

## INCIDENCE OF YOUNG ONSET INSULIN-REQUIRING DIABETES MELLITUS AMONG 18- TO 30-YEAR-OLDS IN DHAKA, BANGLADESH (1994–2003)

SAIKA NIZAM<sup>1</sup>, MD. KHALEQUZZAMAN<sup>1</sup>, HIROSHI YATSUYA<sup>2</sup>, PARVIN AKTER KHANAM<sup>3</sup>, M. ABU SAYEED<sup>4</sup>, HISAO NAITO<sup>1</sup> and TAMIE NAKAJIMA<sup>1</sup>

<sup>1</sup>*Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya, Japan*  
<sup>2</sup>*Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan*  
<sup>3</sup>*Department of Epidemiology and Biostatistics Research Division, Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh*  
<sup>4</sup>*Department of Community Medicine, Ibrahim Medical College, Dhaka, Bangladesh*

### ABSTRACT

Little information is available regarding the epidemiology of young onset insulin-requiring diabetes mellitus (IRDM). We described the incidence of young onset IRDM and its trend in males and females of Dhaka, Bangladesh. Subsequently, factors related to possible sex difference were investigated. Young onset IRDM was defined as diabetic patients aged 18–30 years who required three months or more insulin treatment but presented no ketonuria. Between 1994 to 2003, 1,804 cases were registered. Incidence rates were calculated with denominators based on the population census 2001. The overall annual incidence of young onset IRDM for the period 1994–2003 was 8.5 per 100,000 persons (95% CI: 7.2–7.9), and the corresponding value for females (10.9 per 100,000 persons, 95% CI: 9.2–12.1) was higher than that in males (6.7 per 100,000 persons, 95% CI 5.6–7.9). The incidence rate significantly increased in females during the investigated period, but not in males ( $p$  for sex interaction  $< 0.01$ ). There was a significantly higher increment of female cases with a body mass index  $\geq 25.0$  kg/m<sup>2</sup> (overweight/obesity) (19 percentage point) compared to that of males (3 percentage point) between 1994–1998 and 1999–2003 ( $p$  for sex interaction  $< 0.01$ ). The incidence of young onset IRDM is increasing in the Dhaka City population among females, which is attributed to the increase in overweight/obese female cases.

Key Words: Insulin-requiring diabetes mellitus, incidence, body mass index, Bangladesh

### INTRODUCTION

Approximately 180 million people worldwide suffer from diabetes mellitus, and 80% of diabetes mellitus deaths occur in low to middle income countries.<sup>1)</sup> Although diabetes mellitus is usually classified as type 1 and type 2, there is a group of patients with young onset, usually before 30 years, who require insulin treatment for glycemic control, but rarely develop ketoacidosis or ketonuria.<sup>2)</sup> This type of diabetes can be distinguished from type 1 and type 2 diabetes

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Corresponding Author: Tamie Nakajima, PhD

Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan.

Phone: +81-52-744-2124, Fax: +81-52-744-2126, E-mail: tnasu23@med.nagoya-u.ac.jp

mellitus and was first described in 1955.<sup>3)</sup> In 1985, the World Health Organization acknowledged this type of diabetes mellitus as a third category of diabetes, in addition to type 1 and type 2. This third category was initially designated as malnutrition-related diabetes mellitus, and is also called insulin-requiring diabetes mellitus (IRDM).<sup>4)</sup> This IRDM has been reported discretely from a number of tropical regions around the world including Uganda, Nigeria, and other parts of Africa, Brazil, Thailand, and India.<sup>5-10)</sup> The disease may be more prevalent in men as one study found a three times greater incidence of IRDM in males than in females.<sup>11)</sup> The peak age of incidences ranged between 25 and 29 years in both sexes,<sup>12)</sup> which largely differs from the peak ages of type 1 diabetes, puberty or early childhood (0–4) years.<sup>13)</sup> However, IRDM was dropped from the 1999 classification.<sup>14)</sup> Recently, however, a study in Ethiopia reported that this type of diabetes indeed occurred with a high incidence, and proposed to reopen this issue.<sup>12)</sup>

Bangladesh is carrying a heavy burden of type 2 diabetes mellitus. A study conducted in Dhaka, Bangladesh, reported a high prevalence of type 2 diabetes mellitus, 11.2% of the urban population, which is far higher than the world average of 2.8%.<sup>15)</sup> There are no reported data concerning type 1 diabetes mellitus in the Bangladeshi population. Also, very little is known about IRDM in Bangladesh. Limited information is available only on the clinical characteristics of IRDM patients in Bangladesh.<sup>16,17)</sup> This unavailability of epidemiological information about the disease, including its incidence and possible differences between sexes is a great hindrance to both physicians and health policy makers in the country.

