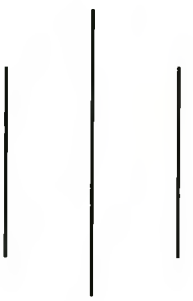
PREDICTORS OF RISKS FOR VASCULAR COMPLICATIONS OF DIABETES AND THEIR PROBABILITY IN THE DIABETIC POPULATION OF BANGLADESH



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- Author

ABSTRACT

Background and objectives: Diabetes mellitus, hypertension and coronary heart disease are considered as major health problems in South East Asian Region and Bangladeshis among them had highest mortality and attack rate. Prevention of diabetic complication through continued lifelong follow-up was endeavored by BIRDEM, a referral center, in Bangladesh. This center, since its birth in 1956, has been maintaining diabetes health care and preserving the follow up data. Thus, it happens to be a privilege to retrieve and examine the follow up data of registered diabetic patients in this center. The goal of BIRDEM is to control glycemia, triglyceridemia and hypertension through lifelong follow up. The objective of this study was to find out the prevalence of complications in a Bangladeshi diabetic population attending BIRDEM and to determine the type of complications among them. In addition, the study-design aimed to evaluate the effectiveness of BIRDEM-outpatient follow-up care in achieving glycemic control of the diabetic patients. So the duration of sample collection was maintained for twelve months with a view to increase the sample size.

Methodology: The study is basically a historical cohort and analyzed retrospective data of diabetic patients who were registered up to December 1985. Thus, the follow up period was 10 - 15-years or more. All types of clinical, anthropometric and biochemical information at registration and subsequent follow up are preserved in BIRDEM or in the patient's guidebook. Up to 31 December 1985, 49,510 diabetic subjects were registered. The data of these patients were retrieved and analyzed.

Results: Micro-vascular complications (retinopathy and nephropathy) were the highest among both the older and middle groups. Compared with the middle group, retinopathy was significantly higher in the older subjects (34.4 vs. 48.5 %: χ^2 =11.5, p <0.001). Similarly,

nephropathy was also significantly higher in the older patients (24.0 vs. 39.2 %: χ^2 = 15.6, p<0.001).

In contrast, mixed type of diabetic complications were significantly higher in the middle than in the older group. Thus, compared with the older group, the middle group showed higher prevalence of orodental (18.1 vs. 27.4%: χ^2 = 6.0, p<0.02) and skin infections (18.1 vs. 25.8%: χ^2 = 4.3, p<0.05) and the differences were significant.

All types of complications were found increasing with the duration of follow up. For older patients, the increasing trend of cerebrovascular accident (stroke) and coronary heart disease (CHD) was significant (p<0.01 and p<0.001); whereas, the trend in peripheral vascular disease with foot-ulcer was not significant. Similarly, micro-vascular complications like nephropathy and retinopathy showed also a significant increasing trend. The mixed-type-complication events like hypertension, skin-lesion and orodental diseases were no exception to this finding.

None of the study patient maintained desired glycemic control (FBG <6.1 and / or 2hBG <7.8 mmol/l) when taken the mean blood glucose of total follow up visits. Thus, all of them had moderate to severe hyperglycemia. The comparison between subjects with and without severe hyperglycemia (2hPG: <10.0 vs. ≥10.0 mmol/l) showed very little difference of complication. Diabetic nephropathy, in older diabetic patients, was observed in about 20% of them at registration in either sex. 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). There was almost similar observation encountered in the middle group that the female patients developed significantly higher nephropathy than their male counterpart (14.3 vs. 26.5%; χ^2 =14.0, p<0.001). Prevalence of diabetic retinopathy was about 10% in either sex of older group at registration. The subsequent follow up showed greater increase in women than men, but the difference was not

significant. For the middle group, retinopathy prevalence was found affecting men and women equally (35.3 vs. 32.3%).

Quantifying all the covariates for hazard ratio (forward stepwise entry) of the predictor variables it was found that among the significant covariates, female gender and decreased frequency of follow-up visit were found most significant and also most consistent. The next important factor proved important was the duration of diabetes or more correctly, the duration of follow up. Mean arterial blood pressure was found important only for CHD and nephropathy. The increasing age over 40 years showed significant risk for CHD and hypertension. Reduced physical work had the hazard for developing retinopathy.

Conclusion: Compared with retinopathy and nephropathy the subjects with CHD, stroke and PVD were less frequent. More importantly, those who developed CHD, stroke and foot ulcer before 1980 were almost all lost to follow up. It indicates that compared with the microvascular complications the macrovascular events either resulted in completely disabled for long-term follow up or in early death. The most important and consistent predictors were female gender, decreased visit frequency and duration of diabetes.

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Abbreviations

BMI	Body mass index: weight in kg / height in m^2
BP	Blood pressure
CHD	Coronary heart disease
Chol	Total cholesterol
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DNP	Diabetic Nephropathy
DRP	Diabetic Retinipathy
Echo	Echocardiography
FPG	Fasting plasma glucose
F-Ulcer	Foot Ulcer
2-hPG	Post-challenge plasma glucose, 2 hr after 75 gm glucose drink
Ht	Height in cm
HTN	Hypertension
IDDM	Insulin-dependent diabetes mellitus or type 1 diabetes
IGT	Impaired glucose tolerance test
mmHg	mm of mercury
mM or mmol/L	millimol/Liter
NIDDM	Non-insulin-dependent diabetes mellitus or type 2 diabetes
OGTT	Oral glucose tolerance test
OPD	Out-Patient Department
sHTN	Systolic hypertension, SBP (140 mmHg
WHO	World Health Organization
Wt	Weight in kg

Chapter 1

INTRODUCTION

INTRODUCTION

1.1 Background

Early detection of diabetes mellitus and monitoring of glycemic control is always desirable for prevention of diabetic complications. All types of acute complications like diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar non-ketotic coma (HONC) and hypoglycemia are life threatening. To avoid these complications one needs close monitoring to maintain normal blood glucose. It has been proved that maintenance of normal blood glucose unequivocally reduced mortality of acute events (or complications) in diabetic population. It has also been unanimous among diabetologists that normoglycemia is always desirable for wellbeing of the diabetic subjects [1].

The chronic complications mainly refer to micro- and 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). Two most world-famous prospective studies – Diabetes Complication Control Trial (DCCT) [2] and United Kingdom Prospective Diabetes Study (UKPDS) [3] concluded that strict monitoring and maintenance of normal blood glucose certainly prevents micro-angiopathy or microvascular complications. In contrast, both the studies could not confirm whether or not 'strict control of blood glucose' effectively prevent macrovascular complications and prevent atherosclerotic mortality [3,4].

1.2 Risk factors related to diabetes

Epidemiological studies in different populations unequivocally showed that other than genetic predisposition, increasing age, obesity, and sedentary habits are the most important risk factors for type-2 diabetes [5]. Recently, central obesity (high waist to hip ratio [WHR])

is considered more important than general obesity (high BMI) [6]. Most studies observed that subjects with increased WHR had excess risk for insulin resistance syndrome or syndrome 'X'. This syndrome encompasses central obesity, hyperglycemia, hyperinsulinemia, hypertension and dyslipidemia [6,7].

1.3 Risk factors related to diabetic complications

Several risk factors are well known to develop diabetic complications. Persistent hyperglycemia has been proved, by prospective design, as an independent risk factor for microvascular complications (nephropathy, retinopathy and neuropathy) [2,3]. In contrast, hyperglycemia could not be proved as a significant risk factor for macrovascular or cardiovascular complications (CAD, PVD, and CVD), [3,4,8]. These cardiovascular complications are the leading cause of mortality in people with diabetes [9,10]. Most of these deaths are due to atherosclerosis or CAD [10]. The people with diabetes have two to four fold higher risks of CAD events than the age matched non-diabetic subjects [10].

Though the exact mechanism of the development of atherosclerotic complications in diabetic population has not been established, most epidemiological investigations showed that hypertension, dyslipidemia and central obesity were the significant risks for CAD [8-10]. The risk factors may be classified mainly into two groups – a. modifiable (e.g. hyperglycemia, hypertension, obesity, physical inactivity, dyslipidemias) and b) non-modifiable (age and genetic factor). The human effort is directed to modify the modifiable risk factors. And these are control of blood glucose, control of blood pressure, reduction of body weight, increase of physical activity and correction of dyslipidemia.

1.4 Poor social status is also risk factor related to diabetes and its complications

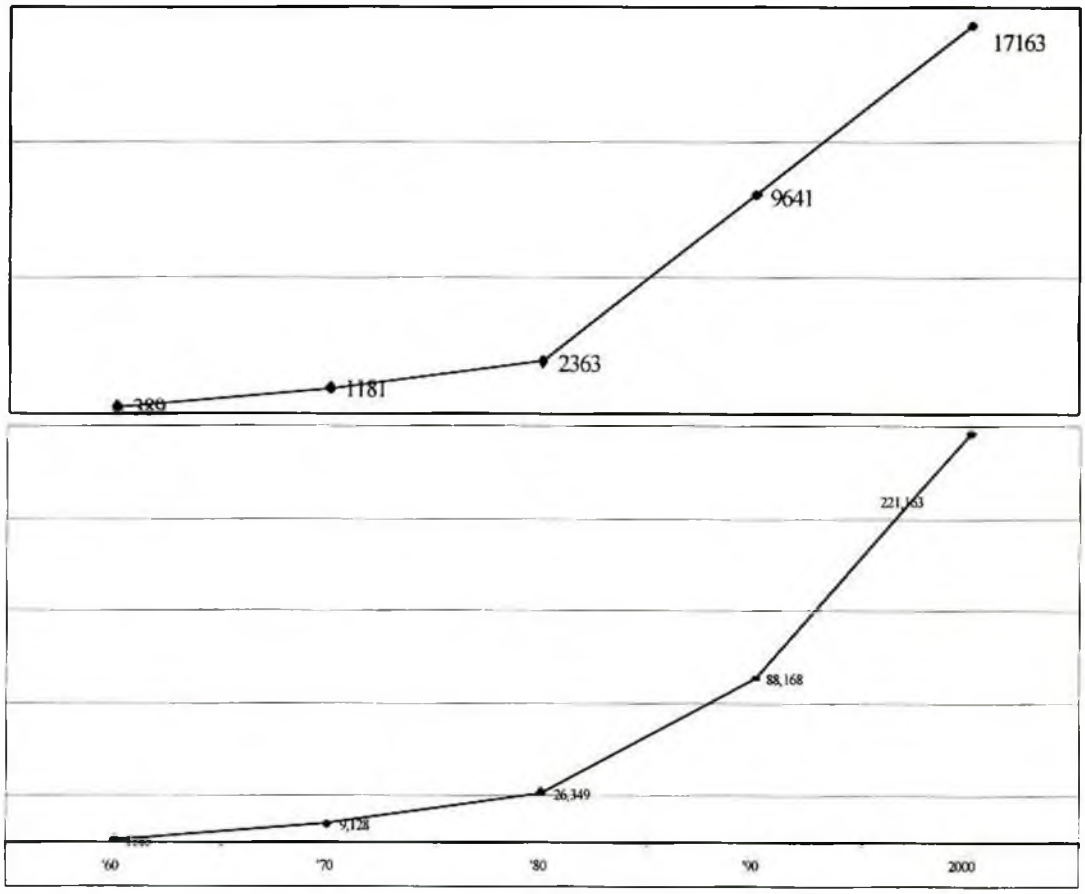
Poor class is prone to develop diabetes and its complication. There has been substantial number of publication in this regard [11-23]. The hypothesis is that 'low birth weight,

undernutrition in pregnant mother and in early childhood predispose to diabetes and cardiovascular diseases' [15]. Barker et.al. reported a relation between infant mortality and adult mortality from stroke, which they suggested may be mediated by differences in blood pressure [16,23].

The low income group is likely to develop complication as predictably detected late when already they had developed symptoms of complication [15,16]. Malnutrition and infectious diseases in early life predispose to impaired insulin store and / or secretion that lead to diabetes in adult [17-19]. There are evidences suggest that an adverse environmental insults during early childhood has an important effect on the later risk of cardiovascular disease [22-23]. For example, in our poor community, usually the patients come to doctor with visual impairment when they have already developed diabetic retinopathy that seriously affecting vision. Some patients present with chronic renal failure following diabetic nephropathy [24].

Considering all these observation one can think how much Bangladesh is facing the epidemics of diabetes and cardiovascular diseases in future. Low birth weight and undernutrition in childhood are very much prevalent in Bangladesh. These are, in fact, observed as the acute problems and never thought of their future consequences. An increasing trend of diabetes registry and of community surveys is shown overleaf-

Increasing trend of diabetes registry in a referral hospital



Yearly registry of diabetic patients (top), cumulative frequency of registered patients (bottom) at BIRDEM from 1960 to 2000

1.5 Historical perspective of diabetes mellitus – a brief review

1.5.1 The term 'diabetes' came from the ancient Ionian Greek

Diabetes Mellitus is a disease, which was recognized in antiquity but its history has been characterized by numerous cycles of discovery, neglect and rediscovery [25]. The term 'diabetes', which is Ionian Greek and means to 'run through' or a siphon; was first used by Aretaeus of Cappadocia in the 2nd century AD as a generic description for conditions causing increased urine output. Aretaeus wrote an accurate factual description of the condition that is instantly recognizable today and concluded that it was due to a fault in the kidney [25]. The Roman physician, Galen (AD 131 - 201), like Aretaeus, though diabetes to be rare disease and apparently encounter only two cases, employed alternative terms for diabetes, including 'diarrhea urinosa' and 'dipsakos', the latter emphasizing the cardinal symptoms of excessive thirst and drinking.

1.5.2 Diabetic urine tastes sweet first reported by Indian physician

The association of polyuria with a sweet tasting substance in the urine was first reported in sanskrit literature dating from the 5 - 6th ccenturies AD at the time of two notable Indian physicians,Susruta and Charuka [26].The urine of polyuric patients was described as tasting like honey, being sticky to the touch and strongly attracting ants. Indian descriptions of this time appear to distinguish two forms of diabetes - one affecting older, fatter people and the other thin people who did not survive long. During the same era, Chinese and Japanese physicians also described diabetes and the sweetness of diabetic urine, which apparently attracted dogs [27]. They also observed that people with diabetes were prone to develop boils and an affliction, which clinically resembles tuberculosis. The fact that diabetic urine tasted sweet was subsequently emphasized by Arabic medical texts during the 9th - 11th centuries, when Arabic medicine was as its peak of achievement. Avicenna (AD 960 - 1037) described

accurately the clinical features of diabetes and mentions two specific complications of the disease namely, gangrene and the ' Collapse' of sexual function. The 16th century Swiss physician Von Hohenheim reported that diabetic urine contained an abnormal substance that remained as a white powder after evaporation. He concluded, however, that this substance was salt and that diabetes was due to the deposition of salt in the kidneys, causing ' thirst' and ' polyuria'. It was not until the 17th century that Thomas Wills (1621 - 75) made reference to the sweet taste of diabetic urine [27] and thereby duplicated the observation which had first appeared in Eastern medical writings over one thousand years previously [25-27]. Willis made several other intelligent observations about the disease, which still ring true today. As to what belongs the cure, it seems a most hard thing in this disease to draw propositions for curing, for that its cause lies so deeply hid, and hath its origin so deep and remote [25].

