Prevalence and incidence of micro- and macro-vascular complications in a diabetic population of Bangladesh: a retrospective cohort study

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Abstract

Background and objectives: Diabetes mellitus (DM) is a major health problem in South Asian Region including Bangladesh. Increasing prevalence of DM is likely to cause higher morbidity and mortality. The objective of this study was to find out the prevalence and incidence of diabetic complications in a Bangladeshi diabetic cohort attending BIRDEM, a largest referral center in Bangladesh for endocrine and metabolic diseases.

Methodology: The study was conducted in BIRDEM-OPD (outpatient department) from 1 January to 31 December of 1995 and analyzed the data of diabetic cases preserved in BIRDEM registry since 1956. Up to 31 December 1985, the REFERENCE NUMBER (Ref No) of last case was '49,510'. Therefore, this retrospective cohort comprised of all those patients having Ref No 49,510 or less and attending BIRDEM-OPD for follow-up. In the year 1995, the cohort had follow-up for at least ten years. The duration of follow-up was 39 years (1956 to 1995). The study also retrieved follow-up data from the guidebook of each registered diabetic patient. All data regarding clinical, anthropometric and biochemical investigations preserved in BIRDEM registry and in the patient's guidebook were retrieved and analyzed. The cohort was categorized into three groups (Gr1, 2 and 3) based on follow-up duration: >15, 10-15 and <10years, respectively.

Results: Micro-vascular complications (retinopathy and nephropathy) were the highest among both Gr1 with follow-up >15y and Gr2 with follow-up 10-15y. Compared with the Gr2, retinopathy (34.4 vs. 48.5 %: χ^2 =11.5, p <0.001) and nephropathy (24.0 vs. 39.2 %: χ^2 = 15.6, p<0.001) were significantly higher in the Gr1. In contrast, HTN, skin-lesion and periodontal diseases were significantly higher in the Gr2 than in Gr1. All types of complications were found increasing with the duration of follow-up. For Gr1, the increasing trend of cerebrovascular accident (CVD/ stroke) and CHD was significant (p<0.01 and p<0.001). Mean blood glucose of study population revealed moderate to severe hyperglycemia in successive follow-up visits. The comparison between patients with and without severe hyperglycemia (2hPG: <10.0 vs. ≥10.0 mmol/l) showed very little difference of complications. The increasing age over 40 years showed significant risk for CHD and hypertension.

Conclusion: CHD, stroke and PVD were less frequent compared to those with retinopathy and nephropathy. Compared to microvascular complications the macrovascular events resulted in either early death or complete disability to pursue long-term follow-up. The most important and consistent predictors were female gender and duration of diabetes.

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Introduction

It has been proved that maintenance of normal blood glucose unequivocally reduces mortality from acute events (or complications) in diabetic population [1,2]. It has also been unanimous among diabetologists that normoglycemia is always desirable for wellbeing of the diabetic subjects [1]. The most common chronic complications were the development of either micro- or macro-vascular complications. The microvascular lesions encompass retinopathy, nephropathy and neuropathy. The macrovascular complications are related to atherosclerosis and include mainly coronary artery disease (CAD), peripheral vascular disease (PVD) and cerebrovascular disease (CVD or stroke). Three most world famous prospective studies – Diabetes Complication Control Trial (DCCT) [2], United Kingdom Prospective Diabetes Study (UKPDS) [3] and Minnesota study [4] concluded that strict monitoring and maintenance of normal blood glucose certainly prevents microvascular complications. In contrast, both the studies could not confirm whether and not 'strict control of blood glucose' effectively prevents macrovascular complications and prevents atherosclerotic mortality [3,5]. However, there have been a very few cohort studies to assess the diabetes complications in the south-east Asian region. This cohort study addressed to determine the prevalence and incidence of micro- and macro-vascular complications in a diabetes population of Bangladesh.

Study design

The study basically analyzed retrospective data of a cohort of diabetic patients who were registered in the past at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). BIRDEM is the largest national referral center for diabetes and endocrine diseases in Bangladesh. BIRDEM started registration and follow-up of diabetic patients since 28 February 1956. The diabetic patients from all areas of the country are usually referred to this center. The patients are registered after confirmation of diagnosis. Once registered, they get a unique 'Reference Number' (Ref No) printed on the guidebook for follow-up care throughout life. Baseline information of all registered patients is stored in the center. Follow- up care records are maintained in the BIRDEM registry and also written in the guidebook of the patient. The first registration was started on the 28 February 1956 with Ref No 00001.

This study cohort included all registered diabetic patients from the first Ref No 00001 (28February 1956) to the last Ref No 49,510 registered on the 31 December 1985. A total of 49,510 diabetic subjects were registered during this period. The selection criteria of the cohort was, therefore, all diabetes patients registered at BIRDEM during this period and attending BIDEM-OPD with their guidebooks for regular follow-up visits. The data collection period was one year, starting from the first January to the 31December 1995.

Prior to the study, the doctors and health staff of BIRDEM-OPD were discussed about the study protocol. It was decided that whoever attends with reference number $\leq$49,510 would be received in a special counter designed for this cohort study (Figure-1). The guide-books were photocopied for retrieval of data. The BIRDEM history-sheet and guide book were the sources of data.

