256 (56.5)	0.001
Chicken	240 (53.0)	157 (34.7)	< 0.001
Fish	189 (41.7)	113 (24.9)	< 0.001
Type of drink			
Arabic coffee	342 (75.5)	337 (74.4)	0.759
Turkish coffee	55 (12.1)	49 (10.8)	0.602
Nescafe	170 (37.5)	54 (11.9)	< 0.001
Juice	100 (22.1)	78 (17.2)	0.079
Tea	361 (79.7)	367 (81.0)	0.676

[1]At least 30 min walking per day. [2]Multiple option. BMI: Body mass index; GI: Gastrointestinal.

contribute to a high medical utilization in primary health care settings. Co-morbidity seems to play an essential role in increasing symptoms. The study detected higher levels of gastrointestinal symptoms in the diabetic population with depression and anxiety compared to the general population. However, patients with diabetes are almost twice as likely to suffer from anxiety and depression than the general population[16].

In the study sample, the prevalence of severe depression (9.5% *vs* 4.4%, $P < 0.001$) and anxiety (26.3% *vs* 13.7%) was significantly higher in diabetic patients than in the healthy population. Koloski *et al*[17] reported that psychological distress is linked to having persistent GI symptoms and frequently seeking health care. More than half of the diabetic patients (58.3%) evaluated reported at least two or more troublesome GI symptoms, which is very close to the figure reported in a study by Talley *et al*[18] (40%), with a significant difference with the healthy subjects. An increased prevalence of GI symptoms in patients with diabetes was reported in the study sample which is in agreement with previous studies[1,19]. In a Chinese diabetic population[20], it was found that 70% of them had GI symptoms which was much higher than in their non-diabetic controls. The difference in GI symptoms prevalence among studies depends on the specific diabetic population. The majority of the diabetic patients (39.3%) with gastrointestinal symptoms were observed in the age group 45-54 years.

In our diabetic population, patients were more depressed with the GI symptoms of anal blockage (46.5% *vs* 20.0%), heartburn (41.9% *vs* 12.5%), < 3 bowels/wk (51.2% *vs* 18.8%), > 3 bowels/d (48.8% *vs* 20.0%), early satiety (41.9% *vs* 5%) and fecal incontinence (37.2% *vs* 5%) compared to healthy subjects. In a study by Kolaski *et al*[17], it was found that increased levels of psychological distress were associated with persistent GI symptoms, in particular abdominal pain, constipation and bloating, which is similar to our study results. De Kort *et al*[21] indicated that GI symptoms were considerably higher in the diabetic population with 17.9% for diarrhea, 16.1% for constipation, 19.6% for bloating and 12.5% for early satiety. Bytzer *et al*[19] showed an increased prevalence of diarrhea or constipation (15.6%), bloating (12.3%) and early satiety (54%) in diabetic patients. Even the odd ratios revealed that early satiety (OR = 10.8), fecal incontinence (OR = 8.89), heartburn (OR = 5.04), < 3 bowels/wk (OR = 4.54), > 3 bowels/d (OR = 4.14) and anal blockage (OR = 3.77) were significantly different in diabetic depressed patients from healthy subjects. These data show that gastrointestinal symptoms were more closely related to psychiatric disturbances. On the other hand, it is also possible that unpleasant GI symptoms lead to increased anxiety and depression.

Even so, the studied diabetic patients were significantly more anxious with the GI symptoms of anal blockage (53.3% *vs* 35.5%), heartburn (34.6% *vs* 17.7%), loose/watery stools (26.2% *vs* 11.3%) and postprandial illness (26.2% *vs* 12.9%) and they were significantly different from their counterparts. It is documented that psychological vulnerability is associated with a poorer outcome for people with chronic GI symptoms[22]. In studied diabetic patients with severe anxiety, odd ratios revealed that loose/watery stools (OR = 2.79), heart burn (OR = 2.45), postprandial fullness (OR = 2.39), anal blockage (OR = 2.07) and dysphasia (OR = 1.98) symptoms remained significantly different from healthy subjects. Odd ratios reported in a study revealed that suffering diabetes was associated with suffering a mental disorder[23]. Gastrointestinal symptoms negatively affect health related quality of life in diabetes and clinicians should consider psychological factors in the treatment of GI symptoms.