1.5.3 Blood fluid contains sweet sugar first reported by Dobson (1735 - 84)

Mathew Dobson, a physician in Liverpool was a gifted natural philosopher and experimental physiologist and a skilled clinical observer with a wide range of interests [27]. He had treated nine patients with diabetes - a modest clinical load in comparison with diabetic clinics in present day Liverpool - when he published in 1776, a series of experiments showing that the serum of a diabetic patient, as well as his urine contained a substance with a sweet taste [27]. Moreover, he proved that this substance was sugar and concluded that this had previously existed in the serum rather than being formed in the kidneys. He wrote ' this idea of the disease explains its emaciating effects from so large a proportion of the alimentary matter being down off by the kidneys, before it is perfectly assimilated and applied to the purpose of nutrition'. This was the first evidence that diabetes might be a generalized disorder.

1.5.4 Diabetes mellitus and diabetes insipidus were differentiated by their characteristics

A few years after Dobson's important paper, another English physician, John Rollo (1809), published a study entitled, ' An account of two cases of the diabetes mellitus, with remarks as they arose during the progress of the cure' [28]. He was one of the first to the adjective 'mellitus' (from the Latin and Greek roots for 'honey') used to distinguish the condition from other polyuric diseases in which glycosuria was absent and the urine tasteless (Latin, Insipidus). Rollo made other contributions to the study of diabetes, including descriptions of diabetic cataracts and the odor of acetone (which he likened to decaying apples) on the breath of some diabetic subjects [28].

1.5.5 The organ pancreas was first suspected as related to diabetes

Another important observation made at this time was the report by Thomas Cawley in 1788 that diabetes may follow damage to the pancreas, such as through calculus formation [29]. The 19th century was extremely important for branches of medicine; it is no exaggeration to suggest that the science and practice of medicine gained more during these hundred years than they had during all the previous centuries together.

1.5.6 First reporting on glycemia induced by stress

Among the physiologist who contributed much to the understanding of diabetes at that time, a special place must be given to Claud Bernard (1813 - 78). Bernard made numerous discoveries, including the observation that the sugar that appears in diabetic urine was stored in the liver in the form of glycogen. He also demonstrated that the central nervous system was involved in controlling the blood glucose concentration when during attempts to stimulate the vagal motor nuclei, he induced transient glycemia by transfixing the medulla of a conscious rabbit with a blunt needle [30]. The significance of this observation was named

'Piqure Diabetes' (french,piquer = to prick), and soon eclipsed by discoveries implicating the pancreas as the likely seat of diabetes.

1.5.7 Systemic experiments on pancreas started: diabetes artificially induced and clinical features identified

Bernard performed many systematic experiments on the pancreas [31]. Although he himself did not attribute any endocrine activity to the gland, he developed the technique of ligating the pancreatic duct that was subsequently shown by others to cause degeneration of the exocrine tissue while leaving its endocrine function intact. Other notable discoveries were made in the study of diabetes during the middle of the 19th century. Pront (1785 - 1859) of Guy's Hospital first recognized coma as a complication of diabetes [25]. He made other contributions in the field of clinical chemistry including the introduction of iodine to treat goiter. In 1869, an American ophthalmologist Noyes observed that a form of 'Retinitis' occurred in glycosuric patients and in 1874, Kussmaul (1822 -1902) of Freiburg University described the 'Air Hunger'of ketoacidosis.

1.5.8 All typical signs and symptoms were confirmed after pancreactomy

The endocrine, blood glucose lowering properties of the pancreas began to be clarified in the second half of the 19th century. Important studies were performed in Strasbourg in 1889 by Oskar Minkowski (1858 -1931) and Josef Mering (1849 - 1908) [32]. They removed the pancreas from a dog in order to discover whether the organ was essential to life. After the operation, the animal unexpectedly displayed the typical signs of severe diabetes, with polyuria and incontinence, insatiable thirst hyperphagia and wasting. Minkowski found the dog to be glycosuric and hyperglycemia [32]. This observation firmly established the role of pancreatic disorders in causing diabetes and stimulated many workers to try to isolate the active pancreatic principle as a possible treatment for the disease. The source of the blood-glucose-lowering substance remained a mystery for some years.

1.5.9 Insulin from islets of Langerhans was isolated

In 1869, while working in Berlin for his doctorate, Paul Langerhans (1847 - 1888) had noticed small clusters of cells in teased preparations of pancreas which stood out against and could be separated from the surrounding exocrine and ductal tissue [33]. Langerhans simply described these structures without speculating as to their possible function. It was only in 1893 that Edonard Laguesse (1861 - 1927) suggested that these clumps of cells, which he named the 'Islets of Langerhans', might constitute the endocrine tissue of the pancreas. This theme was continued by the Belgian physician, Jean de Meyer, who in 1909 gave the name 'Insulin' (Latin, insula = island) to the glucose - lowering hormone, whose existence at that time was still hypothetical, which he postulated was produced by the islet tissue. Between 1895 and 1921 experimental work developed in two directions. One was the careful histological study of the islets, which led to the finding of several distinct cell types, thus foreshadowing our present knowledge that the islets of Langerhans are the site of production and secretion of several hormones in addition to insulin [33].

1.5.10 Search intensified for isolating suitable antidiabetic component

There was a search for insulin itself. The requirements for insulin as a potential therapeutic agent were stringent - 1) the preparation had to be of consistent potency; 2) it should reverse the metabolic abnormalities of the depancreatized animal; 3) it should reverse the signs, symptoms, and chemical abnormalities of human diabetes; and 4) it should produce no harmful side effects. The difficulties in the early attempts to isolate insulin were legion. There was total ignorance of the chemical nature of the postulated antidiabetic substance making the extraction procedure a hit-or-miss proposition. At that time, quantitative estimates of the blood sugar required inordinate amounts of blood and the procedure was not generally available. Because ignorance about the profound effects of low blood sugar levels on the nervous system (hypoglycemic convulsions), they were also not recognized as such and were

initially attributed to a "toxic" action of the extract. In addition, fever and infections were frequent sequel of the injections of extracts. In view of the protein nature of the hormone (which of course was not yet known), it is obvious that those workers who used oral administration of the extract were bound to fail.

1.5.11 Pancreatic extract might be useful as an antidiabetic agent

Of the many forerunners of Banting and Best, those who came closest to the mark were - Scott, Israel Kleiner, Ludwig Zuelzer and Nicolas Paulesco. Indeed Paulesco, a distinguished Romanian physiologist, produced a pancreatic extract that fulfilled all the criteria on animal experimentation for an "insulin", but he did not succeed in showing its application in human diabetes [34]. Thus the significance of his contribution was appreciated only much later. Before the discovery of insulin at the University of Toronto in 1921-2, there was no effective treatment for insulin-dependent diabetes mellitus. At best it was possible by systematic undernutrition through the 'starvation' diet promoted by Allen to abolish glycosuria and prolong life by some months. With rigid adherence to diet, some insulin-dependent diabetic patients survived for 2 or 3 years after onset before being overcome by the effects of starvation.

1.5.12 Search continued and pancreatic transplant was tried to treat diabetes

At 2 a.m. on 31 October 1920, Frederic Grant Banting (1891-1941), a practising physician and surgeon in London, Ontario, jotted down the following entry in his notebook: 'Diabetes. Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretion of these to relieve glycosuria.' The idea that this procedure might protect the internal secretion against destruction by pancreatic juices had come to Banting in the course of background reading about the pancreas. He was a well-trained surgeon with no experience in either diabetes or serious research, but was enthusiastic at the thought of making useful discoveries and approached Macleod (1876-1935), then Professor

of Physiology at the University of Toronto. Macleod promised him laboratory space, dogs and a student assistance to conduct experiments in the summer of 1921. One of Macleod's student assistants, Charles Best (1899-1978), won the toss of a coin for the right to help Banting in the experiments. Macleod, Scots-born scientist with an international reputation, supervised the research and advised Banting from the beginning. Banting's notebook indicates that he was exploring the feasibility of transplanting healthy islet-cell tissue from ligated, atrophied pancreas into a pancreatectomized diabetic subject.

1.5.13 Transplant idea was abandoned

Banting and Best began work on 17 May, 1921. At the end of July, they abandoned the transplantation proposal and began injecting chilled extracts of atrophied pancreas, prepared according to Macleod's suggestions, into pancreatectomized diabetic animals. They were greatly encouraged by the frequent finding of declines in blood glucose levels after injection and tended to interpret all of their data favorably. Macleod, who had been in Scotland during the summer's experiments, encouraged them to repeat and amplify their findings that autumn. By December, the team had realized that extracts of chilled whole pancreas would produce the same results, making Banting's ligation procedures superfluous. At Banting's request, Macleod invited a trained biochemist, Collip (1892-1965), to join the team later that month. The first public presentation of the research results, at a meeting of the American Physiological society on 30 December, was received with considerable skepticism. Banting and Best's paper (later published in the Journal of laboratory and clinical medicine (10) was open to severe criticism on many counts, not least their failure to check for fever and other symptoms of toxicity which had bedeviled other researchers. Indeed, Banting's and Best's results were arguably not as good as those of Paulesco or Kleiner. Collip, however, was already engaged in a vital series of buttressing experiments, the most important of which

were the discoveries that the pancreatic extract enabled diabetic liver to mobilize glycogen and that it could clear ketonuria.

1.5.14 Exciting historical events: insulin effectively and reproducibly reduced glycosuria and ketonuria

On 11 January 1922, an extract made by Banting and Best was injected into Leonard Thompson, a 14-year-old boy dying of diabetes in Toronto General Hospital. It failed to relieve his symptoms, caused a sterile abscess to from, and was judged a failure. On 23 January, however, a separate extract made by Collip reduced Thompson's blood sugar to normal, abolished his glycosuria and ketonuria, and thereby inaugurated the use of insulin in the treatment of diabetes mellitus. Collip had developed an extraction technique, which removed the toxic contaminants from Banting and Best's crude and variable extract, and so was able to isolate the active principle effectively and convincingly. On 3 May, 1922, the Toronto group delivered a paper to the Association of American Physicians in Washington, DC, entitled " The effect produced on diabetes of extracts of pancreas". There were given a standing ovation for what the audience acclaimed as one of the greatest achievements of modern medicine. By then, the group had accepted Macleod's suggestion to name the extract ' Insulin' after the Latin root for the islet cells in the pancreas. It was later learned that others had earlier suggested the same name for the then -hypothetical secretion, insulin is therefore a substance that was named before it was discovered. Collip's technique was crude and sometimes ineffective. The team's problems in producing insulin - which continued while desperate diabetic patients flocked to Toronto -- were not finally solved until chemists at Eli Lilly and Company of Indiana, with whom the group decided to collaborate, developed commercially viable extraction techniques involving isoelectric precipitation. Under license from the University of Toronto, this held the patents on manufacturing techniques, Danish and other scientists (including a group at the Medical Research Council in England), soon became involved in the development and use of insulin.

1.5.15 Quickest ever recognition to award the Nobel prize for discovery of insulin

By October 1923, insulin was widely available in North America and Europe. In one of the Nobel Committee's quickest ever recognition, Banting and Macleod were awarded the 1923 prize in physiology of medicine for the discovery of insulin. Banting announced that he would share his prize money equally with Best; Macleod shared his with Collip. At the time, and for many years afterwards, there was much controversy about the awards and the relative contributions of the Toronto team. Banting and Best, who were both deeply insecure, suspicious men, believed that they had discovered insulin while working on their own in the summer of 1921. With rather more justification, Macleod and Collip believed that Banting and Best's interesting but inconclusive studies could not have led to insulin without their own work. In fact, insulin was discovered at the University of Toronto through a truly collaborative effort, directed by Macleod, and based on experiments initiated by Banting with the help of Best.

Collip, who perhaps deserved a formal share of the Nobel Prize, made the greatest single breakthrough in the research. The University of Toronto and its financial supporters contributed substantially to the discovery by providing this team with what, at the time, were first-rate research facilities and techniques together with unlimited supplies of experimental animals. The controversy was secondary to the wonder of the discovery. As a speaker said at a dinner to honor the Nobel laureates, 'in insulin there is glory enough for all'. No one knew this better than the starving diabetic children and their parents who were experiencing one of the most dramatic reprieves in the history of medicine. Suddenly in 1922, that of the quality of life with insulin replaced the question of speed of death in diabetes. Leonard Thompson lived until 1935; at least two of the 'doomed' children who were first treated in Toronto in 1922 outlived all four of insulin's discoverers. One of the children, Ted Ryder, was alive and in good health when this text first went to press in 1990 [25].

1.6 Diabetes mellitus: definition, diagnosis and classification

Although the discovery of insulin revolutionized the overall management of diabetes, much discrimination and controversy continued regarding classification and diagnostic criteria. Different study groups and authors were using different criteria for diagnosing and defining diabetes mellitus. Thus, for the uniform epidemiological study, most study groups felt the need of a general agreement or consensus. National Diabetes Data Group (NDDG) was the first to propose definition, classification and diagnostic criteria for diabetes syndrome [36]. World Health Organization (WHO) Expert Committee on diabetes recommended the NDDG reports after some minor modification in 1980 [37]. After five years, WHO proposed another modified classification of diabetes and that was unanimously accepted in 1985 [38]. In 1997, American Diabetes Association sponsored Expert Committee on Diabetes proposed a recent diagnostic classification, which is being studied by many groups in different communities for final recommendation [39].

In the untreated state, diabetes mellitus is recognized by chronic elevation of the concentration of glucose in the blood (hyperglycemia) This is sometimes accompanied by symptoms of severe thirst, profuse urination, weight loss, and stupor, culminating in coma and death in the absence of effective treatment. More often, presenting symptoms are much less severe without disturbance of consciousness; occasionally symptoms are totally absent. The high concentration of blood glucose and other biochemical abnormalities result from deficient production or action of insulin, a hormone that controls glucose, fat, and amino acid metabolism. Several processes can cause the diabetic state. The severity of its symptoms is largely determined by the degree to which the insulin action is deficient. Characteristically, the diabetic has a long-term risk of developing progressive disease of the retina and kidney, damage to peripheral nerves, and aggravated atherosclerotic disease of the heart, legs, and brain.