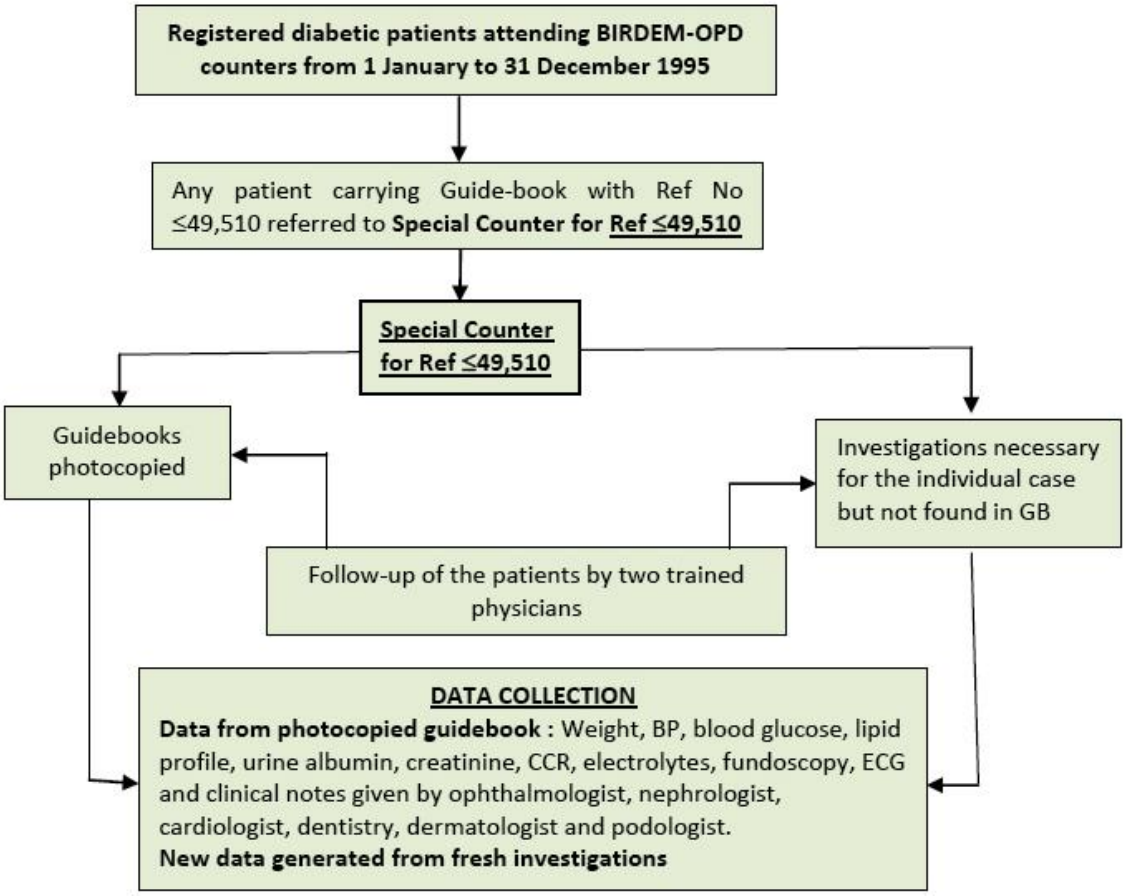

Figure-1: *Steps for collecting data from the patient's guidebook and from the newly generated investigations' reports. BP – blood pressure; ECG – electrocardiogram; CCR – creatinine clearance; GB – guidebook*

The baseline information included socioeconomic status, smoking habits, and family history of diabetes, hypertension, coronary heart disease, peripheral vascular disease and foot ulcer. The clinical and anthropometric examination included age, height, weight and calculated body mass index. In addition, measurements of blood pressure (for hypertension), peripheral arterial pulse for peripheral arterial disease (PAD), peripheral sensation (for neuropathy), electrocardiogram (for CHD), ophthalmoscopy (for retinopathy) and urinary albumin (for nephropathy) were taken. Similarly, for the assessment of biochemical risk factors for micro- and macro-vascular organic lesion some biochemical investigations were also included. These were plasma glucose, blood lipids, urea, creatinine, electrolytes and total urinary protein.

The duration of study cohort was 39 years ranged from 1956 to 1995. We categorized the cohort into three groups: Gr1 with >15 years follow-up, Gr2 with 10-15 years and Gr3 with <10 years. Gr3 was included in the study as the reference for comparative analysis between the recent and the older subjects with varying duration of follow-ups. The biophysical (BMI, BP, 2hPG) characteristics of the patients with shorter duration were compared with the longer duration.

Statistical analyses: The prevalence of complications was shown in percentages. Comparison between groups (men vs. women, rural vs. urban, Gr1 vs. Gr2) were estimated by unpaired t-test. Chi-sq test was used to determine the associations between variables. Chi-sq trend test estimated the trend of complications with increasing duration. The level of significance was accepted $p<0.05$. SPSS Window 19.0 Version was used for all these analyses.

Results

According BIRDEM registry 26,349 diabetic patients were registered up to 31 December 1980. This was Gr1 cohort. Of the total 26,349, only 171 (0.7%) were found attending BIRDEM-OPD for follow up. The baseline and follow up data (complications, hospitalization and other investigations) of these 171 patents were retrieved either from their guidebooks or from the BIRDEM registry. The Gr2 cohort comprised 23,161 patients registered from 1 January 1981 to 31 December 1985. Of them, 625 (2.7%) were found attending BIRDEM-OPD for follow up. The Gr3 consisted of only 110 diabetic patients, supposedly, with fewer complications. They were registered from January 1986 through December 1990. The socio-demographic characteristics of Gr1 and Gr2 are shown in Table-1 and 2. The tables also depicted the number of patents attended follow up in successive 5 years interval. Both the groups showed urban predominance than the rural plus suburban. The predominance of female was found in Gr2 but of male in Gr1.

Table-1: *Area and sex distribution of the study population, registered up to December 1980 (Gr1), and according to successive 5-year follow-up (n = 171).*

Period	Total case	Male n (%)	Female n (%)	Urban n (%)	Rural +suburban n (%)
At registration Up to Dec'1980	171	107 (62.6)	64 (37.4)	148 (86.5)	23 (13.5)
Follow-up 1981-85	151	92 (60.9)	59 (39.1)	132 (87.4)	19 (12.6)
Follow-up 1986-90	157	95 (60.5)	62 (39.5)	140 (89.2)	17 (10.8)
Follow-up 1991 – 95*	171	107 (62.6)	64 (37.4)	148 (86.5)	23 (13.5)

*Note: * - Data collected throughout the year 1996*

Table-2: *Area and sex distribution of the study population, registered from Jan 1981 through December 1985 (Gr2), and according to successive 5-year follow-up (n = 625).*

Period	Total case	Male n (%)	Female n (%)	Urban n (%)	Rural + suburban n (%)
At registration From Jan' 1981 through 1985	625	300 (48.0)	325 (52.0)	533 (85.3)	92 (14.7)
Follow up 86-90	588	283 (48.1)	305 (51.9)	490 (83.4)	98 (16.6)
Follow up 91 – 95*	625	300 (48.0)	325 (52.0)	533 (85.3)	92 (14.7)

** - Data collected throughout the year 1995*

Table-3: *Mean post-prandial plasma glucose level of study population observed at registration and in the successive 5-year follow-up for ≥15-year follow-up study (male + female, n=171, Gr1).*

Period		Number	Post-prandial plasma glucose (mmol/L)†	
			Mean ± SD	95 % CI
At registration up to Dec 1980		171	8.3 ± 3.6	7.8 – 8.9
Follow up				
First 5-year	1981- 85	151	9.3 ± 2.3	9.0 – 9.7*
Second 5-year	1986 - 90	157	11.7 ± 2.6	11.3 – 12.1*
Third 5-year	1991 - 95	171	12.9 ± 2.6	12.5 – 13.3*
Total follow-up	≥ 15 year	171	10.6 ± 3.4	10.3 – 10.8*

** - ANOVA: F=90.2, p<0.00; † - 2h after breakfast; SD - standard deviation; CI - confidence interval*

Table-4: *Comparison of mean post-prandial plasma glucose level of the study population observed between at registration and last 5-year follow-up period for male and female*