Thus, we attempted to examine the incidence and characteristics of IRDM in individuals aged 18–30 years by sex in Dhaka City, Bangladesh.

## SUBJECTS AND METHODS

The present study used a database clinically registered in the Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders (BIRDEM), located in Dhaka City, Bangladesh, from 1994 to 2003. BIRDEM is the only specialist diabetic hospital which offers free diabetic medical care nationwide. Since there is no general medical insurance system in Bangladesh, and the government hospitals and private clinics do not have enough capacity to appropriately manage diabetic care, it can be assumed that almost all diagnosed patients in Dhaka City visit BIRDEM either voluntarily or by referral.

IRDM was defined as young onset diabetic patients who were hyperglycemic ( $\geq 7$  mmol/l), had no ketonuria, but did not respond to oral hypoglycemic agents along with dietary and exercise advices, and required insulin administration for glycemic control.<sup>2)</sup> The date of diagnosis was recorded as the initiation date of insulin treatment in BIRDEM. From 1994 to 2003, a total of 1,935 IRDM patients aged 0–30 years who were residents of one of the 90 wards of Dhaka City Corporation, were registered in the BIRDEM hospital. Among them, 1,804 were between 18–30 years. We restricted the present analysis to IRDM patients aged 18 to 30 years at onset. We excluded IRDM patients aged 0–17 years from the analyses due to their small number, except for the presentation of the incidence rate.

This study was conducted with prior approval from the Ethical Review Committee of Nagoya University School of Medicine, Japan and the BIRDEM, Bangladesh hospital authority.

### *Variables*

Information obtained from each subject included address of residence, sex, height, weight, date of diagnosis, type of work, amount of physical activity during leisure time, family history of diabetes, environmental hygiene condition, blood pressure, and fasting blood glucose level.

The type of work was self-reported. The possible choices were manual, clerical, both, and not employed. No examples of specific job names or descriptions were provided for the patients for this question item. However, manual jobs would include rickshaw puller, construction worker, factory worker, maid servants, while clerical jobs would require a minimal level of physical activity such as office workers. Other information was recorded from patients during their initial visit by asking them to recall their usual lifestyle before diagnosis. Family history of any diabetes was defined as the history among first-degree relatives, i.e., parents or siblings. Environmental hygiene conditions were categorized into 3 types. Corrugated tin/brick built houses with access to supplied piped water and sanitary latrine were defined as good environmental hygiene. Thatch-made houses with no access to supplied piped water and sanitary latrines were characterized as bad environmental hygiene. Corrugated tin/brick built houses with access to only either supplied piped water or sanitary latrine were defined as average environmental hygiene. If a patient indicated that he or she had been engaged in walking for more than 60 minutes daily or had some free hand exercise, he/she was considered to perform physical activity in leisure time. This activity did not include work-related activity. Body mass index (BMI) of the patient was calculated as weight in kg divided by squared height in meters. Following the classification by the WHO, BMI  $<18.5$  kg/m<sup>2</sup> was considered underweight; lower normal weight was defined as BMI of 18.5–22.9 kg/m<sup>2</sup>; a BMI of 23.0–24.9 kg/m<sup>2</sup> was defined as higher normal weight; and a BMI of  $\geq 25.0$  kg/m<sup>2</sup> was considered as overweight/obese.<sup>18)</sup>

#### *Statistical analysis*

Sex-specific IRDM incidence rates were calculated. The denominators were based on the 2001 population census data published by the Bangladesh Bureau of Statistics.<sup>19)</sup> Poisson regression models were used to estimate 95% confidence intervals of incidence rates, and to assess the temporal trends. Specifically, the number of cases each year was modeled with the year, sex, and logarithm of the sex-specific population size as the offset using the SAS GENMOD procedure. The year by sex interaction was tested, found to be significant ( $p < 0.05$ ), and stratified analysis by sex was performed subsequently. The proportion of BMI categories by sex and by periods (1994–1998 and 1999–2003) was described, and the secular change in the distribution was tested by chi-squared test for males and females separately. To examine whether changes in the BMI distribution differs by sex, ordinal logistic regression analysis was used taking BMI categories as a dependent variable, and periods, sex, and period by sex interaction as independent variables. Ordinal integers (1–4) were assigned for BMI categories in the model.