The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst and urine volume, unexplained weight loss and, in severe cases, drowsiness and coma; high levels of glycosuria are usually present. But these clinical features are encountered mostly in advanced stage of the disease. However, for early detection, the proposed blood glucose values are given in a tabulated form as recommended by WHO Expert Committee [38].

Diagnostic values for the oral glucose tolerance test [37,38]

	Glucose concentration, mmol/L (mg/dl)			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes mellitus (DM)				
Fasting value	=6.7 (=120)	=6.7 (=120)	=7.8 (=140)	=7.8 (=140)
2 hrs after glucose load	=10.0 (=180)	=11.1 (=200)	=11.1 (=200)	=12.2 (=200)
Impaired glucose tolerance (IGT)				
Fasting value	<6.7 (<120)	<6.7 (<120)	<7.8 (<140)	<7.8 (<140)
2 hrs after glucose load	6.7-10.0(120-180)	7.8-11.1(140-200)	7.8-11.1(140-200)	8.9-12.2(160-220)

For Epidemiological and population screening purposes the 2-hour value after 75g oral glucose may be used alone or with fasting value.

Classification of diabetes mellitus and allied categories of glucose intolerance [38]

A. Clinical classes:

Diabetes mellitus (DM)

Insulin-dependent diabetes mellitus (IDDM)

Non-insulin-dependent diabetes mellitus (NIDDM)

(i) Non-obese

(ii) Obese

Malnutrition-related diabetes mellitus (MRDM)

Other types of diabetes associated with certain conditions and syndromes:

- pancreatic disease;
- disease of hormonal etiology;
- drug-induced or chemical-induced conditions;
- abnormalities of insulin or its receptors;
- certain genetic syndromes;
- miscellaneous.

Impaired glucose tolerance (IGT)

(i) Non-obese

(ii) Obese

(iii) Associated with certain conditions and syndromes

Gestational diabetes mellitus (GDM)

B. Statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes):

- Previous abnormality of glucose tolerance
- Potential abnormality of glucose tolerance

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* Expert Committee Report of World Health Organization [38].

1.7 Obesity, hypertension, hyperglycemia and dyslipidemia constitute a deadly quartet

Epidemiological studies revealed that obesity is associated with increased mortality and morbidity from cardiovascular disease, and the association persists even when age, blood pressure, smoking history, cholesterol, and diabetes are factored out [40-50]. Since obesity is clearly associated with known cardiovascular risk factors such as diabetes and hypertension, these contribute additionally to the risk of cardiovascular disease. Some investigators coined 'the deadly quartet' when upper-body obesity, glucose intolerance, hypertriglyceridemia and hypertension coexist in an individual [50].

Obesity per se, though the need for perfusion through an increased mass of tissue results in increased cardiac work. Blood volume, stroke volume, and cardiac output are all increased [51]. These physiologic changes, and the resultant increased ventricular mass, are reversible with weight loss [51,53]. Obesity also is associated with as atherogenic lipid profile, i.e., increased low-density lipoprotein (LDL) cholesterol, increased VLDL and triglyceride, and decreased high-density lipoprotein (HDL) cholesterol [52]. This profile tends to occur in persons with abdominal obesity [50] and appears to result at least in part from overproduction of VLDL, perhaps through the effects of insulin on the liver [52].

Obesity is a cause of reversible hypertension that is typically associated with increases in both peripheral resistance and cardiac output [49,67]. Several possible causes for this association have been put forward. There is evidence to support an increased output of the sympathetic nervous system in obesity [53, 65], as assessed imperfectly through determination of norepinephrine levels, and these do decrease with weight loss, suggesting a role for dietary regulation of activity of the sympathetic nervous system. Enhanced sensitivity to the effect of dietary salt on blood pressure has also been seen in certain groups [49].

Currently, there is strong interest in the possible role of insulin as a pathophysiologic factor in the hypertension of obesity as well as in the hypertension in some subjects without obesity [54-64]. This interest is based on the observation that hyperinsulinemia is found in hypertensive subjects with or without obesity and on the ability of insulin to exert actions on the kidney (i.e. salt retention), vasculature, and possibly other sites that could elevate systemic blood pressure. A major challenge over the next several years will be to identify molecular mechanisms that will permit insulin to exert specific actions on blood pressure control.

Diabetic subjects are known to have a high frequency of atherosclerosis [65], but the underlying mechanism remains unclear. Hyperglycemia, on which the definition of the disease is based may well not be a direct determinant of the atherosclerotic lesions of diabetes, since the incidence of cardiovascular events in diabetic subjects is not strictly related to the duration of hyperglycemia [65-72]. Furthermore, three large prospective surveys on the risk factors of coronary heart disease independently initiated in the late sixties [57,61,65]. They showed their findings after 5 to 10 years follow up that high insulin levels in healthy men were predictive of coronary heart disease, even after adjustment for the classical risk factors (age, blood pressure, smoking habits, plasma cholesterol); whereas, hyperglycemia and diabetes were not independent predictors [61,73]. Many studies have shown the close metabolic interdependence between carbohydrates and lipids [75-83]. Plasma insulin is also a strong correlate of plasma lipids, especially HDL-cholesterol and triglyceride [74,78], and it is now well established that plasma insulin levels are generally higher in subjects with Type 2 (non-insulin-dependent) diabetes compared to non-diabetic subjects [78-84].

In non-diabetic populations, the relationship between triglyceride plasma level and cardiovascular risk generally appears to be mediated through other metabolic abnormality

[83]. This statement also applies to the results of the global analysis of the Paris Prospective Study [61]. However, there may be some particular metabolic situations where hypertriglyceridemia is an independent marker of CHD risk [81-84]. For example, it has already been shown with the data of the Paris Prospective Study that plasma triglyceride level was an independent predictor of CHD mortality risk in subjects with a low plasma cholesterol level [83].

Both high triglyceride levels and low HDL concentrations are typically found in non-insulin-dependent diabetes and impaired glucose tolerance [80]. This particular form of dyslipidemia could be related to an impairment of insulin action. It is one of the key factors in the regulation of lipoprotein metabolism [81], and accumulating evidence tends to make it a marker of insulin resistance [80-83]. It may possibly be a causal factor of coronary heart disease by itself, through the atherogenicity of VLDL catabolism remnants [78], or because of the enrichment of HDL particles with triglyceride rather than cholesterol, which could lower their capacity for cholesterol uptake and therefore deteriorate their anti-atherogenic power [83,84].

1.8 Diabetes Health Care Situation in Bangladesh

The recent WHO report on diabetes prevalence alarmed that diabetes has posed a serious threat to developing countries in respect to their existing health care service [85]. Diabetes, hyperinsulinemia and coronary risk factors are more prevalent in Bangladeshis compared with other South Asian migrants (Indian, Pakistani) settled in United Kingdom [86] and with the native population [87,88]. It has also been reported that Bangladeshis among the entire South Asians immigrant had highest mortality and attack rate from coronary heart disease (CHD) [89]. The non-communicable diseases (NCD) like diabetes (DM), hypertension (HTN) and CHD are emerging as a major health problem in Bangladesh. These are now given high research priorities by the government of Bangladesh [90]. Some small surveys on

diabetes at community level showed higher prevalence of glucose intolerance and hypertension [91-95].

BIRDEM is a unique referral center for diabetes health care. It has been working as a WHO collaborating center for diabetes care in South East Asian Region since 1982. This is the first referral model, not only in Asia but also in the entire third world countries, to undertake the comprehensive care of a non-communicable disease like diabetes. More than thousand diabetic subjects visit BIRDEM everyday either for registration or for follow-up. The objective of follow up is to control glycemia, triglyceridemia and hypertension, and to maintain body weight. The target for control of glycemia in BIRDEM is given below-

Target for control of diabetes at BIRDEM*

Biophysical variables	Good	Fair	Poor
Fasting blood glucose (mmol / l)	4.4 – 6.1	< 7.8	> 7.8
Random blood glucose (mmol / l)	4.4 – 8.0	< 10.0	> 10.0
HbA1c (%)	≤ 7%	< 8	> 8
Total cholesterol (mg / dl)	≤ 200	< 250	> 250
Triglycerides (mg / dl)	≤ 150	< 180	> 180
Body mass index (Wt in kg / Ht in Meter sq.) for either sex	20 – 25	< 27	> 27
Blood pressure (mmHg)	≤ 130 / 80	< 140 / 90	> 140 / 90

* BIRDEM Research Group, Ibrahim Memorial Diabetes Center.

Considering the increasing trend of diabetes mellitus and also the future need of diabetes health care in the country it seems imperative to determine the prevalence of diabetic complications among the patients undergoing follow up care. Thus, the research questions are – a) which types of complications are most prevalent in our community? b) What is the probability of getting complication(s) among the diabetic population in Bangladesh? d)

Which risk factors are most important to be considered for intervention? e) Could the existing follow up care endeavored by health care provider of BIRDEM achieves control of glycemic status and prevent diabetic complications? This study attempted to explore these research questions.

1.9 RATIONALE

Diabetes, hyperinsulinemia and coronary risk factors are more prevalent in Bangladeshis compared with other South Asian migrants (Indian, Pakistani) settled in United Kingdom [86] and with the native population. It has also been reported that Bangladeshis among the entire South Asians immigrant had highest mortality and attack rate from coronary heart disease (CHD). The non-communicable diseases (NCD) like diabetes (DM), hypertension (HTN) and CHD are emerging as a major health problem in Bangladesh. These are now given high research priorities by the government of Bangladesh [90]. Some small surveys on diabetes at community level showed higher prevalence of glucose intolerance and hypertension. BIRDEM is a unique referral center for diabetes health care. It has been working as a W. H. O. collaborating center for diabetes care in South East Asian Region since 1982. This is the first referral model, not only in Asia but also in the entire third world countries, to undertake the comprehensive care of a non-communicable disease like diabetes. More than thousand diabetic subjects visit BIRDEM everyday either for registration or for follow-up. The objective of follow up is to control glycemia, triglyceridemia and hypertension, and to maintain body weight.

Considering the increasing trend of diabetes mellitus and also the future need of diabetes health care in the country it seems imperative to determine the prevalence of diabetic complications among the patients undergoing follow up care. Thus, the outcome of the study will help in finding out the types of complications most prevalent in our community. It will also estimate the probability of getting complication(s) among the diabetic population in Bangladesh. It is expected that after successful completion of the study the important risk factors will be identified, which in turn will help to undertake intervention measure. All these possibilities will eventually leads to prevent diabetic complications in our population.

1.10 Objectives

General

a) To find out the prevalence of complications in a Bangladeshi diabetic population attending BIRDEM.

b) To determine the type of complications among them.

Specific

a) To determine the prevalence of micro- and macro-vascular complications among the Bangladeshi diabetic patients attending BIRDEM-outpatient for more than 10 years.

b) To find out the prevalence of mixed type of complications other than specific micro- and macro-angiopathic lesions.

c) To determine the association(s) between individual type of complication and the known biophysical risk factors like obesity, hypertension, hyperglycemia and dyslipidemia.

d) To evaluate the effectiveness of BIRDEM-outpatient follow-up care in achieving glycemic control of the diabetic patients.

Chapter 2

MATERIALS AND METHODS

MATERIALS AND METHODS

2.1 Study place

The study was carried out in the Outpatient Department of Bangladesh Institute of Research and Rehabilitation of Diabetes, Endocrine and Metabolic Disorders (BIRDEM-OPD). BIRDEM is the oldest and largest referral center in the country. 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 are likely to get follow up care throughout life. It was established in 1956 by his active initiation of Late National Prof. Dr. M. Ibrahim. Since its foundation, the patients have been provided with lifelong follow up care. Baseline information of all registered patients are stored in the center. Follow up care records are also kept in the guidebook of the individual patient. Diabetes registry has increased in recent years. Consequently, the number of patients for follow up has increased manifold.

2.2 Subject selection for data collection

BIRDEM-OPD was selected for recruitment of the study subjects who were registered in the center. Almost all patients throughout the country after being detected as diabetic, are usually referred to this Institute for – a) confirmation of diagnosis and b) subsequent follow up. More than fifty new patients are registered daily and about 800 – 1300 registered patients visit the OPD for follow-up in each working day. During registration, each patient is given a 'Reference Number' (Ref No) chronologically since inception of BIRDEM. The Ref No is used as his / her identity for follow up and remains valid for life. Moreover, each patient is also provided with a 'Guide-Book'. This book printed with specific 'Ref No' contains basic information and necessary advises related to diabetes management, and blank pages for subsequent follow-up information. For determining the duration of registration and duration of detection of diabetes 'reference number' was used.

2.3 Selection Criteria

- All diabetes patients registered before 31 December 1985 (Ref No. ≤ 49510).
- The diabetes patients with Ref No. ≤ 49510 still attending BIRDEM throughout the year 1995.

2.4 Receiving patients in a special counter in BIRDEM

A total of 49,510 diabetic subjects were registered till 31st December 1985. All of them were considered eligible for this study. Thus, each patient would have been followed up at least for a period of 10 years or more. It was also decided that whoever comes with reference number ≤49,510 would be received in a special counter for this study and his / her guide-book would be photocopied for retrieval of data.