Period	Number	Post-prandial plasma glucose (mmol/L)†	
		Mean ± SD	95% CI
Male			
At registration up to Dec' 1980	107	8.6 ± 3.5	7.9 – 9.2
At last 5 year follow up from1991-1995	107	13.0 ± 2.7	12.4 – 13.5
p value*		t =10.2, p<0.001	
Female			
At registration up to Dec' 1980	64	7.8 ± 3.9	6.9 – 8.8
At last 5 year follow up from 1991-1995	64	12.7 ± 2.3	12.1 – 13.3
p value*		t = 8.7, p<0.001	

**p value is calculated by Student's t-test; † - 2h after breakfast;*
SD-standard deviation; CI- confidence interval

Table-5: *The prevalence of macrovascular complications among the diabetic patients (n=171) who had ≥15 years follow-up.*

Macro-vascular events	Complications (%) observed at registration and in the successive 5yr intervals				
	At registration up to Dec' 1980 n=171	First 5-year n=151	Second 5-year n=157	Third 5-year n=171	χ^2 trend§
Stroke	NA	1.1	1.9	4.7	10.92**
CHD†	1.2	1.3	7.0	18.1	41.03***
F-ulcer & PVD‡	NA	0.7	1.3	2.3	4.64 ns

*Note: § - χ^2 trend = $[\Sigma r_i x_i - R\delta]^2 / p(1-p)[n_i x_i - N \delta^2]$; † - CHD, coronary heart disease: evidence of ischemia on either resting or stress ECG or old myocardial infarction or comments of a cardiologist; ‡ - F-ulcer, foot ulcer; PVD, peripheral vascular disease including amputation; * p<0.05, ** p<0.01, *** p<0.001; ns - not significant; NA - data not available*

Table-6: *The prevalence of microvascular complications among the diabetic patients (n=171, older group) who had ≥15 years follow-up at BIRDEM-OPD.*

Micro-Vascular Events	Complications (%) observed at registration and in the successive 5yr intervals				
	At registration up to Dec' 1980 n=171	First 5-year n=151	Second 5-year n=157	Third 5-year n=171	χ^2 trend§
Nephropathy†	18.7	23.8	32.5	36.8	16.56*
Retinopathy‡	9.9	17.9	34.4	48.5	73.31*

*Note: § - χ^2 trend = $[\Sigma r_i x_l - R\delta]^2 / p(1-p)[n_i x_l - N \delta^2]$; * p<0.001; † - Nephropathy – all types of proteinuria irrespective of serum creatinine level; ‡ - Retinopathy - Background or proliferative retinopathy*

The trend of 2h post-prandial glucose (2hBG) level of Gr1 is shown at registration and in the subsequent 5 year follow-up period in Table-3. The values of 2hBG were increasing significantly in every 5 years. This indicated that glycemic control target (≤7.8mmol/l) could not be maintained over the years. The significant increasing trend was observed in both male and female cases (Table-4).

The prevalence of macrovascular (stroke, CHD, PVD / diabetic foot) and microvascular (nephropathy, retinopathy) complications are shown in Table-5 and 6, respectively. These two tables (5 and 6) depicted the incidence (new) of complications developed in each 5-year intervals.

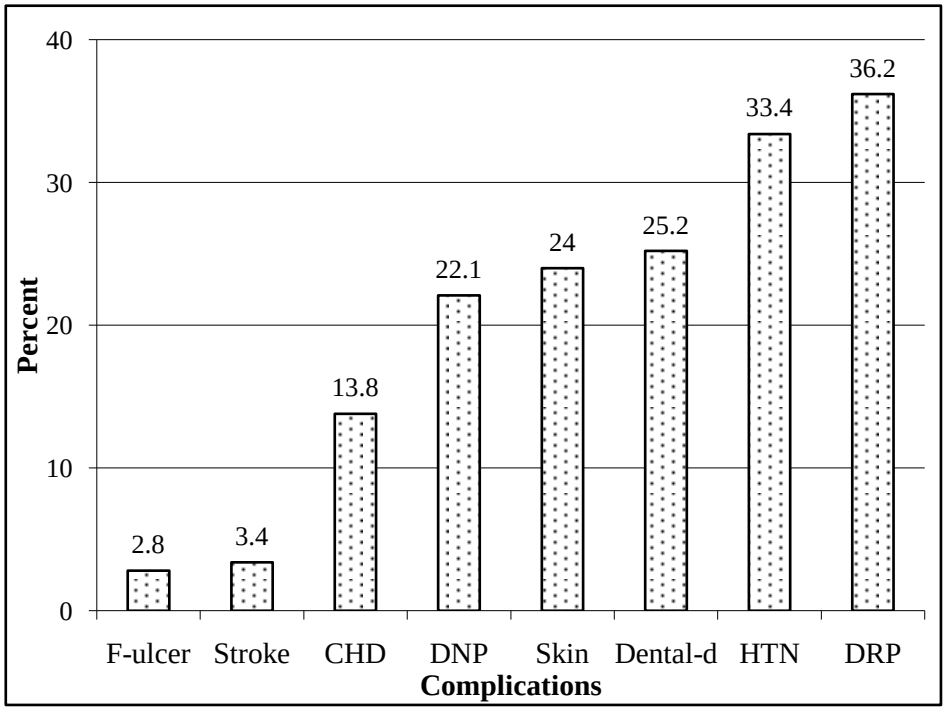

Figure-2: *Prevalence (%) of complications in all subjects (n=906) observed in 1995 irrespective of registration and follow-up. F-ulcer, foot ulcer; CHD, coronary heart disease; DNP, diabetic nephropathy; Skin, skin lesion – infection including other dermopathy; Dental-d, periodondal diseases; HTN, hypertension; DRP, diabetic retinopathy*

Complications of all categories of all patients after 15 years (Gr1) are shown in Figure-2. This is the result of all investigated complications developed after 15 years in 1995. The increasing trend of developing complications from 10 years to 15 years is shown in Figure-2. The highest prevalence of complication was retinopathy (48.5%, almost half of Gr1) in 1995. But it was 34.4% in 1990 with duration of 10-15y follow-up. Thus, the incidence of retinopathy increased 14.1% (Figure-3) from 1990 to 1995. The incidence rates of other complications are compared between follow-up period 1990 and 1995 (>10 yrs vs. >15 yrs) in Figure-2.

The incidence rates of different macro- and micro-vascular complications of Gr1 and Gr2 observed at baseline and in each 5-y interval (1980, 1985, 1990 and 1995) are shown in Figures-3 to 11. The incidence rates are illustrated for all (total), and for men and women separately. The findings of macrovascular complications - HTN, CHD, CVD (stroke) and PVD (foot-ulcer / diabetic foot) are depicted in Figure-4, 5, 6 and 7.

The microvascular complications namely nephropathy and retinopathy are shown in Figure-8 and 9 respectively. In subsequent follow up visits, women developed nephropathy more frequently than the men did and the difference between men and women after 15 year was significant (30.8 vs.46.9%: χ^2 =4.42, p<0.05; Fig-8). Prevalence of diabetic retinopathy though showed greater increase in women than men, but the difference was not significant (Fig-9). The mixed type diabetic complication like skin manifestation is shown in Figure-10 and orodental diseases in Figure-11.