## RESULTS

In the 10-year period from January 1994 to December 2003, a total of 1,804 (male: 774, female: 1,030) young onset IRDM cases aged 18 to 30 years were registered. The overall annual incidence was 8.5 per 100,000 persons (95% CI: 7.2–7.9). The incidence rates were 6.7 per 100,000 persons (95% CI: 5.6–7.9) for males and 10.9 per 100,000 persons (95% CI: 9.2–12.1) for females. The number of IRDM cases in the 0–17 year age group was negligible compared to those in the 18–30 year age group, having an incidence of 0.06 per 100,000 persons.

The majority (77% for male and 84% for female) of the cases did not have physical activity during leisure time (Table 1). Female cases had a significantly higher family history of diabetes than males (48% vs. 36%,  $p < 0.01$ ). For both sexes, more than half were living in a hygienic condition with an average environment.

Clinical characteristics of the young onset IRDM cases are shown in Table 2. The mean

**Table 1** Characteristics of insulin-requiring diabetes mellitus cases, Dhaka, Bangladesh, 1994–2003

	Sex		<sup>a</sup> <i>P</i> value for sex difference
	Male <i>n</i> =774	Female <i>n</i> =1,030	
Type of work, <i>n</i> (%)			<0.01
Manual	166 (21)	294 (28)	
Clerical	136 (18)	46 (5)	
Both	286 (37)	404 (39)	
Not employed	186 (24)	286 (28)	
Physical activity habit in leisure time, <sup>b</sup> <i>n</i> (%)			<0.01
Yes	172 (22)	162 (16)	
No	602 (78)	868 (84)	
Family history of diabetes, <i>n</i> (%)			<0.01
Yes	281 (36)	500 (49)	
No	403 (52)	374 (36)	
Unknown	90 (12)	156 (15)	
Environmental hygiene, <i>n</i> (%)			0.06
Good	260 (34)	396 (38)	
Average	457 (59)	589 (57)	
Bad	57 (7)	45 (5)	

<sup>a</sup>By chi-squared test.<sup>b</sup>Walking or exercising for more than 60 minutes during leisure time.**Table 2** Clinical characteristics of insulin-requiring diabetes mellitus cases, Dhaka, Bangladesh, 1994–2003

Characteristics	Sex		<sup>a</sup> <i>P</i> value for sex difference
	Male <i>n</i> =774	Female <i>n</i> =1,030	
Fasting blood glucose (mmol/l)	17.1 ± 6.8	14.3 ± 6.1	<0.01
Systolic blood pressure (mm Hg)	117.3 ± 12.4	116.6 ± 12.5	0.22
Diastolic blood pressure (mm Hg)	78.9 ± 7.8	78.6 ± 7.7	0.38
Body mass index (kg/m <sup>2</sup> )	19.7 ± 4.0	22.9 ± 5.3	<0.01
Body mass index categories (kg/m <sup>2</sup> ), <i>n</i> (%)		<0.01	
< 18.5	310 (40)	234 (23)	
18.5– 22.9	309 (40)	250 (24)	
23.0– 24.9	94 (12)	162 (16)	
≥ 25.0	61 (8)	384 (37)	

Values are mean ± standard deviation or the number (proportion).

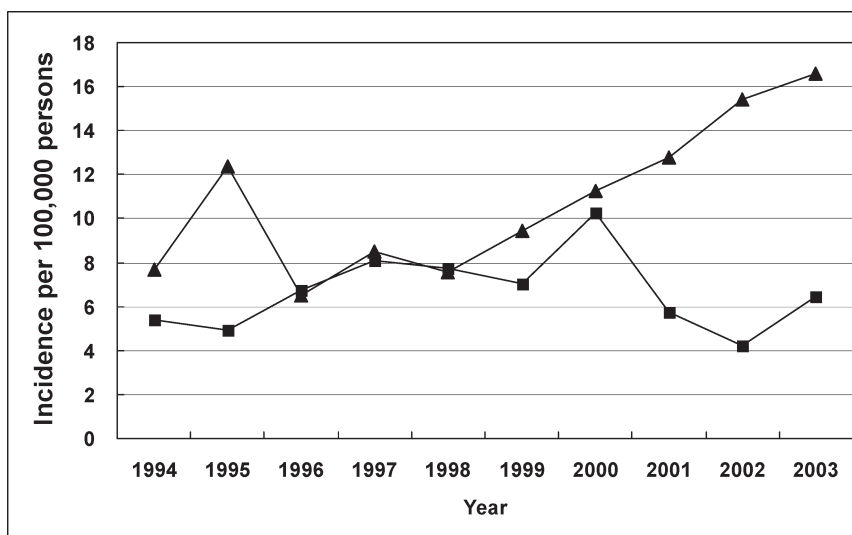
To convert from mmol/l to mg/dl, multiply by 18.