2.5 Retrieval of baseline and follow up data

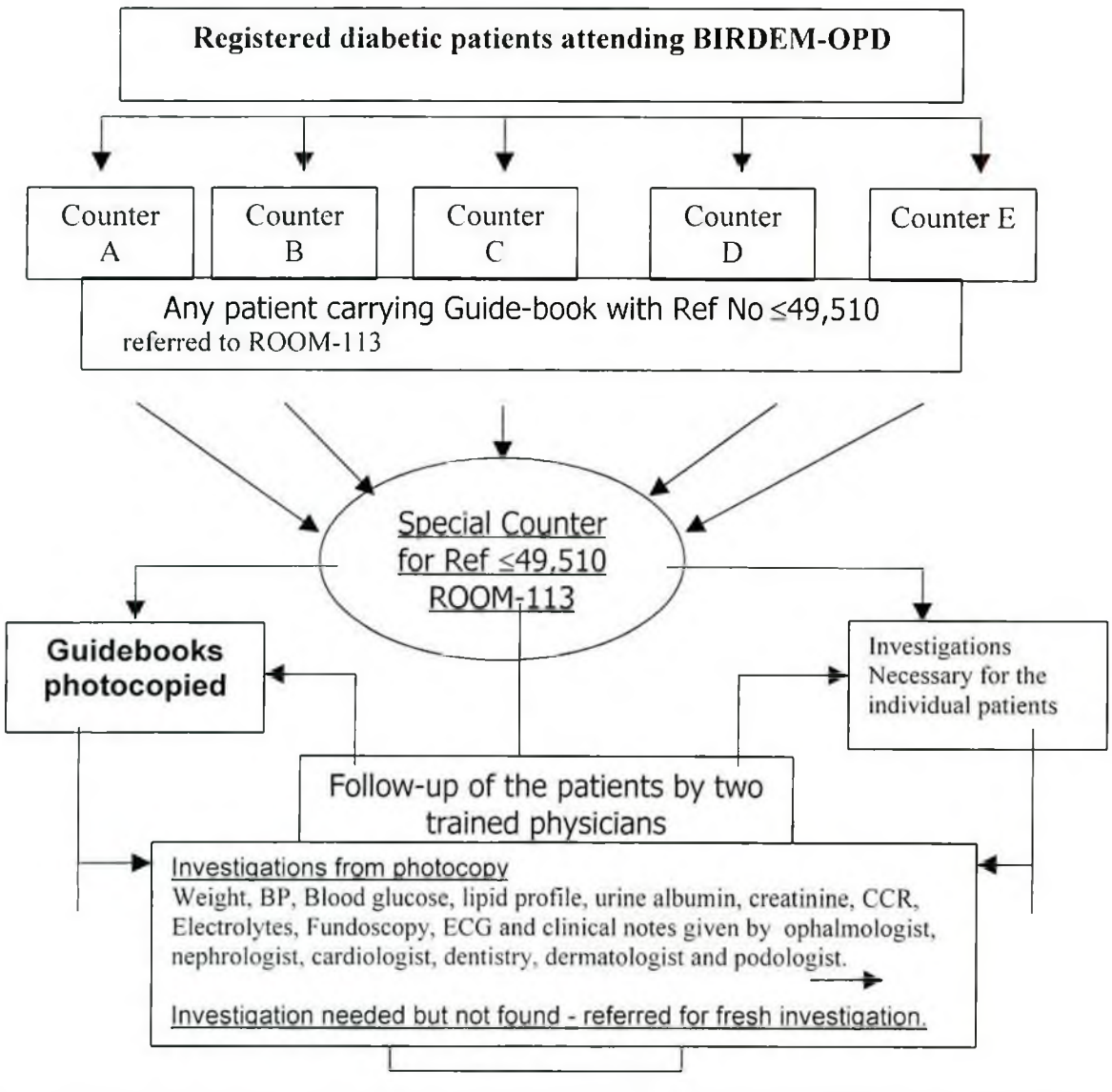
All the counters in the BIRDEM-OPD receiving registered patients were instructed to refer all patients with the 'reference number ≤49,510 ' to the specific new counter. Two trained physicians were employed to follow-up these patients. They used to receive and interview, and to investigate them for clinical and biochemical information as and when there was missing necessary information. Moreover, the baseline information and the previous follow-up data were retrieved from the Guidebook and entered in a structured questionnaire [Appendix 1].

2.6 The baseline information

The baseline information included socioeconomic status, smoking habits, family history of diabetes, hypertension, coronary heart disease (CHD), 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, lipids, blood urea, creatinine, electrolytes and total urinary protein. The scheme of data collection is shown in algorithm below –

Algorithm depicts the steps for data collection



2.7 Guiding principles maintained for the validity and reproducibility of data

Two employed physicians were trained for six months in inpatient and six months in outpatient setting and proved to be efficient in detecting and diagnosing the acute and chronic complications of diabetes mellitus. They had to ascertain each information recorded in the guidebook.

2.8 Anthropometry

Anthropometric measurement included height and weight. Both the measures needed for estimation of body mass index (BMI), a known index of generalized obesity. Patients' weight was measured after standardization of stadiometer (Dectomedic -Beam Balance) daily by known standard weight. For height, the subject stood in erect posture vertically touching occiput, back, hip and heels on the wall gazing horizontally in front keeping tragus of ear and lateral orbital margin in the same horizontal plane.

2.9 Measurement of blood pressure

Factors affecting blood pressure were the major concerns of the blood pressure measurement. Considerable variation occurs in blood pressure from moment to moment with respiration, emotion, exercise, meals, tobacco, alcohol, temperature, bladder distension and pain. These situations were taken into account while measuring blood pressure, and were always avoided as far as practicable [84]. Blood pressure was measured thrice and taking the mean to rule out hypertension among the study subjects. The subjects who showed blood pressure in the hypertensive (SBP $\geq$ 140 or DBP $\geq$ 90 mmHg) range for the first time were requested to recheck in the next morning [84,107]. Thus, the mean of the six readings was accepted. Those who were taking antihypertensive drug were taken as hypertensive subjects.

2.10 Diagnostic criteria of hypertension

For all practical purpose, the attempts were taken to make the patient relaxed in a quiet room and a fifteen minutes rest ensured preceding the measurement of blood pressure. In particular, sufficient time was given to settle down for the achievement of an accurate measurement. During measurement, the arm was supported horizontally at heart level denoted by the midsternal position. Systolic and diastolic hypertension (sHTN and dHTN)) were defined as SBP ≥140 or DBP ≥90 mmHg, respectively for two consecutive occasions, disregarding age and sex [84, 107].

2.11 Diagnostic criteria of coronary heart disease (CHD)

Diagnosis of CHD either due to ischemia or infarction was based mainly on changes in electrocardiographic (ECG) tracing. However, for complex findings the final diagnosis was made in consultation with the cardiologists in BIRDEM. Those who had no ECG report for last 12 months underwent ECG tracing to rule out CHD.

Overall, the diagnosis of CHD was based on a) history of angina plus ECG-positive either on rest or on stress b) post-myocardial infarction (MI) with Q-wave MI or non-Q-MI or echocardigraphic evidence(s) [5,108,109].

2.12 Diagnostic criteria of nephropathy

In the past, there was no provision of microalbuminuria estimation. Therefore, diagnosis of diabetic nephropathy based on macro-proteinuria without evidence of urinary tract infection. In addition, the values of serum creatinine (>2.0 mg / dl), urea nitrogen (>20 mg /dl) and creatinine clearance rate (CCR < 85 ml/min) in two consecutive occasions were taken as development of nephropathy.

2.13 Diagnostic criteria of retinopathy

Diagnosis of retinopathy was detected by fundoscopic examination. Presence of micro-aneurysm, exudates (soft & hard), hemorrhage, maculopathy and neovascularization were considered for the diagnosis of retinopathy. It was customary to use the term proliferative retinopathy for the latter situation. All other conditions were diagnosed as background (or preproliferative) retinopathy.

2.14 Diagnostic criteria of skin lesion (dermopathy)

Any lesion in the skin including any type of infection (bacterial, fungal, viral), delayed (>8wks) wound healing, shin-spots, necrobiosis lipoidica diabeticorum and other skin changes associated with hyperglycemia were considered as skin complications.

2.15 Diagnostic criteria of foot ulcer

Any diabetic subject with foot ulcer not healed within 8 weeks despite adequate cleaning, dressing and antibiotics (after identification of bacterial sensitivity) was diagnosed as diabetic foot.

2.16 Diagnostic criteria of orodental diseases

Periodonditis, gingivitis, periodontal abscess including stomatitis, glossitis were included in this category.

2.17 Sample collection and laboratory investigation

In BIRDEM, a standard protocol is always maintained for sample collection and biochemical investigation.

Oral glucose tolerance test (OGTT) is the initial investigation undertaken for confirmation of diagnosis. All participants were advised to attend BIRDEM with a 12 hour fast. Each participant was interviewed for social status and family history, and examined clinically.

Informed consent was taken for taking two blood samples after venepuncture. After about a 12-hour fast 5 ml of venous blood sample was collected for fasting plasma glucose (FPG), SGPT, serum creatinine and lipid. All possible aseptic measures were taken during venepuncture. Then, a 75-g anhydrous glucose drink in 300 ml of water was given. Two hour after the drink a second sample (2 ml) was taken in a fluoridated test tube for 2-h post-challenge plasma glucose (2-hPG). Fasting sample was aliquoted into two test tubes. Two ml was taken in a fluoridated test tube for FPG and 3 ml in a plain test tube for total cholesterol (Chol), triglycerides (TG) and high-density-lipoprotein (HDL) cholesterol.

The fluoridated test tubes were centrifuged for separation of venous plasma within 4 hours after collection. The measurement of plasma glucose was done after enzymatic oxidation in the presence of glucose-oxidase. The formed hydrogen peroxide reacts under catalysis of peroxidase with phenol and 4-aminophenazone to form a red-violet quinoneimine dye as an indicator.

Glucose was stable in plasma for 24 hour as it was separated just after collection. Plasma glucose was measured by glucose oxidase-peroxidase method using Technicon M-II auto-analyzer. The coefficient of variation (CV) was allowed <3%. Thus measured plasma glucose values gave the diagnosis of NIDDM subjects according to World Health Organization criteria [93] shown in the text.

The plain test tubes were allowed to settle down for at least half-an-hour. These were centrifuged and serum was collected for estimation of Chol, TG and HDL by Hitachi-704 auto-analyzer using enzymatic method. When the measurements of total Chol, HDL and TG (<400mg/dL) were available the value of LDL-chol was calculated as:

LDL-chol = Total Chol - (HDL-chol + TG / 5).

2.18 Statistical analyses

The prevalence of diabetic complications were estimated in simple percentages. The comparison of independent variables between subjects with and without complications was done by Student's t-test. The means and standard deviations (mean ± SD) of variables among the groups based on successive 5-year follow-up were compared by ANOVA and 95% confidence interval showed the significant difference [110]. The associations between the complication events and risk variables were assessed by Chi-sq-test. Chi-sq trend test estimated the trend of complications with increasing duration of diabetes as well as age.

The probability of complication for a given length of time was determined by application of ***survival curve or Kaplan-Meier (K-M) curve*** [111]**.** Finally, to explore the effects of several variables (risk factors) on complication the Cox regression analysis was used. This analysis tested the predictor variables (biophysical and socio-demographic data) for their effect in developing complication events [111]. The best chosen models included age, sex, body mass index, blood pressure, post-load plasma glucose, geographical location, education status and social class. Finally, the frequency of visit was also entered in the equation. An approximate test of significance for each variable was obtained by dividing the regression estimate by its standard error and comparing the result with the standard Normal distribution.

SPSS Window 9.0 Version was used for all these analyses.

Chapter 3

RESULTS

RESULTS

3.1 Diabetic patients classified according to duration of follow up

Follow-up information of 1065 diabetic patients was retrieved throughout the year 1995. Of them, only 906 patients could provide complete follow up data. All of them were divided into three groups according to the duration of follow up. They were **'older'**, **'middle'** and **'recent'** with ≥ 15 years, ≥ 10 years and 5-10 years follow up, respectively.

According BIRDEM registry 26,349 patients were registered up to 31 December 1980. These patients were taken as **older group**. Of them, only 0.7% (n=171) attended BIRDEM-OPD for follow up and the data of these subjects were available for analysis to determine the complications they had during ≥ 15 years period.

Starting from 1 January 1981 through 31 December 1985, 23,161 patients were registered and they constitute the **middle group.** Of them, only 2.7% (n=625) were found attending BIRDEM for follow up in the (12 mo) investigation period. They had follow up period for ≥10 years and the data were analyzed as a separate group to find out complication events among them.

The **recent group** consisted of only 110 diabetic patients, supposedly, with fewer complications. They were registered from January 1986 through December 1990 and were included in the study as the reference cases for comparative analysis between the recent and the older subjects with varying duration of follow up. In addition, the biophysical (BMI, BP, 2hPG) characteristics of the patients with shorter duration were compared with the longer duration.

3.1.1 Analysis of follow-up-visit events

Total visits of all patients were 46,694. We collected data from all these visit events. The data of visit-events included date, weight, blood pressure, glycemic status, lipid profiles and other biochemical and imaging investigation according to the need of the individual patients. These

data were either recorded in the guidebook previously or advised recently by the attending physician.

The visit events were analyzed. It was observed that the median of visit frequency was 27. The mean (±SD) of visit frequency was 32.3 ± 24.9; and the quintiles of visit events from low to high were 12, 27 and 47. The visit frequency ranged from one to 171. The highest visit frequency (n=171) was observed in a patient who was registered in 1962 and attending BIRDEM-OPD regularly. More than 80 visits in the older group accounted for only top 5 percentile of the total visits.

3.1.2 Area and sex distribution of study population

The distribution of the **older patients** of the study population was shown according to gender and area in table-1. The table also showed the distribution in each successive 5-year follow up. Almost two-thirds were male both at registration and also throughout the follow up period. More than four-fifths of the study subjects were from the urban and in the second 5-year follow up in 1986 – 90 the rural subjects attended only one-tenth of study subjects.

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

	Total Subjects	Men	Women	Urban	Rural + suburban
At registration Up to Dec 1980	171	107 (62.6)	64 (37.4)	148 (86.5)	23 (13.5)
Follow up 81-85	151	92 (60.9)	59 (39.1)	132 (87.4)	19 (12.6)
Follow up 86-90	157	95 (60.5)	62 (39.5)	140 (89.2)	17 (10.8)
Follow up 91 – 95*	171	107 (62.6)	64 (37.4)	148 (86.5)	23 (13.5)

* - Data collected throughout the year 1995
Figures within parenthesis are percentages.

For the **middle group** (Table-2), the male to female ratio showed changes and it was just reverse. The female outnumbered male subjects (51.9 vs. 48.0%) and it was consistently observed throughout their follow up period. The **recent group** (1986 – 90) also showed the same distribution (table not shown).

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

At registration From Jan 1980 through 1985	**Total Subjects**	**Men**	**Women**	**Urban**	**Rural + suburban**
	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
Figures within parenthesis are percentages.

3. 1.3 Glycemic status at registration and in subsequent follow-up

Two-hour post-load plasma glucose (2hPG) levels at registration and at subsequent 5-year follow up of the older patients (n = 171) were shown in table-3. The mean (SD) of 2hPG at registration was 8.3 (3.6) mmol/l that gradually and consistently increased to each successive 5-year follow up and reached to 12.9 (2.6) mmol/l at third 5-year. The increments from registration to the first follow-up, and then to second and third follow up were all significant, as tested by ANOVA.

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 (men + women, n=171, older group).

			Post-prandial plasma glucose (mmol/L)†		
		n	**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

3. 1.4 Plasma glucose levels continued to increase despite follow up

The mean plasma glucose levels, in either sex, increased significantly from the time of registration to last 5-year follow up in men (95% CI 7.9 – 9.2 to 12.4 – 13.5 mmol/l) and in women (95% CI 6.9 – 8.8 to 12.1 – 13.3 mmol/l) [Table-4].