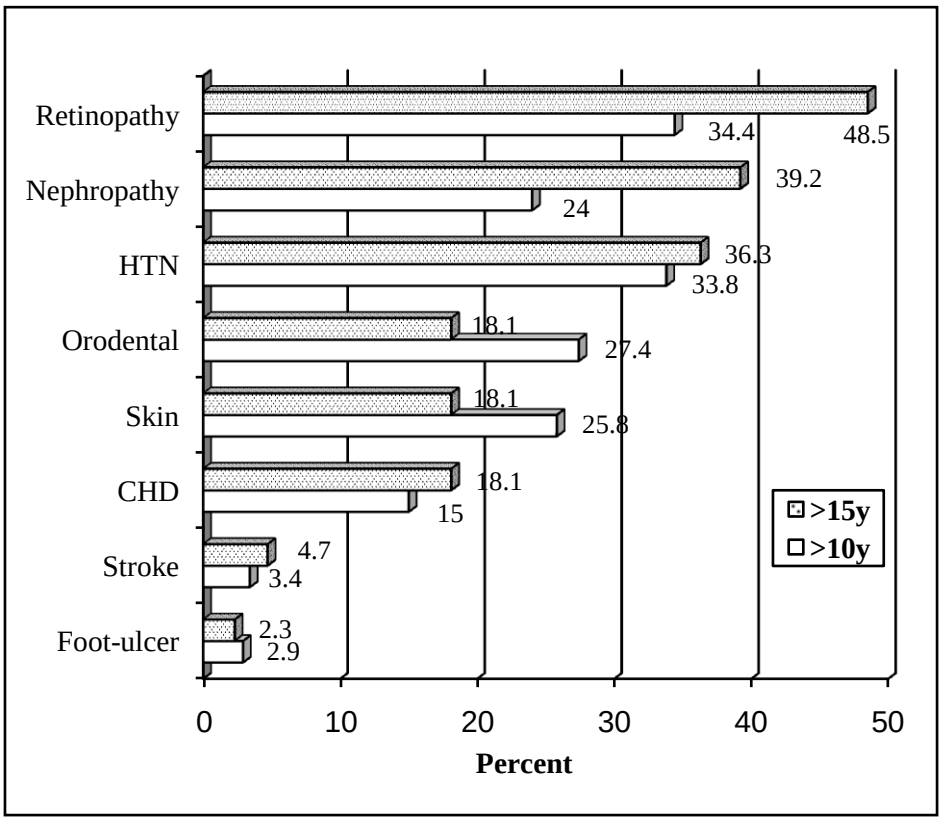

Figure-3: *Comparison of prevalence (%) of different types of complications between Gr1 with >15years and Gr2 with 10-15 years follow- up.*

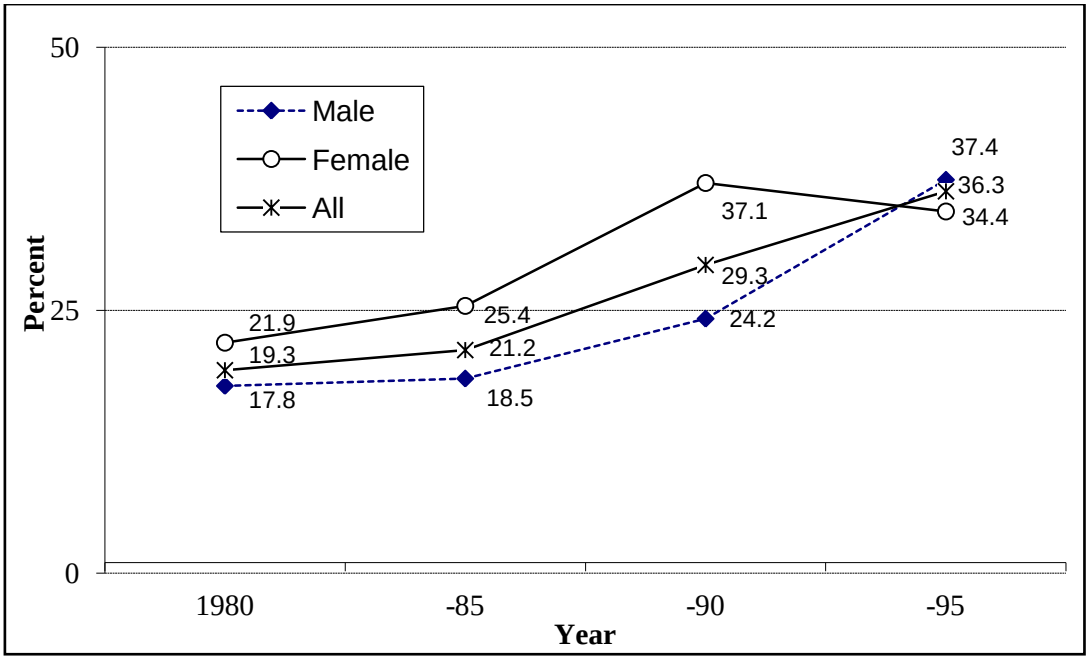

Figure-4: *Prevalence (%) of hypertension (Gr1) observed at registration and in each successive 5-year follow-up by gender (>15years follow up study: n=171)*

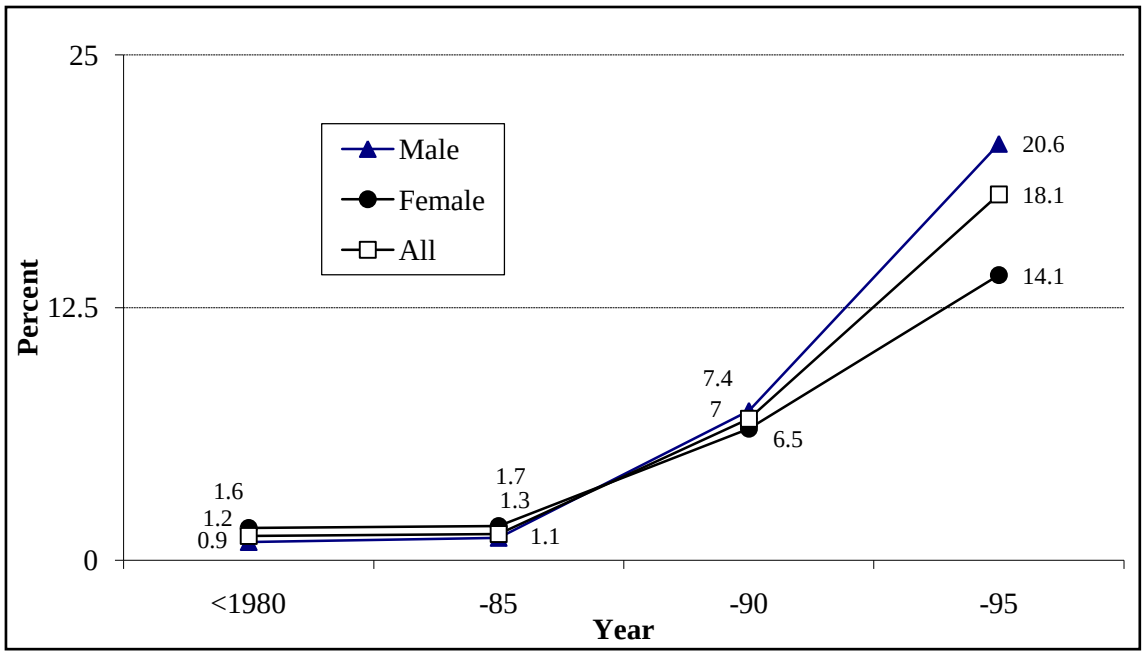

Figure-5: *Prevalence (%) of coronary heart disease (CHD) of Gr1 patients observed at registration and in each successive 5-year follow-up by gender (>15years follow up study: n=171)*