The study findings show that psychological distress may be one important underlying component of the condition and should be considered by physicians in their treatment of patients. One study suggests that physicians could usefully explore the fear and anxiety of patients about their symptoms to reduce subsequent health care seeking[24]. In our diabetic population, psychological factors seem to affect GI symptoms to a large extent and should be taken into account when considering treatment of these symptoms. The current high prevalence of type 2 diabetes is likely to result in a heavy burden of diabetes complications; this will pose a significant challenge to individuals, communities and health care systems during the coming decades.

Table 3 Comparison of gastrointestinal symptoms between diabetic patients and healthy subjects with severe anxiety and depression (n = 906)

Variables	Severe anxiety[1]		*P* value	Severe depression[2]		*P* value
	DM with GI	Healthy subjects		DM with GI	Healthy subjects	
GI symptoms	n = 107	n = 62		n = 43	n = 20	
Anal blockage	57 (53.3)	22 (35.5)	0.026	20 (46.5)	4 (20)	0.050
Bloating	54 (50.5)	25 (40.3)	0.203	18 (41.9)	6 (30)	0.416
Urgency	54 (50.5)	24 (38.7)	0.139	17(39.5)	5 (25)	0.395
Vomiting	37 (34.6)	16 (25.8)	0.236	18 (41.9)	5 (25)	0.264
Dysphasia	44 (41.1)	-	-	26 (60.5)		-
Nausea	38 (35.5)	19 (30.6)	0.519	13 (30.2)	6 (30)	0.980
Heartburn	37 (34.6)	11 (17.7)	0.019	18 (41.9)	3 (15)	0.046
< 3 bowels/wk	36 (33.6)	18 (29.0)	0.805	22 (51.2)	4 (20)	0.028
> 3 Bowels/d	32 (29.9)	18 (29.0)	0.993	21 (48.8)	4 (20)	0.050
Abdominal pain	22 (20.6)	16 (25.8)	0.431	10 (23.3)	5 (25)	0.989
Lumpy/hard stools	30 (28.0)	13 (21.0)	0.309	13 (30.2)	5 (25)	0.770
Blood in stool	24 (22.4)	19 (30.6)	0.237	6 (14.0)	5 (25)	0.304
Early satiety	28 (26.2)	17 (27.4)	0.859	18 (41.9)	1 (5)	0.003
Loose/watery stools	28 (26.2)	7 (11.3)	0.021	10 (23.3)	5 (25)	0.989
Fecal incontinence	25 (23.4)	17 (27.4)	0.557	16 (37.2)	1 (5)	0.007
Weight loss	25 (23.4)	10 (16.1)	0.263	6 (14.0)	6 (30)	0.172
Postprandial fullness	28 (26.2)	8 (12.9)	0.042	7 (16.3)	4 (20)	0.732

[1]Severe anxiety (GAD7 $\geqslant$ 11). [2]Severe depression (PHQ $\geqslant$ 15). DM: Diabetes mellitus; GI: Gastrointestinal; PHQ: Patient Health Questionnaire; GAD: General Anxiety Disorders.

Table 4 Odd ratios and 95% CI of gastrointestinal symptoms on anxiety and depression in diabetes mellitus patients *vs* controls

GI symptoms	OR	95% CI	*P* value
Anxiety			
Loose/watery stools	2.79	(1.14-6.83)	0.029
Heartburn	2.45	(1.14-5.26)	0.022
Postprandial fullness	2.39	(1.01-5.65)	0.042
Anal blockage	2.07	(1.10-3.95)	0.026
Dysphasia	1.98	(1.67-2.36)	< 0.001
Depression			
Early satiety	10.8	(1.30-89.34)	0.009
Fecal incontinence	8.89	(1.07-73.8)	0.024
Heartburn	5.04	(1.02-24.98)	0.036
< 3 bowels/wk	4.54	(1.13-18.26)	0.038
> 3 Bowels/d	4.14	(1.03-16.6)	0.043
Anal blockage	3.77	(0.94-15.41)	0.050

GI: Gastrointestinal; OR: Odd ratios.

The study findings revealed that all GI symptoms occur frequently in diabetic patients compared with community controls. Also, GI symptoms in diabetes are strongly linked to depression and anxiety. The study has observed a significantly increased prevalence of the GI symptoms like anal blockage, heartburn, < 3 bowel/wk, < 3 bowels/d and fecal incontinence in depressed diabetic patients compared to healthy subjects. Anxiety, loose/watery stools, heartburn, postprandial fullness, anal blockage and dysphasia were significantly different from controls. Further studies are recommended to clarify the potential causal relationship between GI symptoms and psychological factors in diabetes.