Table 4. Comparison of mean post-prandial plasma glucose level in the study population observed between at registration and last 5-year follow–up period for men (n = 107) and women (n = 64).

			Post-prandial plasma glucose (mmol/L)†		
		n	Mean	SD‡	95 % CI¶
Men					
At registration up to Dec 1980		107	8.6	3.5	7.9 – 9.2
At last 5 year follow-up	1991-95	107	13.0	2.7	12.4 – 13.5*
Women					
At registration up to Dec 1980		64	7.8	3.9	6.9 – 8.8
At last 5 year follow-up	1991-95	64	12.7	2.3	12.1 – 13.3*

* - Student's t-test: men, t =10.2, p<0.001; women t, t = 8.7, p<0.001;
† - 2h after breakfast; ‡ - SD, standard deviation
¶ - CI, confidence interval

The increasing trend of plasma glucose level with increasing duration of follow up was observed in both urban and rural plus suburban patients. The trend was more consistent and more significant in urban subjects than their rural and suburban counterparts [Table-5].

Table 5. Mean post-prandial plasma glucose observed at registration and in successive 5-year follow-up for ≥15-year retrospective study in urban (n=148) and rural plus suburban (n=23) subjects.

		Post-prandial plasma glucose (mmol/L)†		
Urban	n	Mean	SD‡	95 % CI¶
At registration up to Dec 1980	148	8.1	3.4	7.5 – 8.6
Subsequent Follow-up				
First 5-year 1981- 85	132	9.3	2.3	8.9 – 9.7*
Second 5-year 1986 - 90	140	11.7	2.4	11.3 – 12.1*
Third 5-year 1991 - 95	148	12.9	3.3	12.5 – 13.3*
Rural + Suburban				
At registration up to Dec 1980	23	10.0	4.9	7.9 – 12.1
Subsequent Follow-up				
First 5-year 1981- 85	19	9.5	2.5	8.3 – 10.7*
Second 5-year 1986 - 90	17	11.8	2.9	10.3 – 13.3
Third 5-year 1991 - 95	23	12.7	3.5	11.2 – 14.2*

* - ANOVA for urban: F=95.9, P<0.001and for rural + suburban: first 5y vs. third 5y, F=3.6, P<0.02;
† - 2h after breakfast; ‡ - SD, standard deviation
¶ - CI, confidence interval

3.2 Prevalence of complications

3.2.1 Micro-vascular vs. macro-vascular complications

Prevalence of complications was shown in figure-1 and 2. Macro-vascular complications (foot ulcer, stroke and coronary heart disease) were lower than micro-vascular (nephropathy and retinopathy) and also mixed (HTN, skin-lesion and periodondal diseases) type complications.

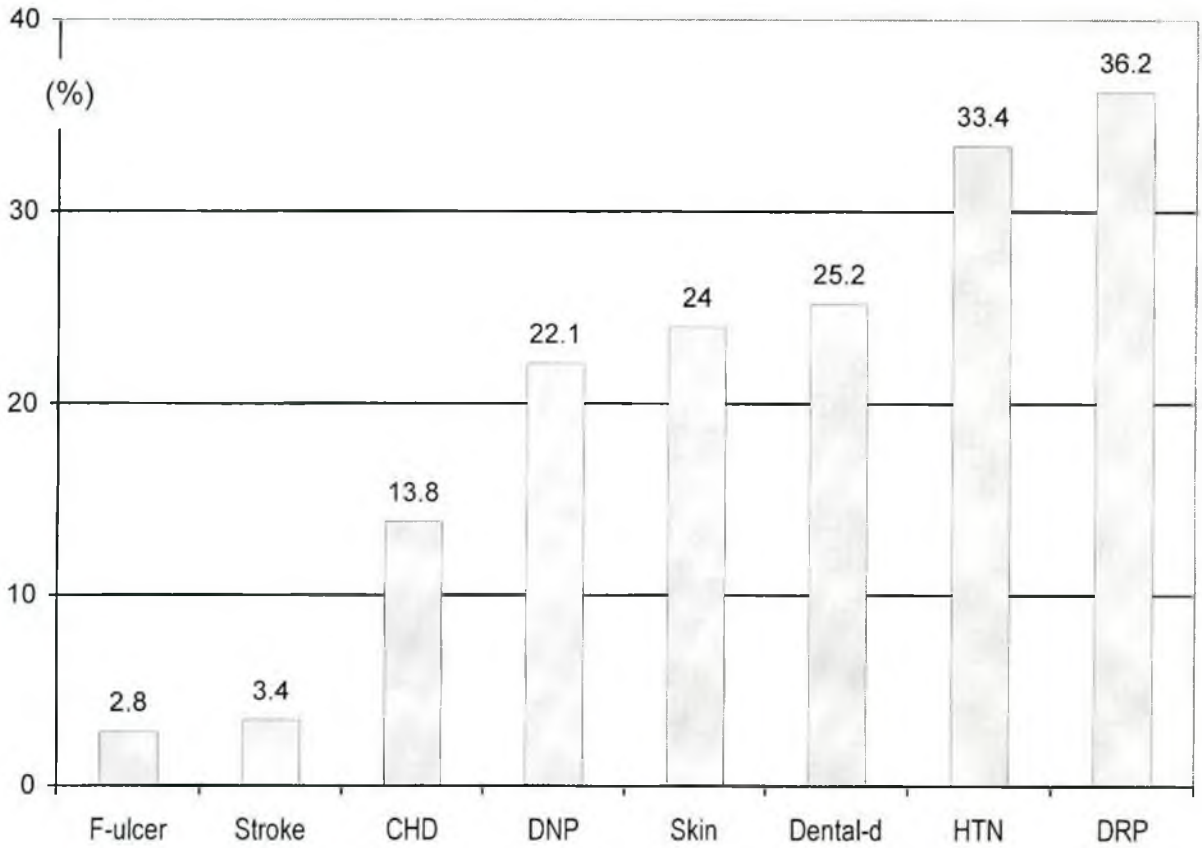


Figure 1. Prevalence (%) of complications in all subjects (n=906) observed in 1995 irrespective of registration and follow-up.

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.

3. 2.2 Older group vs. middle group

The prevalence of both types of vasculopathy (micro- and macro-vascular lesion) and mixed type were compared between older and middle groups (figure-2). Micro-vascular complications (retinopathy and nephropathy) were the highest among both the older and

middle groups. Compared with the middle group, retinopathy was significantly higher in the older subjects (34.4 vs. 48.5 %: χ^2 =11.5, p <0.001). Similarly, nephropathy was also significantly higher in the older patients (24 vs. 39.2 %: χ^2 = 15.6, p<0.001). In contrast, mixed type of diabetic complications were significantly higher in the middle than in the older group. Thus, compared with the older group, the middle group showed higher prevalence of orodental (18.1 vs. 27.4%: χ^2 = 6.0, p<0.02) and skin (18.1 vs. 25.8%: χ^2 = 4.3, p<0.05) infections and the differences were significant. For macrovascular complications (CHD, stroke and foot-ulcer) in both (older and middle) groups were less prevalent and there was no significant difference between them.

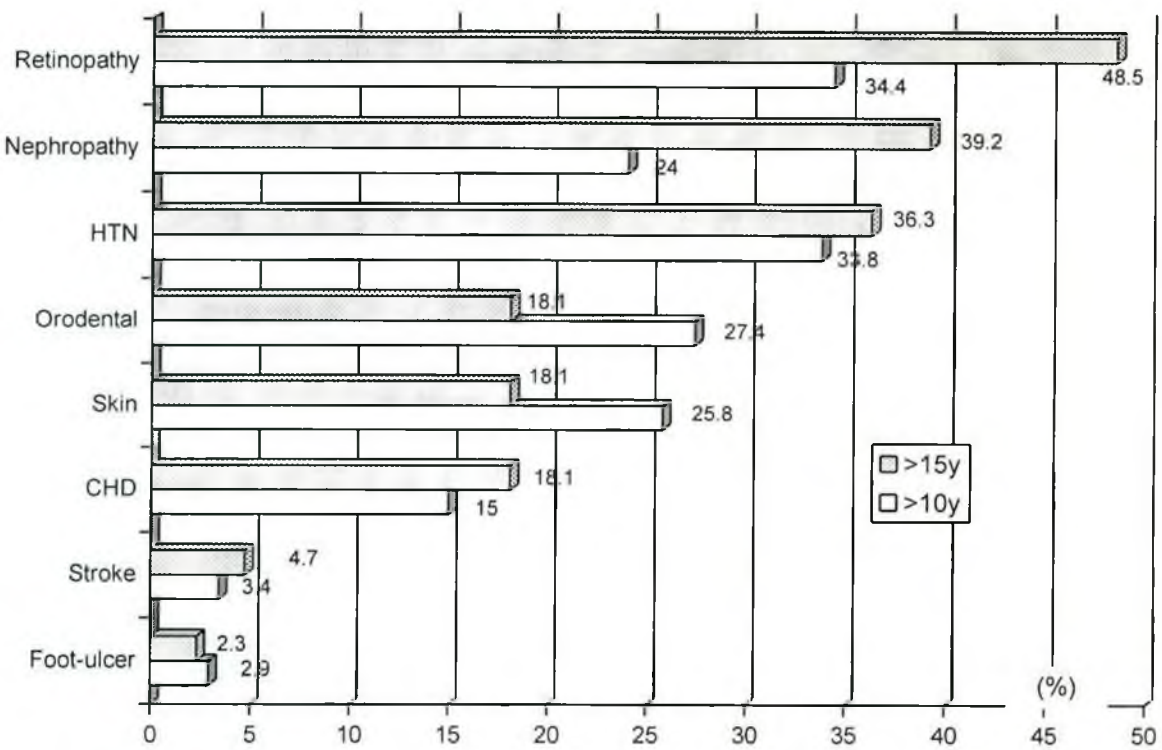


Figure 2. Comparison of prevalence rates of different types of complications between ≥10-years and ≥15-years follow-up in the study population.

3. 2.3 Prevalence of complications increased with duration of follow-up

All types of complications were found increasing with the duration of follow up [Table 6 – 11]. The data were shown separately for older group (n = 171) in table 6 – 8 and for middle group (n = 625) in table 9 – 11.

For older patients, the increasing trend of cerebro-vascular accident (stroke) and coronary heart disease (CHD) was significant ($p<0.01$ and $p<0.001$); whereas, the trend in peripheral vascular disease with foot-ulcer was not significant [Table 6].

Table 6. The prevalence of macrovascular complications among the diabetic patients (n=171) who had ≥15 years follow-up.

	Complications (%) observed at registration and in the successive 5yr intervals				
Macro-vascular Events	At registration up to Dec 1980	First 5-year 1981 - 85	Second 5-year 1986- 90	Third 5-year 1991-95	X^2 *trend§*
n	*171*	*151*	*157*	*171*	
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

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$
† - 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.

Similarly, micro-vascular complications like nephropathy and retinopathy showed also a significant increasing trend [Table 7].

Table 7. 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 5-yr intervals				
	At registration up to Dec 1980	First 5-year 1981 - 85	Second 5-year 1986- 90	Third 5-year 1991-95	X^2 *trend§*
n	*171*	*151*	*157*	*171*	
Nephropathy†	18.7	23.8	32.5	36.8	16.56***
Retinopathy‡	9.9	17.9	34.4	48.5	73.31***

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$, *** p<0.001
† - Nephropathy – all types of proteinuria irrespective of serum creatinine level
‡ - Retinopathy - Background or proliferative retinopathy

The mixed-type-complication events like hypertension, dermopathy and orodental diseases were no exception to this finding [Table 8].

Table 8. The prevalence of mixed type of complications among the diabetic patients (n=171) who had ≥15 years follow-up at BIRDEM-OPD.

Mixed Events	Complications (%) observed at registration and in the successive 5-yr intervals				
	At registration up to Dec 1980	First 5-year 1981 - 85	Second 5-year 1986- 90	Third 5-year 1991-95	X^2 *trend§*
HTN†	19.3	21.2	29.3	36.3	14.94***
Dermopathy††	0.6	3.3	11.5	18.1	52.8***
Orodental dis. ‡	NA	NA	8.3	18.1	73.31***

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$; *** p<0.001
† - HTN, hypertension: systolic blood pressure ≥ 140 or, diastolic blood pressure ≥90 mmHg
†† - Dermopathy: all types of infected lesion in the skin, shin spots, necrobiosis lipoidica diabetocorium
‡ - Orodental dis: periodonditis, gingivitis, glossitis and other orodental infection.

Middle group patients also had the similar increasing trend of complications [Table 9-11].

Table 9. The prevalence of macrovascular complications among those who had 10-15 year follow up (Middle group, n=625) at BIRDEM-OPD.

Macro-vascular Events	Complications (%) observed at registration and in the successive 5-yr intervals			
	At registration up to Dec 1980	First 5-year	Second 5-year	X^2 *trend§*
	1981 - 85	1986- 90	1991-95	
Stroke	0.3	0.7	3.4	19.96***
CHD†	3.5	5.1	14.1	49.52***
F-ulcer‡ & PVD	0.2	1.4	2.9	15.97***

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$; *** p<0.001
† - Coronary heart disease: evidence of ischemia on either resting or stress ECG or old myocardial infarction or comments of a cardiologist
‡ - Foot ulcer, peripheral vascular disease including amputation

Table 10. The prevalence of microvascular complications among those who had 10-15 year follow up (Middle group, n=625) at BIRDEM-OPD.

Micro-vascular Events	Complications (%)observed at registration and in the following 5 year intervals			
	At registration up to Dec 1980	First 5-year	Second 5-year	X^2 *trend§*
	1981 - 85	1986- 90	1991-95	
Nephropathy†	16.6	16.5	20.6	3.39 ns
Retinopathy‡	12.3	23.3	33.8	80.81***

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$, *** p<0.001
ns – not significant.
† - Nephropathy – all types of proteinuria irrespective of serum creatinine level
‡ - Retinopathy - Background or proliferative retinopathy

Table 11. The prevalence (%) of mixed type of complications among the diabetic patients who had 10-15 years follow-up (middle group, n=625) at BIRDEM-OPD.

Mixed Events	Complications (%) observed at registration and in the following 5 year intervals			
	At registration up to Dec 1980	First 5-year	Second 5-year	X^2 *trend§*
	1981 - 85	1986- 90	1991-95	
HTN†	25.3	25.3	33.8	11.10**
Dermopathy††	3.8	12.9	25.8	123.24***
Orodental dis‡	0.5	10.4	27.4	202.49***

§ - χ^2 trend = $[\Sigma r_i x_i - R\bar{X}]^2 / p(1-p)[n_i x_i - N\bar{X}^2]$; ** $p<0.01$, *** $p<0.001$
† - HTN, hypertension: systolic blood pressure ≥ 140 or, diastolic blood pressure ≥90 mmHg
†† - Dermopathy: all types of infected lesion in the skin, shin spots, necrobiosis lipoidica diabetocorium
‡ - Orodental dis: periodonditis, gingivitis, glossitis and other orodental infection.