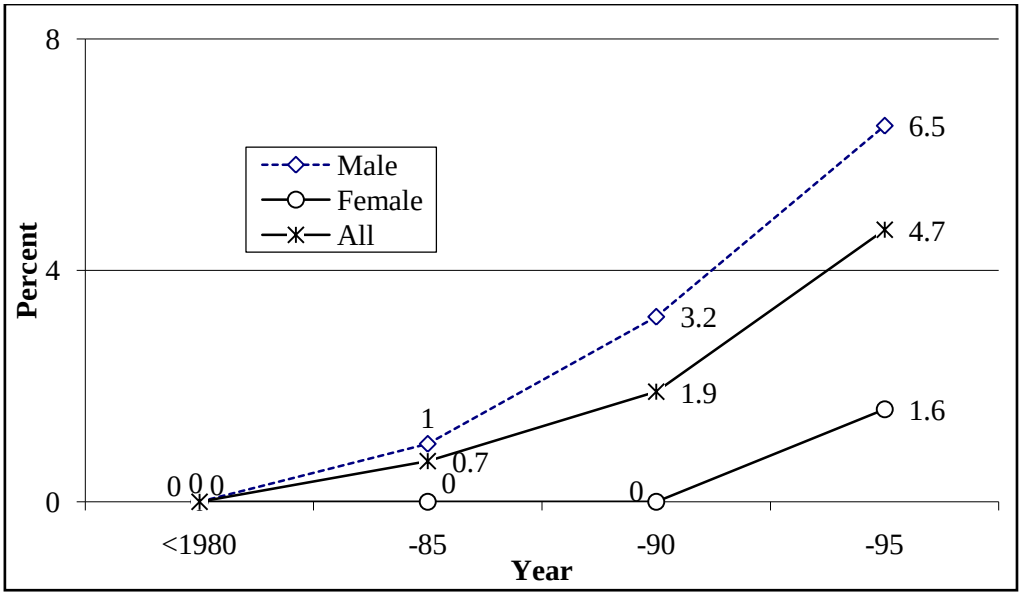

Figure-6: *Prevalence (%) of stroke (Gr1) observed at registration and according to the duration of diabetes in each successive 5-year follow-up by gender (>15years follow up study; n = 171)*

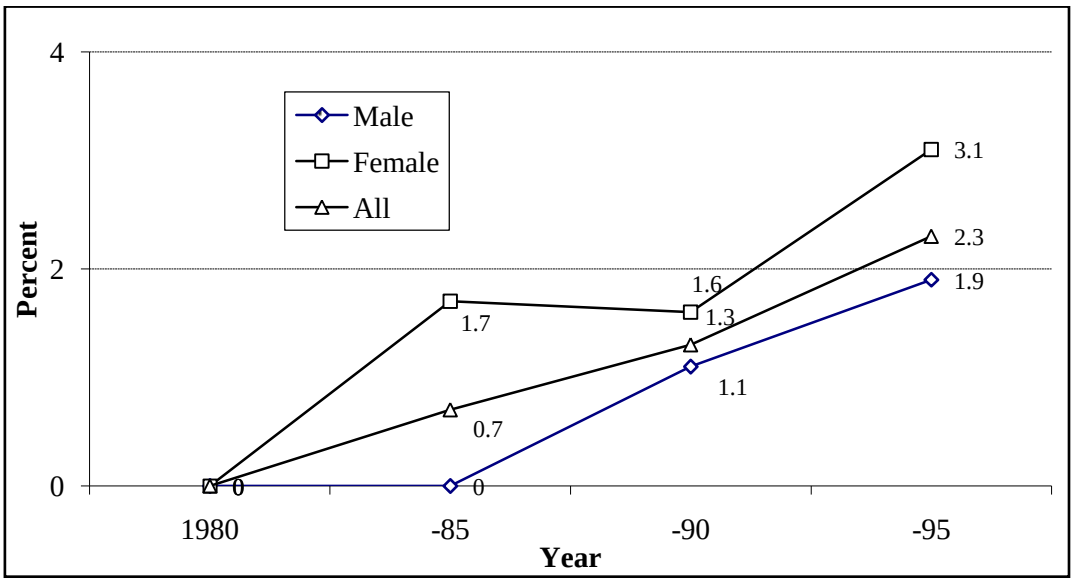

Figure-7: *Prevalence (%) of foot-ulcer / diabetic foot (Gr1) observed at registration and according to the duration of diabetes in each successive 5-year follow-up by gender (>15years follow up study; n = 171)*