<sup>a</sup>By Student's *t* test or chi-squared test.

FBG level was significantly higher in males than in females ( $p < 0.01$ ). The mean BMI was significantly higher in females than in males ( $p < 0.01$ ), and the prevalence of overweight/obesity (BMI ≥ 25.0 kg/m<sup>2</sup>) was also significantly higher in females (37%) than in males (8%).

Fig. 1 depicts the temporal trends of young onset IRDM incidence in males and females from 1994 to 2003. Although a short-term spike in incidence existed in 2000, an overall increasing trend did not exist in males ( $p = 0.87$ ). The incidence increased in females after 1998 and

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**Fig. 1** Yearly incidences of insulin-requiring diabetes mellitus cases, Dhaka, Bangladesh, 1994–2003  
 ■ Indicates males and ▲ indicates females

**Table 3** Change in distribution of body mass index categories of insulin-requiring diabetes mellitus cases, Dhaka, Bangladesh, between 1994–1998 and 1999–2003

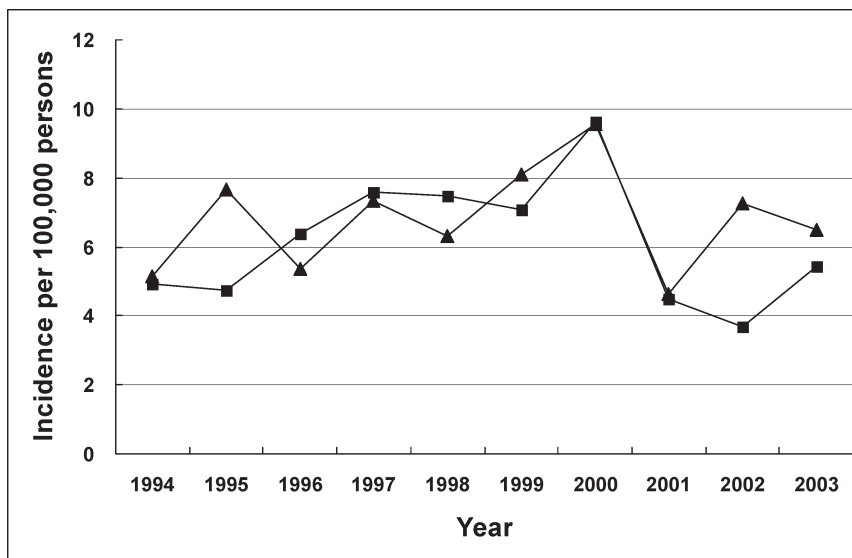
Body mass index categories (kg/m <sup>2</sup> )	1994–1998 <i>n</i> =788	1999–2003 <i>n</i> =1,016	<sup>a</sup> <i>P</i> value for earlier to later period difference in each sex	<sup>b</sup> <i>P</i> value for sex-period interaction
Male, <i>n</i> (%)	<i>n</i> =382	<i>n</i> =392	<0.01	<0.01
< 18.5	188 (49)	122 (31)		
18.5– 22.9	143 (37)	168 (43)		
23.0– 24.9	30 (8)	66 (17)		
≥25.0	21 (6)	36 (9)		
Female, <i>n</i> (%)	<i>n</i> =406	<i>n</i> =624	<0.01	
< 18.5	138 (34)	96 (15)		
18.5– 22.9	109 (27)	143 (23)		
23.0– 24.9	57 (14)	109 (18)		
≥ 25.0	102 (25)	276 (44)		

<sup>a</sup>By chi-squared test.

<sup>b</sup>By ordinal logistic regression for body mass index category with sex, period, and period by sex interaction. Body mass index categories were assigned ordinal integers (1–4) in this model.

was statistically significant ( $p < 0.01$  and  $p$  for sex-year interaction  $< 0.01$ ).

Table 3 shows percentages of BMI according to periods (1994–1998 and 1999–2003) and sex. The distribution of BMI categories by periods changed significantly for both males and females (both  $p < 0.01$ ). The prevalence of overweight/obesity increased from 6% to 9% in males and from 26% to 45% in females over the two time periods. The interaction for sex by periods was statistically significant ( $p < 0.01$ ). No apparent increasing trend was observed in the incidence



**Fig. 2** Yearly incidences of insulin-requiring diabetes mellitus cases with body mass index lower than 25 kg/m<sup>2</sup>, Dhaka, Bangladesh, 1994–2003  
 ■ Indicates males and ▲ indicates females

rates for both male and female IRDM cases when the analysis was restricted to the cases with BMI < 25.0 kg/m<sup>2</sup> (Fig. 2).