On the other hand, recent group (n=110) who were registered 1986 through 1990 had very little complication events [Table 12 – 15]. In fact, with some few exceptions, there was no significant difference of complications observed between the time at registration and five years after follow up.

Table 12. The prevalence (%) of macrovascular complications among those who had 5-10 years follow up (Recent group, n=110) at BIRDEM-OPD.

Macro- vascular Events	Complications observed at registration and in the following 5yr intervals: At registration up to Dec 1980 1986- 90	Second 5-year 1991-95	X^2 §
Stroke	0	1.8	ns
CHD†	2.7	5.5	ns
F-ulcer‡	0	2.7	ns

§ - χ^2; ns – not significant
† - CHD, Coronary heart disease
‡ - F-ulcer, foot ulcer, peripheral vascular disease including amputation

Table 13. The prevalence (%) of microvascular complications among those who had 5-10 years follow up (Recent group, n=110) at BIRDEM-OPD.

Micro-vascular events	Complications observed at registration and in the following 5 year intervals: Subjects Registered In '86-90	first 5 year 1991-95	X^2 §
Nephropathy	7.3	7.3	ns
Retinopathy	28.2	28.2	ns

§ - χ^2 ns – not significant

Table 14. The prevalence (%) of macrovascular complications among those who had 5-10 years follow up (Recent group, n=110) at BIRDEM-OPD.

Mixed Events	Complications observed at registration and in the following 5 year intervals: Subjects Registered In '86-90	first 5 year 1991-95	X^2 §
HTN	30.9	27.3	ns
Dermopathy	7.3	22.7	123.24***
Orodental	4.5	23.6	202.49***

§ - χ^2; * p<0.05, ** p<0.02, *** p<0.001
ns – not significant

When compared between subjects with low and high mean values of plasma glucose during their entire follow up period it was observed that very little difference of complication events was observed between them though the increasing trend with duration of follow up was persistently observed [Table 15].

Table 15. The prevalence of complications compared between diabetic patients of older group (Older group, n-171) who maintained mean 2hPG above and below 10mmol/l throughout their first to last visit.

Complication Events	Complications (%) observed at registration and in the successive 5-yr intervals								
	At registration up to Dec 1980		First 5-year 1981 - 85		Second 5-year 1986- 90		Third 5-year 1991-95		*p after* X^2
	2hPG mmol/l								
	<10	>10	<10	>10	<10	>10	<10	>10	
CHD	2.1	0.8	2.3	0.9	9.5	6.1	14.9	19.4	
Stroke	0	0	0	0.9	0	2.6	2.1	5.6	
Foot ulcer	0	0	0	0.9	0	1.7	0	3.2	
HTN†	12.8	21.8	15.9	23.4	23.8	31.3	17.0	43.5	**'95
Nephropathy	14.9	20.2	18.2	26.2	28.6	33.9	29.8	39.5	**'95
Orodental dis. ‡	0	0	0	0	14.3	6.1	21.3	16.9	
Retinopathy	8.5	10.5	11.4	20.6	26.2	37.4	40.4	51.6	
Dermopathy††	0.0	0.8	2.3	3.7	7.1	13.0	10.6	21.0	

† - HTN, hypertension: systolic blood pressure ≥ 140 or, diastolic blood pressure ≥ 90 mmHg
†† - Dermopathy: all types of infected lesion in the skin, shin spots, necrobiosis lipoidica diabetocorium
‡ - Orodental dis: periodonditis, gingivitis, glossitis and other orodental infection.

3. 2.4 Complication prevalence at registration and in subsequent follow up

Each specific complication event encountered at registration and in subsequent follow up visits in all diabetic patients of older group (n = 171) and of middle group (n = 625) were displayed separately [Figure 3 – 10]. Simultaneously, comparative analyses of complication prevalence between men and women were also shown.

Hypertension (HTN) prevalence is shown according to registration and subsequent follow -up by sex for older and middle group [Figure 3: upper and lower panel].

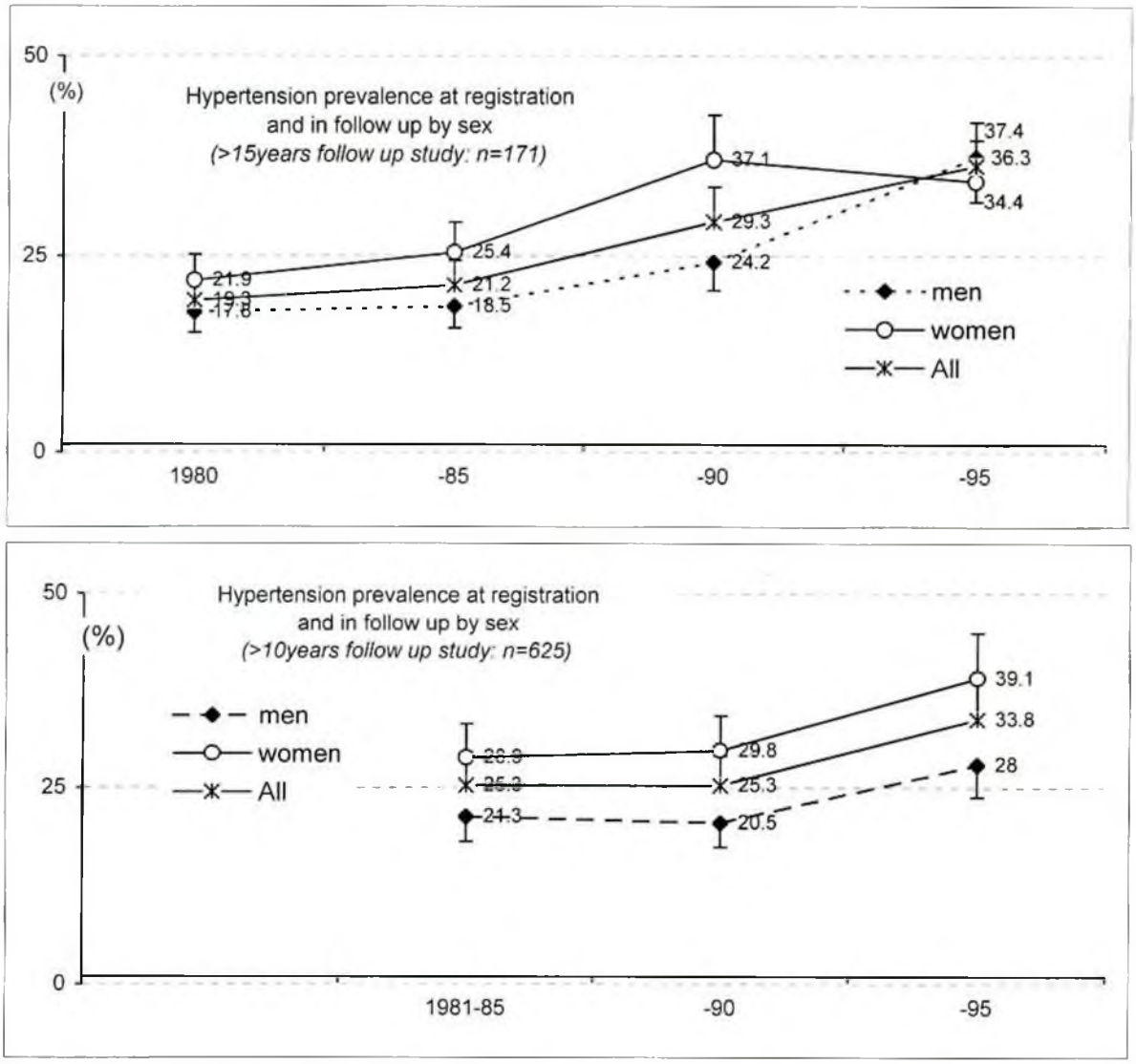


Figure 3. Prevalence (%) of hypertension is shown according to registration and duration of diabetes by sex. The prevalence rates were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

For the older patients, though the difference of hypertension prevalence between men and women was negligible at registration, the female diabetic patients had increasingly higher frequency after 5- and 10- year follow up. This gender difference of prevalence reduced to minimal after 15-year. In contrast, in the middle group, the women showed higher prevalence of hypertension than their male counterpart and almost maintained the same difference throughout their follow up period.

The prevalence of coronary heart disease (CHD), in older and middle group [Figure 4: upper & lower box], showed no difference between men and women at registration. Both the gender had similar CHD event throughout their follow up period except only after 15 years, a slight increase in men than women, though the difference was not significant.

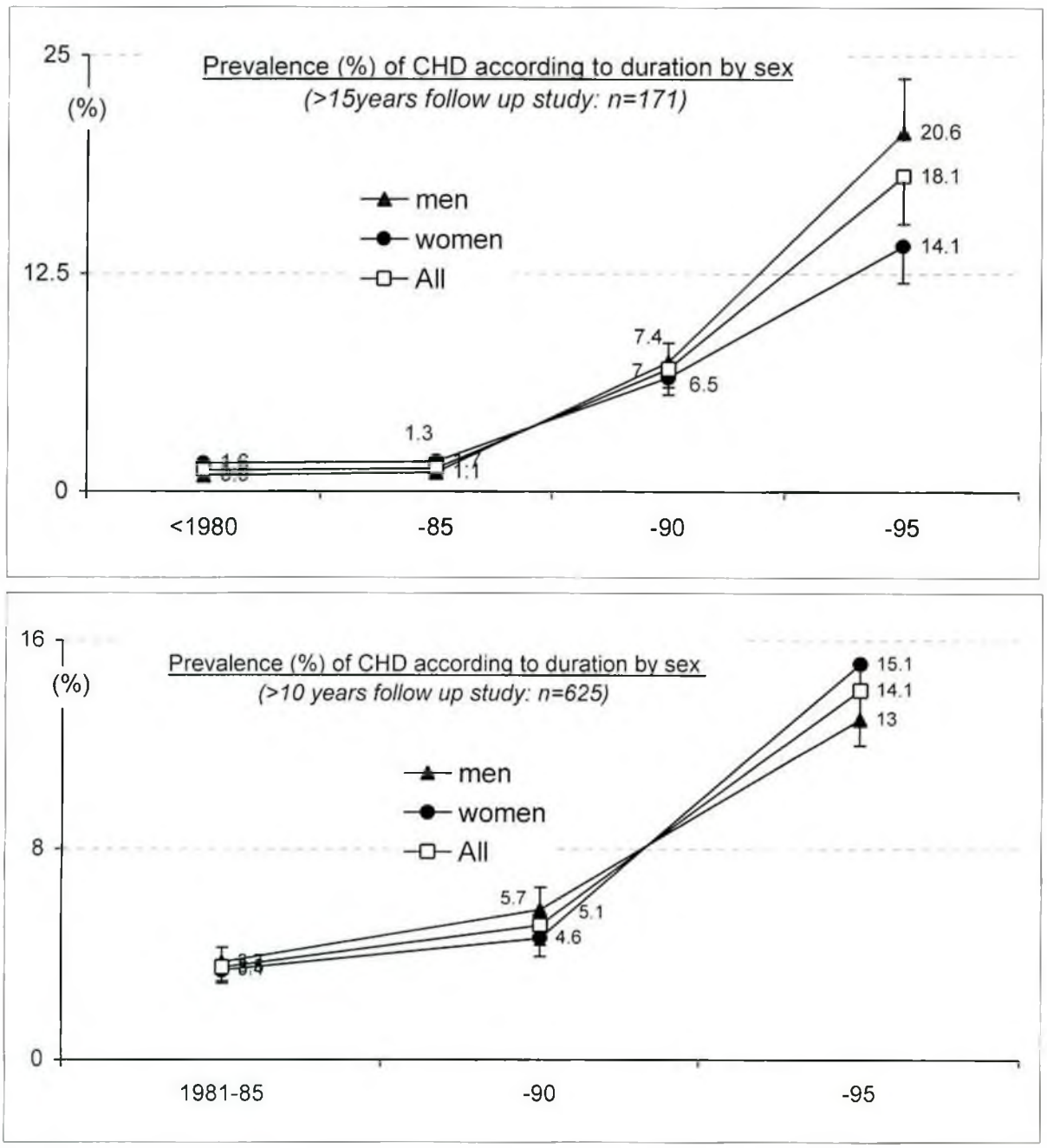


Figure 4. Prevalence of coronary heart disease (CHD) is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

Stroke prevalence in women could not be documented in older subject either at registration or in the first 10-years follow up period [Figure 5: upper box]. Thus, the frequency of stroke in men and women could not be compared in early period. However, the male patients had higher prevalence of cerebro-vascular complications at the later part of the follow up which was significant (χ^2: 4.4, $p<0.05$). For middle group, in contrast, the female patients had stroke almost twice the men (4.3 vs. 2.3%), though the difference was not significant [Figure 5: lower box].