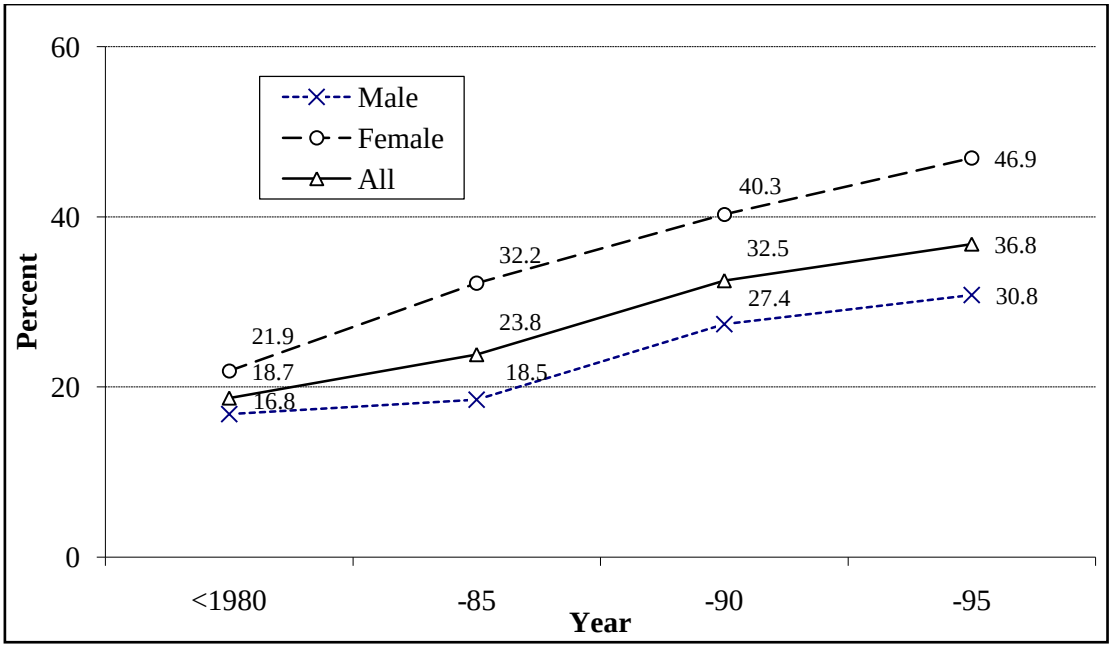

Figure-8: *Prevalence (%) of nephropathy (Gr1) observed at registration and according to the duration of DM in each successive 5-year follow-up by gender (>15 yrs follow up study; n = 171)*

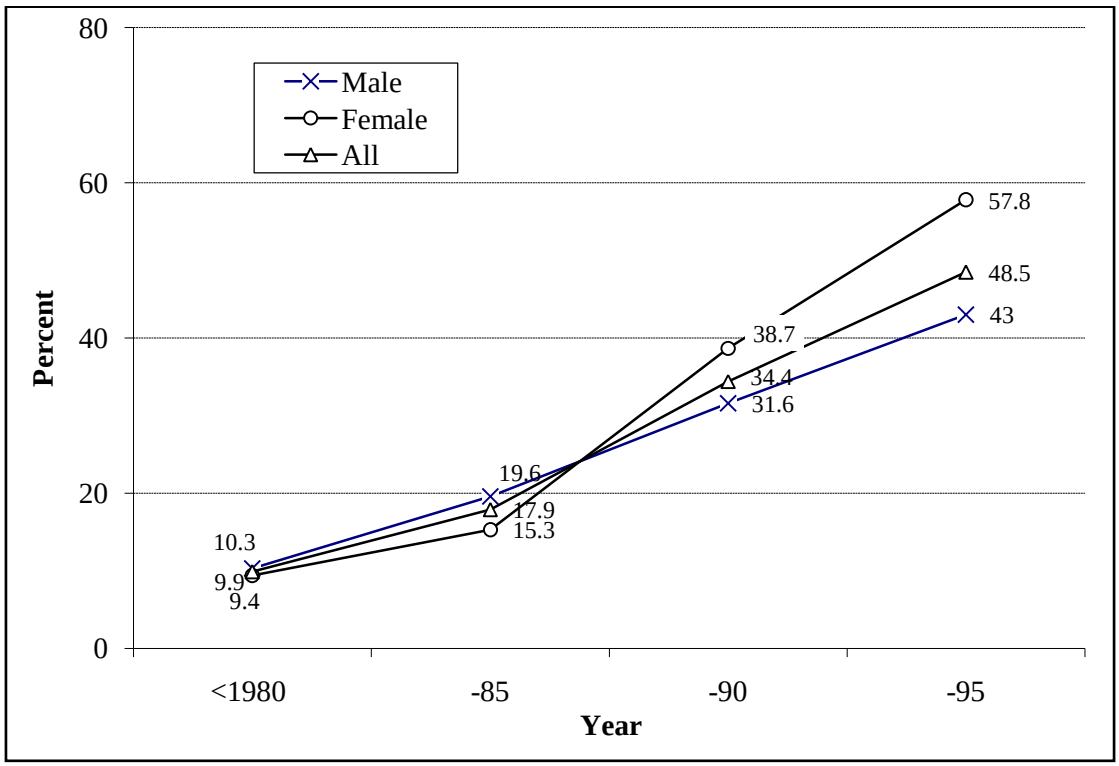

Figure-9: *Prevalence (%) of retinopathy (Gr1)) observed at registration and according to the duration of diabetes in each successive 5-year follow-up by gender (>15years follow up study; n = 171)*

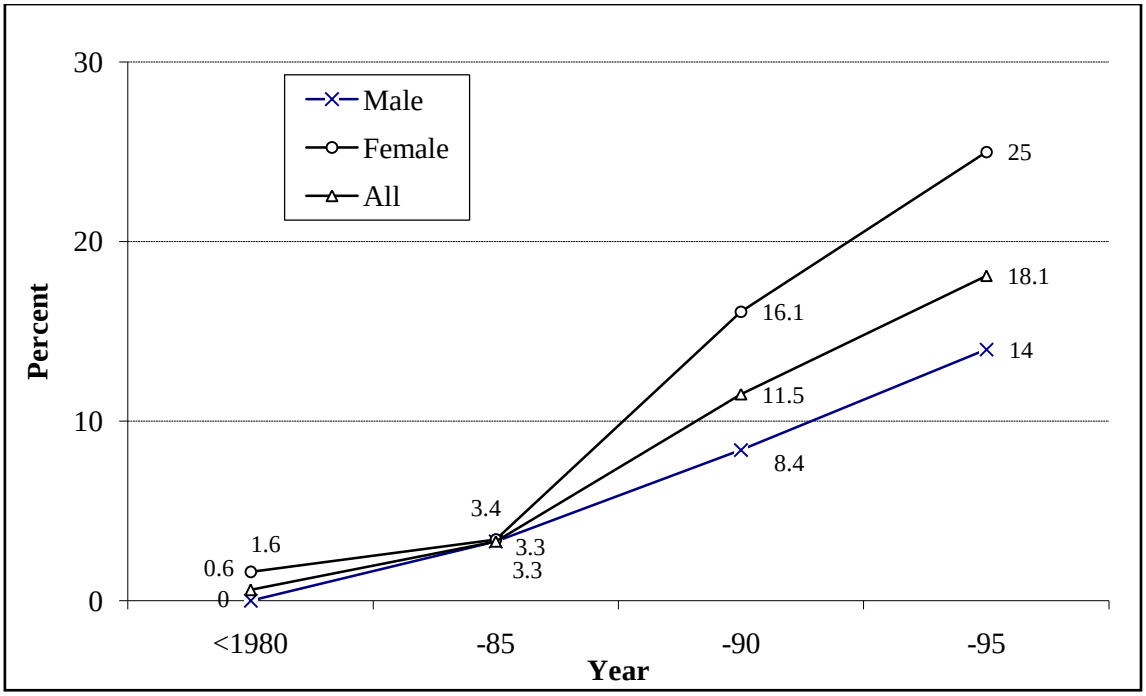

Figure-10: *Prevalence (%) of skin complications (boil, carbuncle, dermatomycosis) of Gr1 observed at registration and according to the duration of diabetes in each successive 5-year follow-up by gender (>15years follow up study; n = 171)*