## DISCUSSION

To our knowledge, this is the first study documenting the incidence of IRDM in the urban community of Dhaka, Bangladesh. We found that the incidence rates of young onset IRDM were higher in females than in males. The yearly incidences showed a significant increase in females whereas they held steady in males. The BMI of the female cases shifted more to higher values than that of the male cases within the studied period. Analysis excluding IRDM cases with BMI  $\geq$  25.0 kg/m<sup>2</sup> confirmed that the increase observed in females was attributed to overweight/obese cases.

The annual IRDM incidence of 8.5 per 100,000 persons, which we found in our study, was much higher than the recently reported rate (2.1 per 100,000 persons) in Ethiopia.<sup>12)</sup> Studies conducted in Ethiopia revealed that males are the main sufferers.<sup>12,20)</sup> In our study, however, both cumulative and yearly incidences were higher in females than in males. In the same study from Ethiopia, low BMI was associated with a higher IRDM incidence rate.<sup>12,20)</sup> We, however, found that the proportion of the cases weighing  $\geq$  25.0 kg/m<sup>2</sup> increased 19 percentage points in females comparing the periods between 1994–1998 and 1999–2003. One possible reason for these discrepancies may be a potentially nonspecific case definition of IRDM. It might be possible that type 2 diabetes that required prolonged insulin treatment was included in IRDM in our study. And the increase could simply be due to the overall increase of type 2 diabetes cases in Bangladesh.<sup>15)</sup> Whether it is really necessary to separate the disease entity from existing types should be investigated by further studies. Another possible reason for the discrepancy may be that in our study, most of the respondents were from middle income families, whereas, in the Ethiopian study, they recruited subjects from areas where most of them were subsistence

farmers or unemployed, and experienced nutritional stunting during childhood following famines. Moreover, in our study, BMI was calculated based on the measurements made at the time of diagnosis while subjects in the Ethiopian study had been in the condition for the median duration of 1.7 years. So, it may also be possible that body weight had changed during the disease course. Further studies need to focus on the possible association of overweight/obesity in IRDM development as well as weight change during the disease progression.

Approximately a half of female cases and one-third of male cases had a positive family history of diabetes in the present study. They are qualitatively much higher than previously reported ones in IRDM (10 to 20%).<sup>16,22)</sup> There is no previous report on the association between physical activity and IRDM. We found in our study that the majority of IRDM cases did not engage in physical activity, nor did an even significantly lower number of female cases. At the same time, the proportion of cases in manual jobs was higher in females than in males. Since cases with manual jobs or without work were less likely to engage in leisure-time physical activity in both males and females (data not shown in Table), the lower proportion of female cases with leisure-time physical activity may be partly due to the higher proportion of female cases with manual jobs or no work. However, these characteristics of IRDM cases in the present study, especially among female cases, could also imply overlap with or contamination of type 2 diabetes cases.

Increased awareness and accessibility to hospital facilities may be another explanation for the increasing trend observed only in females. This speculation could be supported by an observation that significantly more female diabetic cases were registered in 2005 than in 1995 in Dhaka, Bangladesh despite unspecified diabetes types.<sup>23)</sup>

There are some other limitations to our study. First, the case definition relied only on necessity of prolonged insulin treatment to control hyperglycemia and absence of ketonuria, and the presence of auto-antibodies was not checked during the course of diagnosis. Overlaps of type 1 diabetes may also be possible. However, the late age of presentation found in our IRDM cases differs from type 1 diabetes with the peak incidence at the age of puberty.<sup>13)</sup> Second, we assumed that all the diabetic patients of the city were registered in BIRDEM, but we may have missed some IRDM patients, as few of them had the chance to visit other medical practitioners. Third, although studies have provided evidence that low socio-economic status is a strong predictor of diabetes,<sup>24-26)</sup> we could not retrieve annual income data of individual cases, an important piece of socio-economic information. In the registry, there were some missing income-related data on the respondents. The reliability of the income-related information is also doubtful in a country in which the people do not wish to disclose income. However, we consider that the respondents represent the general population of Bangladesh, as most of them came from middle income families. Fourth, due to the slow manual data management system in a developing country like Bangladesh, we had to restrict our study period up to the year 2003.

In summary, this study reports an increase in the incidence of patients diagnosed as IRDM in parallel with their increasing BMI, in females in the Dhaka City population. Taking into account the great morbidity and mortality associated with diabetes mellitus, there is an urgent need for further studies to describe the incidence with more accurate case definition. Eventually, it would be necessary to identify the possible causes, and reduce this possible increase.

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