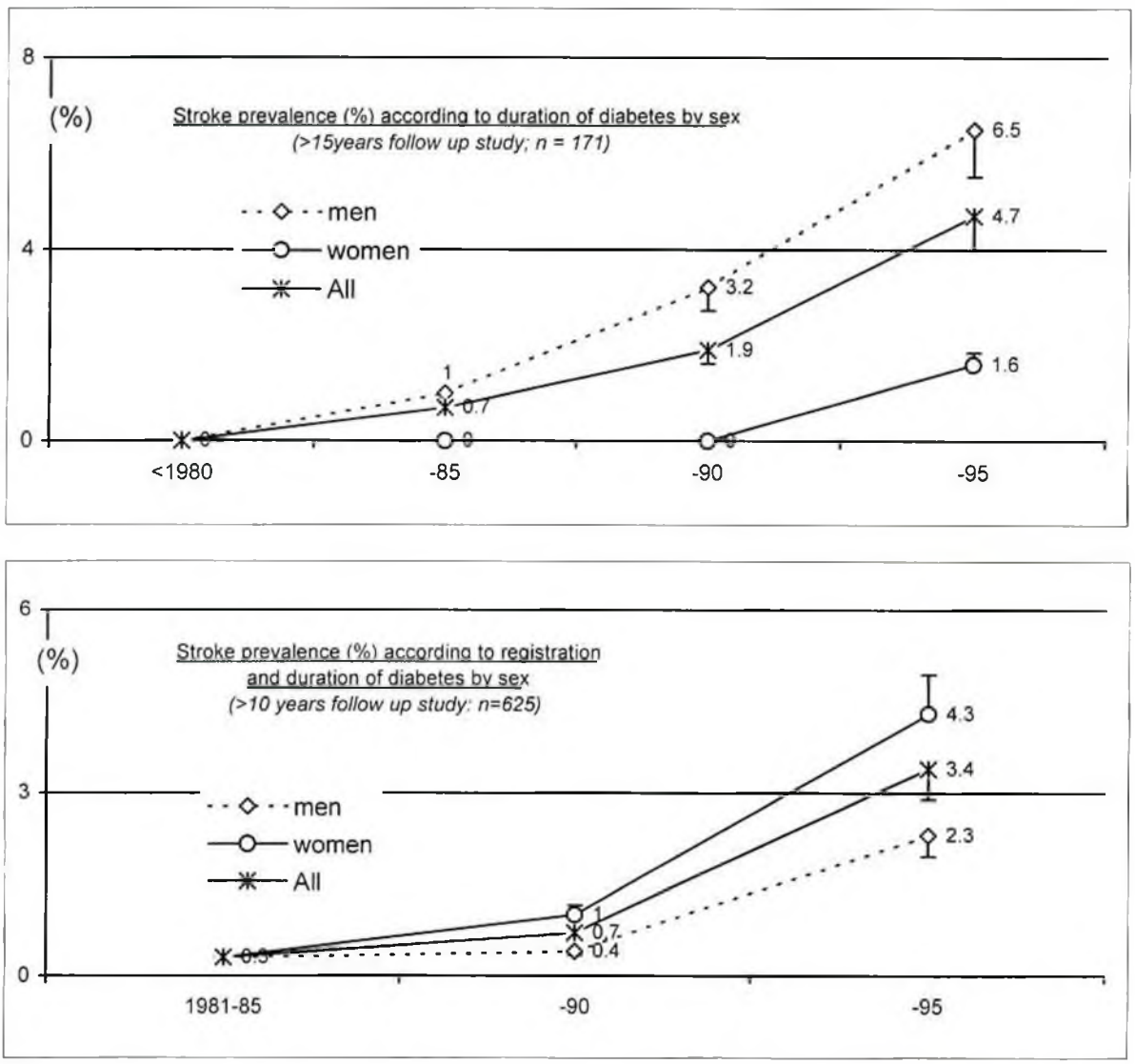


Figure 5. Prevalence of stroke is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

The prevalence of foot ulcer, in older subjects, could be traced back at registration only in women [Figure 6: upper box]. For the subsequent follow up, though men and women both developed foot ulcer, the prevalence was higher in the women; but the gender difference was not significant. Similarly, for the middle group, the female diabetic patients had more foot ulcer than the men did [Figure 6: lower panel]. But here again, there was no significant difference between men and women.

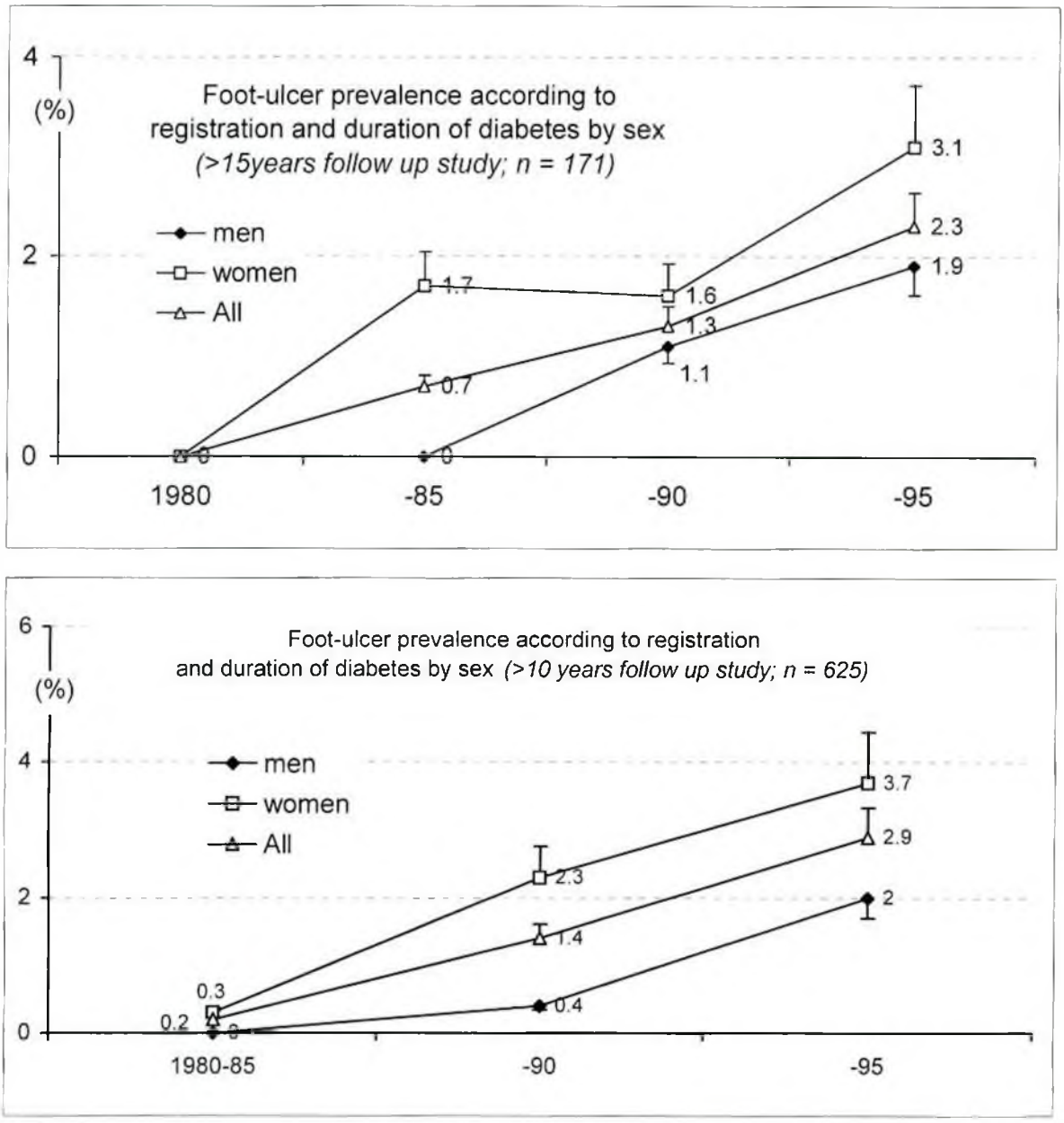
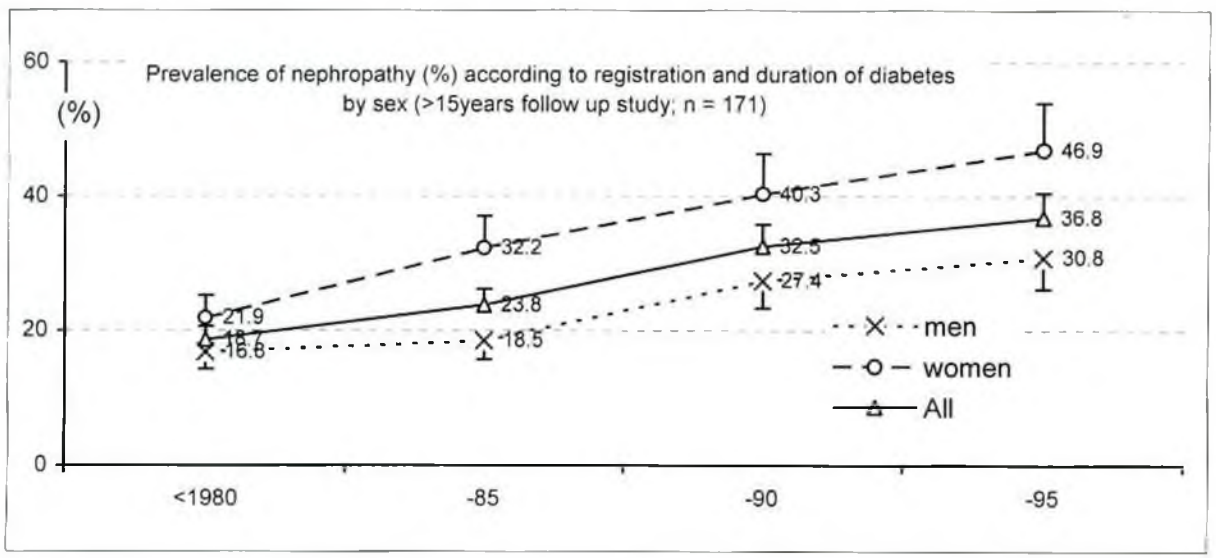


Figure 6. Prevalence of foot-ulcer (including amputation) is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

Diabetic nephropathy, in older diabetic patients, was observed in about 20% of them at registration in either sex. 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) [Figure 7: upper box]. There was almost similar observation encountered in the middle group that the female patients developed significantly higher nephropathy than their male counterpart [Figure 7: lower box] (14.3 vs. 26.5%; χ^2 =14.0, p<0.001).



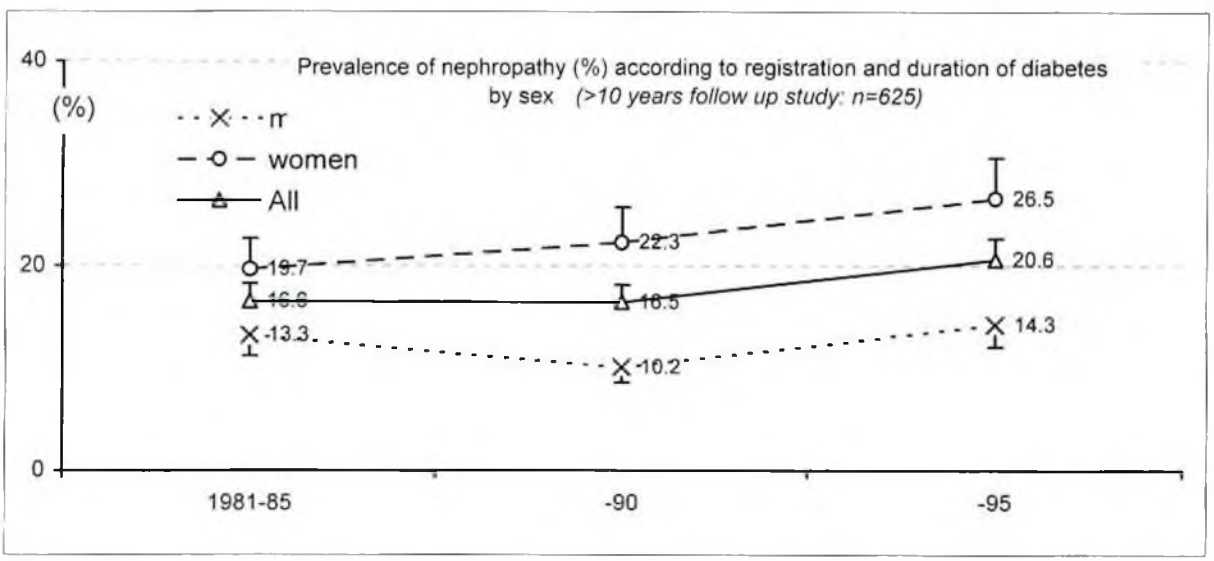


Figure 7. Prevalence of nephropathy is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

Prevalence of diabetic retinopathy was about 10% in either sex of older group at registration [Figure 8: upper box]. The subsequent follow up showed greater increase in female than male patients, but the difference was not significant. For the middle group, retinopathy prevalence was found affecting men and women equally (35.3 vs. 32.3%) [Figure 8: lower box].

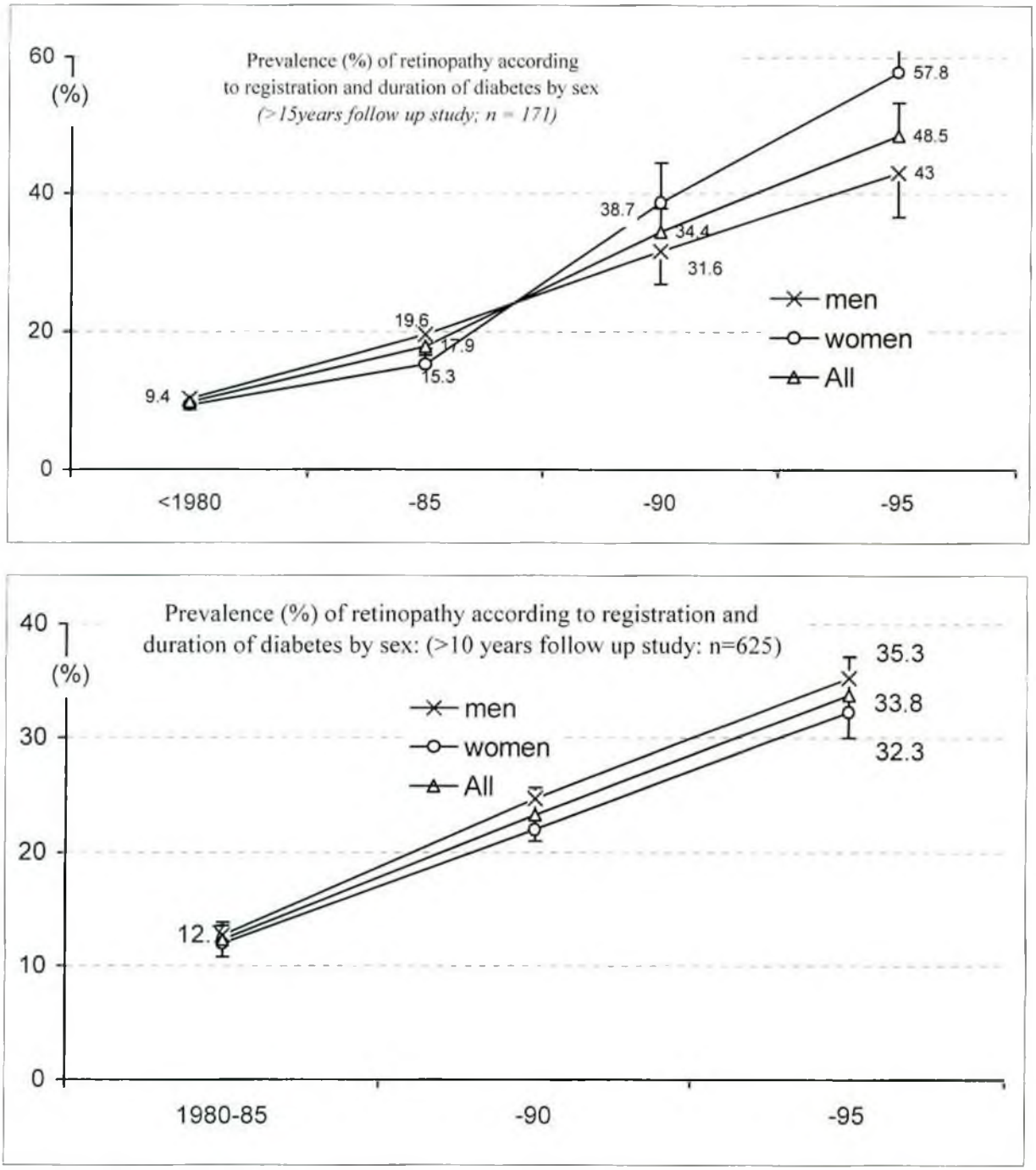


Figure 8. Prevalence of retinopathy is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

Prevalence of skin lesion (dermopathy) of the older diabetic patients was negligible (<3%) at registration [Figure 9: upper panel]. The increasing frequency in the subsequent follow up was more marked in the female patients than their male counterparts. However, the gender difference was not significant. For the middle group, the prevalence of skin lesion at registration was very less in either sex. Compared with the male the female diabetic patients had significantly higher frequency after 5-year (men 7.1 vs. women 18.4%; χ^2 = 16.6, p<0.001) and after 10-year (men 17.7 vs. women 33.2%; χ^2 = 19.8, p<0.001) [Figure 9: lower panel].