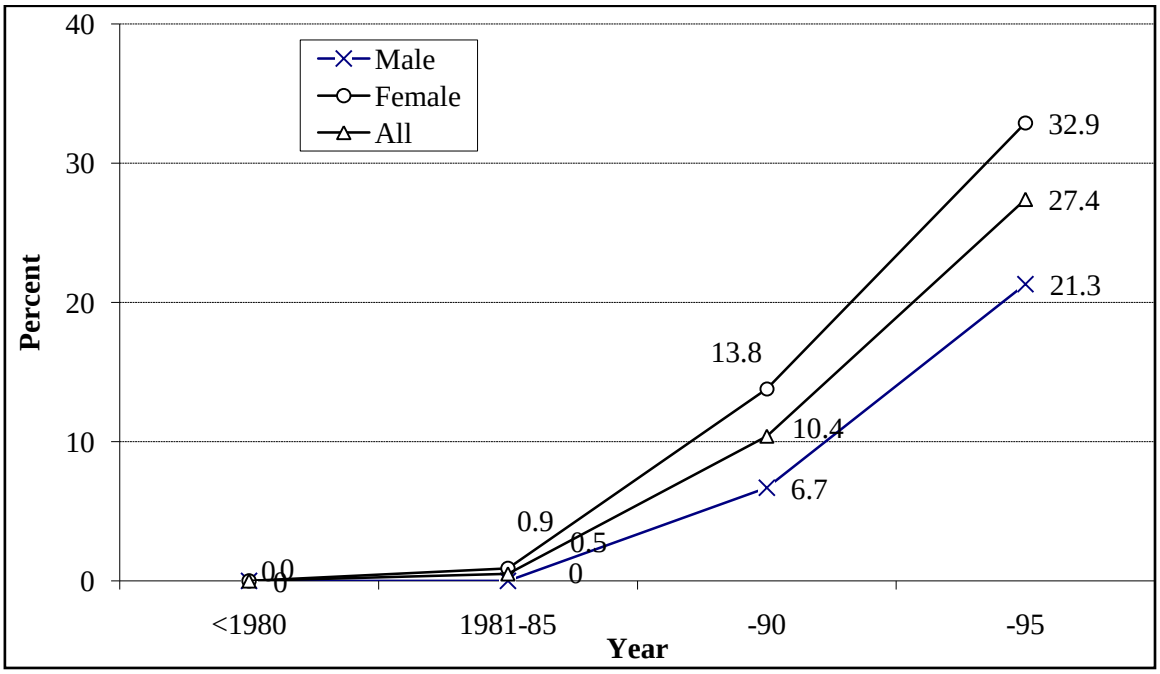

Figure-11: *Prevalence (%) of orodental complications (Gr1) observed at registration and according to the duration of diabetes in each successive 5-year follow-up by gender (>15years follow up study; n = 171; no data available before 1980).*

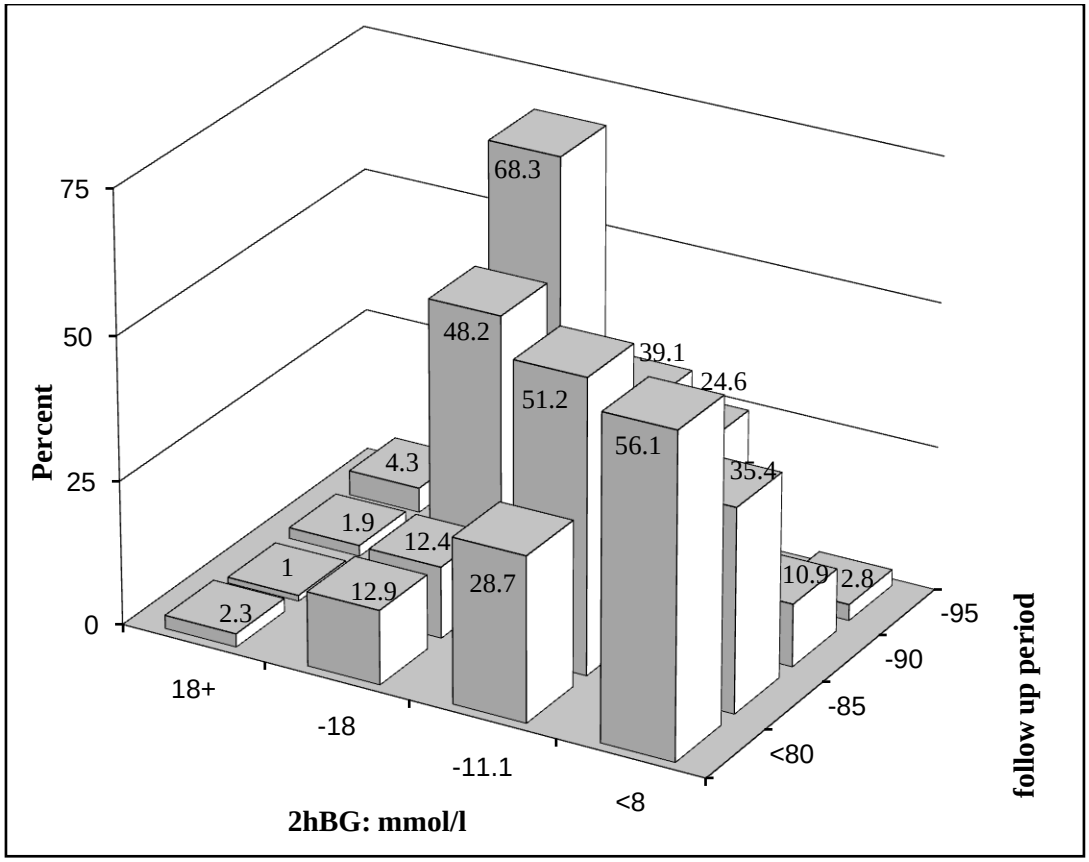

Figure-12: *Quintiles of glycemic status at registration and in subsequent follow-ups. Initially, there was more than half of the population had blood glucose <8.mmol/l. As the duration of diabetes increases the severity of glycemia became more and more frequent. At registration in 1980 diabetic subjects with blood glucose level 2hBG 11.1-18 mmol/l was only 12.9% and as the duration advances the same blood glucose level was found in 68.3% of those who had follow up in 1995.*

Other than the prevalence of different types and trends of diabetic complications the cohort was also analyzed to reveal how much glycemic control was maintained throughout the follow-up period. Figure-12 shows the level of glycemic control observed at baseline and in subsequent follow-ups. For analysis, the values (recorded in the registry and guidebook) of 2-h post-prandial blood glucose were estimated as percentile and transformed into quintiles. Each quintile represents 25% of the observed values. The lowest (Q1) represented lower most 25% and the next upper 25% (Q2), and thus Q3 and Q4.