ACKNOWLEDGMENTS

The authors would like to thank the Hamad Medical Corporation for their support and ethical approval (ref: RP#7100/07).

COMMENTS

Background

Gastrointestinal symptoms are reportedly more common in diabetic patients. Little is known about the natural history of gastrointestinal symptoms and what factors influence gastrointestinal (GI) symptom patterns in diabetic patients. So this study aimed to examine the possible association between gastrointestinal symptoms with anxiety and depression in type 2 diabetes mellitus (T2DM).

Research frontiers

The prevalence of diabetes mellitus and its complications are high in the community. The study highlighted the importance of establishing a disease registry on diabetes mellitus and follow up screening for their complications.

Innovations and breakthroughs

In the present study, the authors report the high occurrence of GI symptoms in diabetic patients compared to the healthy subjects. Also, the study observed a high prevalence of gastrointestinal symptoms in diabetic patients with depression and anxiety. The important study findings of the present article were compared with similar studies so as to allow the readers to understand the situation and major points related to the topic.

Applications

The study recommended further studies to clarify the potential relationship between GI symptoms and psychological factors in diabetes.

Peer review

In this study, the authors attempted to identify the association of psychological distress and gastrointestinal symptoms in T2DM patients. The study suggests that physicians should consider psychological factors in the treatment of GI symptoms in diabetic patients. Readers can understand that the gastrointestinal symptoms affect health related quality of life in diabetes.

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World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/1948-9358office
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World J Diabetes 2012 June 15; 3(6): I
ISSN 1948-9358 (online)
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Acknowledgments to reviewers of *World Journal of Diabetes*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Diabetes*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Diabetes 2012 June 15; 3(6): I
ISSN 1948-9358 (online)
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Events Calendar 2012

January 15-17, 2012
ICADIT 2012: International conference on Advances in Diabetes and Insulin Therapy
Zurich, Switzerland

January 29-February 3, 2012
Genetic and Molecular Basis of Obesity and Body Weight Regulation
Santa Fe, NM, United States

February 3, 2012
The Future of Obesity Treatment
London, United Kingdom

February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

March 1-3, 2012
International conference on Nutrition and Growth
Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
Glasgow, United Kingdom

March 15 -16, 2012
Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
Philadelphia, PA, United States

March 15 -17, 2012
2012 DF Con - Diabetic Foot Global Conference
Hollywood, CA, United States

March 19-22, 2012
Society for Endocrinology BES 2012
Harrogate, United Kingdom

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Rio de Janeiro, Brazil

March 29-31, 2012
The 4th International Conference on Advances in Diabetes and Insulin Therapy
Riga, Latvia

March 29-April 1, 2012
New Frontiers in Diabetes Management
Ocho Rios, Jamaica

April 2-6, 2012
6th Annual Primary Care Spring Conference: Session 1
Palm Coast, FL, United States

April 4-7, 2012
39th Panhellenic Congress of Endocrinology and Metabolism
Athens, Greece

April 11-13, 2012
ICDM 2012: International Conference on Diabetes and Metabolism
Venice, Italy

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 16-17, 2012
Paediatric and Adolescent Diabetes
Birmingham, United Kingdom

April 22-25, 2012
9th International Podocyte Conference
Miami, FL, United States

May 9-12, 2012
19th European Congress on Obesity
Lyon, France

May 23-27, 2012
AACE 21st Annual Scientific and Clinical Congress - American Association of Clinical Endocrinologists
Philadelphia, PA, United States

May 24-27, 2012
27th Annual Clinical Conference on Diabetes
Bonita Springs, FL, United States

June 8-12, 2012
American Diabetes Association's 72nd Scientific Sessions
Philadelphia, PA, United States

June 29-August 2, 2012
ESE Summer School on Endocrinology
Bregenz, Austria

August 1-4, 2012
AADE 39th Annual Meeting - American Association of Diabetes Educators
Indianapolis, IN, United States

September 13-16, 2012
EMBO-EMBL Symposium: Diabetes and Obesity
Heidelberg, Germany

October 1-5, 2012
48th European Association for the Study of Diabetes Annual Meeting
Berlin, Germany

November 7-9, 2012
40th Meeting of the British Society for Paediatric Endocrinology and Diabetes
Leeds, United Kingdom

November 8-11, 2012
The 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Barcelona, Spain

December 4-6, 2012
1st American Diabetes Association Middle East Congress
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World J Diabetes 2012 June 15; 3(6): I-V
ISSN 1948-9358 (online)
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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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Columns

The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

Name of journal

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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