According to baseline (registry) data, more than half of the population (56.1%) had 2hBG in the range of Q1, the lowest quintile or <8 mmol/l (Figure-12). The observed values of 2hBG <8.0 mmol/l was found reduced from 56.1% in 1980 to 2.8% in 1995. On the other hand, 2hBG of >18mmol/l was 12.9% in 1980 and that increased to 68.3% in 1995. The purpose of regular follow-up at BIRDEM-OPD was to achieve 2hBG <7.8mmol/l. This necessitates investigating the cause/s or factor/s not achieving the goal. However, the follow-up was proved to be successful in reducing the weight, an objective of risk reduction (data not shown).

Discussions

This cohort is unique in the south Asian population. It revealed both the prevalence and incidence of

diabetic complications. It explored the types of complications commonly encountered by the diabetic population of this region. A total of 49,510 diabetic subjects were registered up to 31December 1985. Had there been even 5% follow up of the total registered subjects we could have 2,475 patients. Instead, we could collect data only for 1065 patients. Though the sample size was not adequate to evaluate the effectiveness of BIRDEM follow up program it has been very useful to determine the types of complications among those who were still visiting the center.

In the fifteen-year follow up group, retinopathy and nephropathy were the highest among all types of complication. This finding is consistent with other studies that microvascular events are more disabling than macrovascular life threatening complications [6 - 8]. The cohort observed that the incidence (new development) of macro- and micro-vascular complications increased with duration of follow-up. The increasing trend is significant, which is consistent with other studies [8, 9]. Foot-ulcer and lower leg amputation, though increased but not significant. This may be considered an achievement of follow up program of BIRDEM.

The mean plasma glucose levels (2hBG), in either sex, increased significantly from the time of registration to last 5-year follow-up. This finding is consistent with other longitudinal studies [7,8,10]. It may be explained that in Type2 DM, there is always an increasing failure of secretory capacity of Beta-cell with time and that ultimately leads an insulin dependent state [11]. This is also considered as Beta-cell decompensation and is observed irrespective of area and sex [12]. Thus, increasing trend of plasma glucose level with increasing duration of follow-up was observed in both urban and rural-plus-suburban patients. As age advances with duration of DM, insulin is the treatment to achieve target glycemic level (2hBG <7.8mmol/l, BIRDEM protocol). Possibly most of the cohort population could not afford insulin.

Two findings are noteworthy. Firstly, the microvascular events were found more prevalent than the macrovascular ones irrespective of registration time (Figure-3 to 10). It may appear that these patients had less macrovascular (HTN, CHD, Stroke, and PVD) lesions. Secondly, the microvascular events were significantly higher in the older subjects. Both the findings taken together it indicates that there might have a cumulative effect of retinopathy and nephropathy. The finding of less macrovascular events could be due to their death or disability of those people to attend BIRDEM for follow-up. Macrovascular events always had high mortality [13,14]. So, this finding is not inconsistent to other investigations.

Some limitations of the cohort may be noted. Valuable data related to renal function tests and HbA1c were not available and could not be retrieved from the guidebook. In the past, HbA1c estimation was not routinely used for assessment of long-term glycemic status. Lipid profiles were also not included as regular risk assessment. In addition, a substantial number of facts were missing because of damaged or lost guidebook inflicted by natural calamities and careless handlings.

Conclusions

This cohort study concluded that the prevalence of all complications showed increasing trend with duration of diabetes irrespective of vascular pathology (micro- or macro-). The effect of glycemic control was found not significant for macrovascular events e.g. CHD and stroke. In contrast, microvascular complications (nephropathy and retinopathy) were found higher among cases with higher plasma glucose level compared to those having lower levels.

The increasing age over 40 years showed significant risk for CHD and hypertension. Reduced physical work had the hazard for developing retinopathy. Compared with retinopathy and nephropathy the subjects with CHD, stroke and PVD were less frequent. More importantly, those who developed CHD, stroke and PVD before 1980 were almost all lost to follow-up. It indicates that compared with the microvascular complications the macrovascular events either resulted in complete disability to pursue long-term follow- up or early death. It also revealed that very few patients were found to maintain blood glucose at desired (≤7.8 mmol/l) level. However, the higher frequency of follow-up visit significantly reduced most of the complication

events. Frequent visits at BIRDEM-OPD brought opportunity for self-learning by interaction with physicians and other patients seems to be extremely important.

Acknowledgement: We are indebted to the physicians and health staff of BIDEM-OPD and BIRDEM administrator for providing the registry when needed. BIRDEM authority cooperated sincerely to make photocopy of guidebooks of the selected diabetic patients. We are also grateful to BIDEM laboratory staff that helped us receiving the required investigation reports. We must acknowledge the cooperation of the participants.

Conflict of interest: None

Ethical approval: The study was approved by Institutional Review Board

References

1. Vaaler S. Optimal glycemic control in type 2 diabetic patients. *Diabetes Care*. 2000; **23**(suppl.2): B30 – B34.
2. The Diabetes Control and Complication Trial (DCCT) Research Group. The effect of intensive therapy of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *N Eng J Med*. 1993; **329**: 977-986.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998; **352**: 837- 853.
4. Palumbo PJ, Elveback LR, Chu-Pin Chu, Connolly DC, and T Kurland LT. Diabetes mellitus: incidence, prevalence, survivorship, and causes of death in Rochester, Minnesota, 1945–1970. *Diabetes.* 1976; **25**(7): 566-573. https://doi.org /10.2337/diab.25.7.566.
5. Vandor T. Nephroparthy in type 2 diabetes [letter]. *N Eng J Med*. 2000; **342**: 441.
6. Gillum RF. The association of body fat distribution with hypertension, hypertensive heart disease, coronary heart disease, diabetes and cardiovascular risk factors in men and women aged 18-79 years. *J Chronic Dis.* 1987; **40**: 421-428.
7. United Kingdom Prospective Diabetes Study (UKPDS) Group. United Kingdom Prospective Diabetes Study 24. A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Int Med*. 1998; **128**: 165-175.
8. U.K prospective diabetes study 16. Overview of 6-years' therapy of type 2 diabetes: a progressive disease. *Diabetes*. 1995; **44**: 1249-1258.
9. The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Evaluation of pheniformin therapy. *Diabetes*. 1975; **24** Suppl 1: 65-184.
10. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000; **23**(suppl. 2): B21-B29.
11. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diab Res Clin Pract*. 1995; **28**: 103-117.
12. Cahill GF Jr. Beta-cell deficiency, insulin resistance, or both? *N Engl J Med*. 1988; **318**: 1268-1270.
13. Ducimetière P, Eschwège E, Papoz L, Richard JL, Claude JR, Rosselin GE. Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia*. 1980; **19**: 205-160.
14. Eschwège E, Richard JL, Thibult N, Ducimetière P, Warnet JM, Claude JR, et al. Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective Study ten years later. *Horm Metabol Res*. 1985; (Suppl Series 15): 41-46.