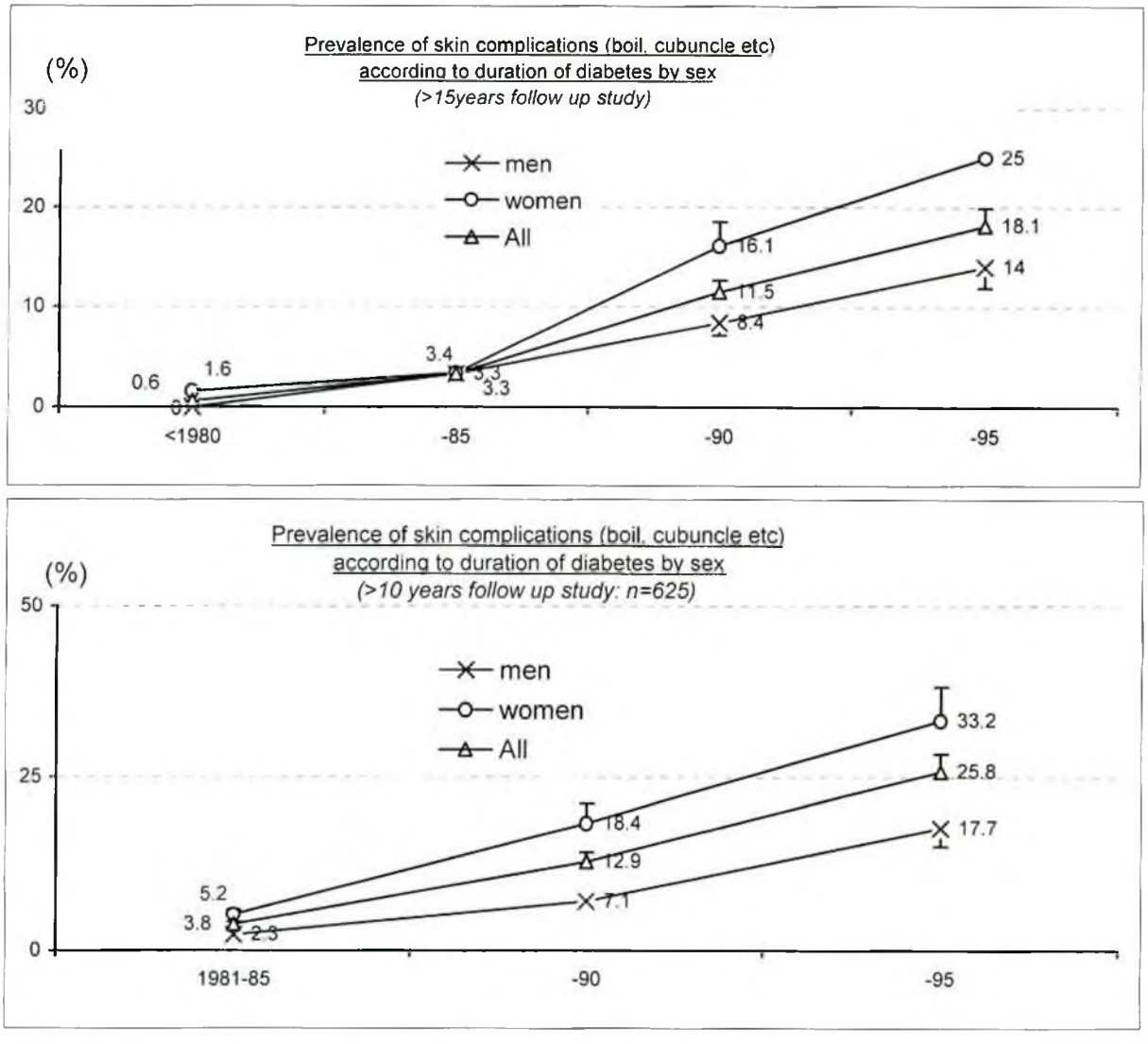


Figure 9. Prevalence of skin complication is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

Orodental complications among the older subjects could be traced very little at registration due to non-availability of the specialized dental health care as well as related data. A small number of data on dental diseases were recorded in the 1981-85 follow up. Afterwards, a substantial number of patients were found affected with orodental lesions [Figure 10: both panels]. Though for the entire follow up period, female patients had more such complications than men in the older and the middle groups there was no significant difference between men and women.

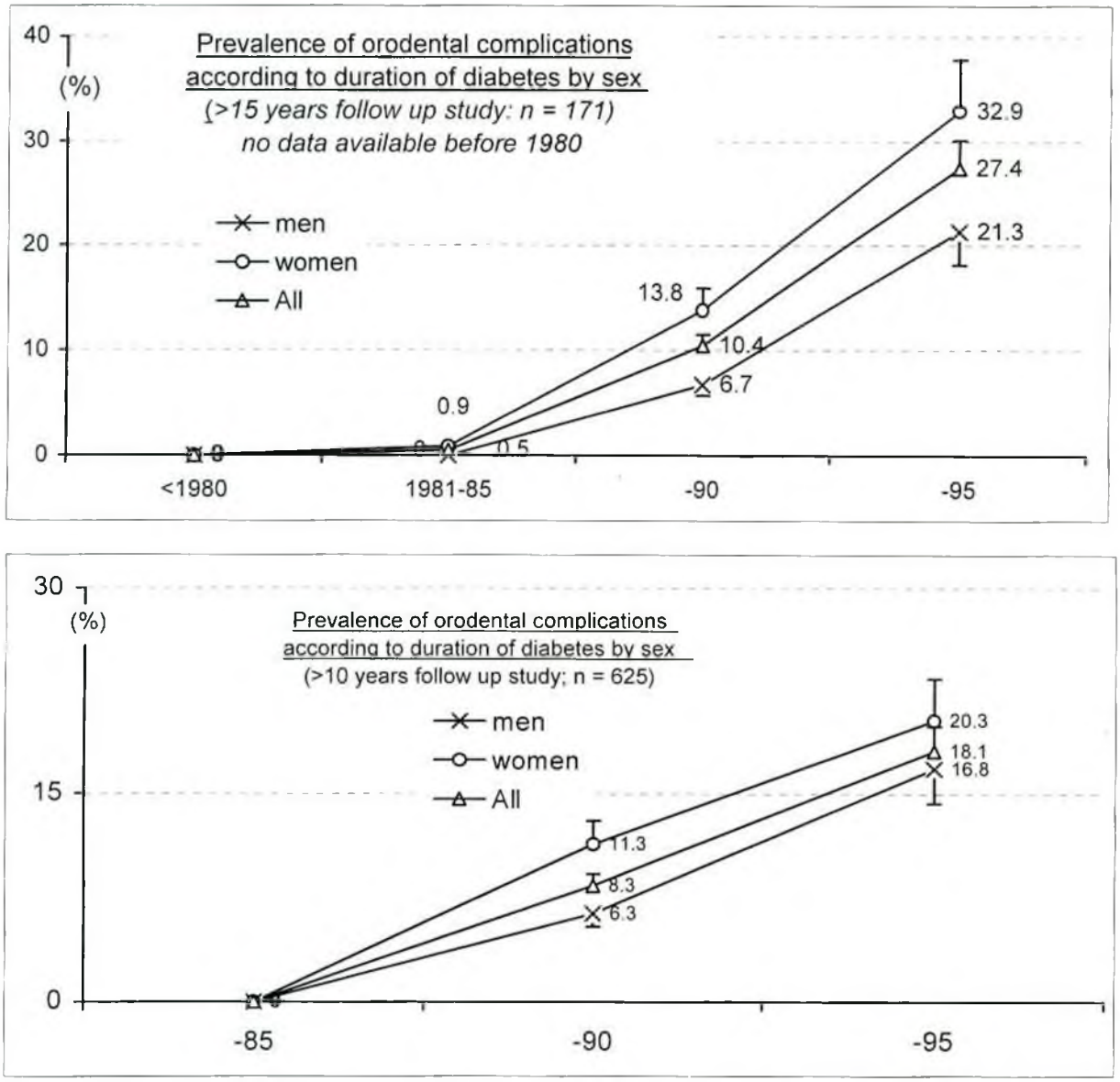


Figure 10. Prevalence of orodental diseases is shown according to registration and duration of diabetes by sex. The prevalence rates (%) were estimated at registration and in each successive 5-year follow-up in BIRDEM-Outpatient Department. The upper and lower panel displays the subjects with ≥15-year and 10-15 year follow up, respectively.

3. 2.5 Effect of glycemic status on the prevalence of diabetic complication

Considering the different grade of glycemic status maintained by study population it was observed that initially, there was more than half of the population (56%) 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 till 1995 [Figure 11].

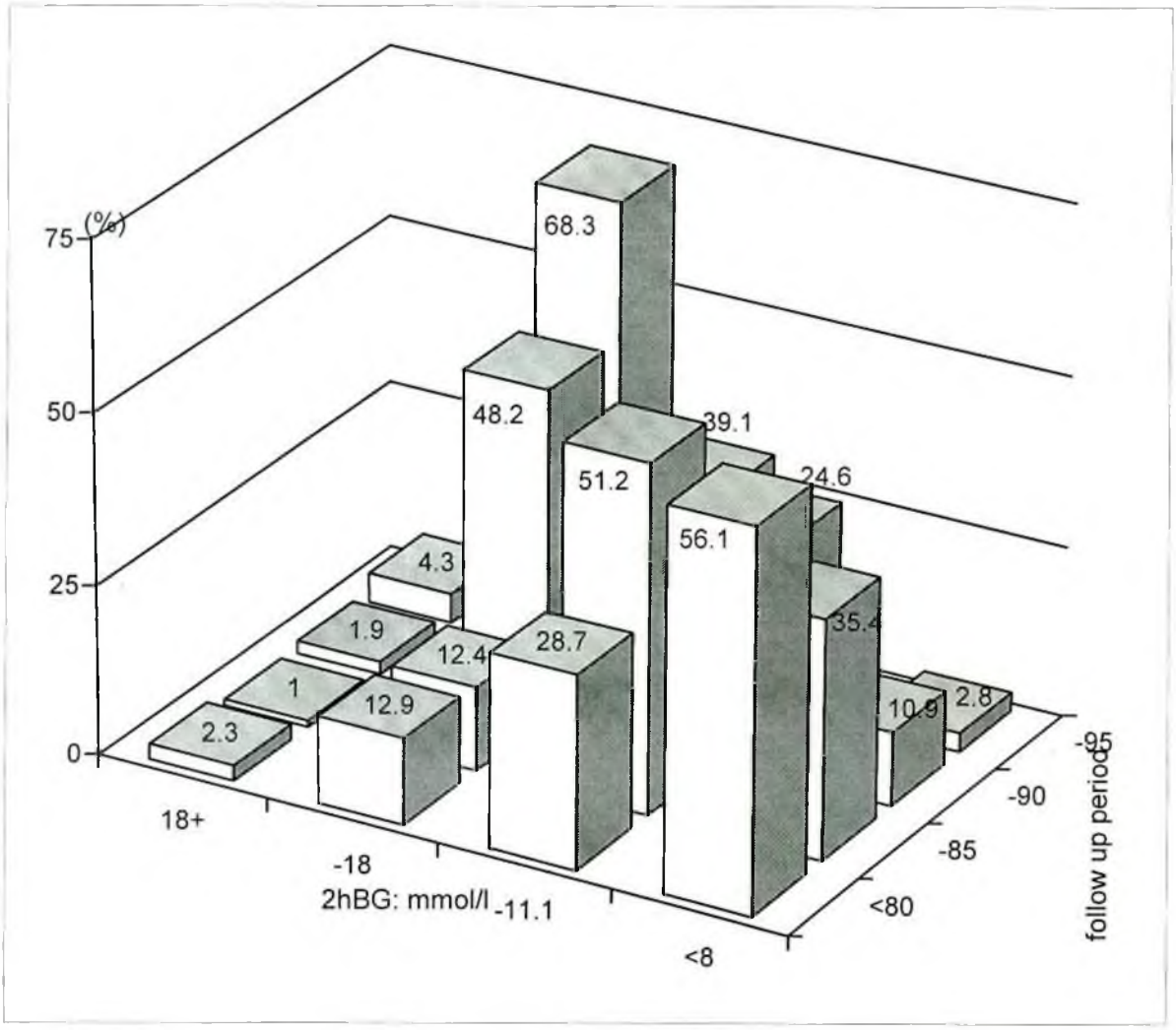


Figure 11. Quintiles of Glycemic status at registration and in subsequent follow up.
Initially, there was more than half of the population had blood glucose <8.mmol/l. As the duration of diabetes increases the severity of glycemia became more and more frequent. At registration in 1980 diabetic subjects 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.

This study addressed whether this different grade of glycemia influenced any specific type of complication. The glycemic status was graded into – I. low (<10.2mmol/l), II. middle (10.3 – 12.3 mmol/l) and III. high (>12.3 mmol/l) tertile of 2-h post-load plasma glucose (2hPG). The prevalence of complications was shown according to the tertile of 2hPG right from the registration up to the last visit recorded in 1995.

Prevalence of coronary heart disease (CHD), in the older group showed increasing trend with duration as described earlier [Figure 12a]. It was also found higher (5.6%) in the high tertile of 2hPG at registration [Figure 12b].

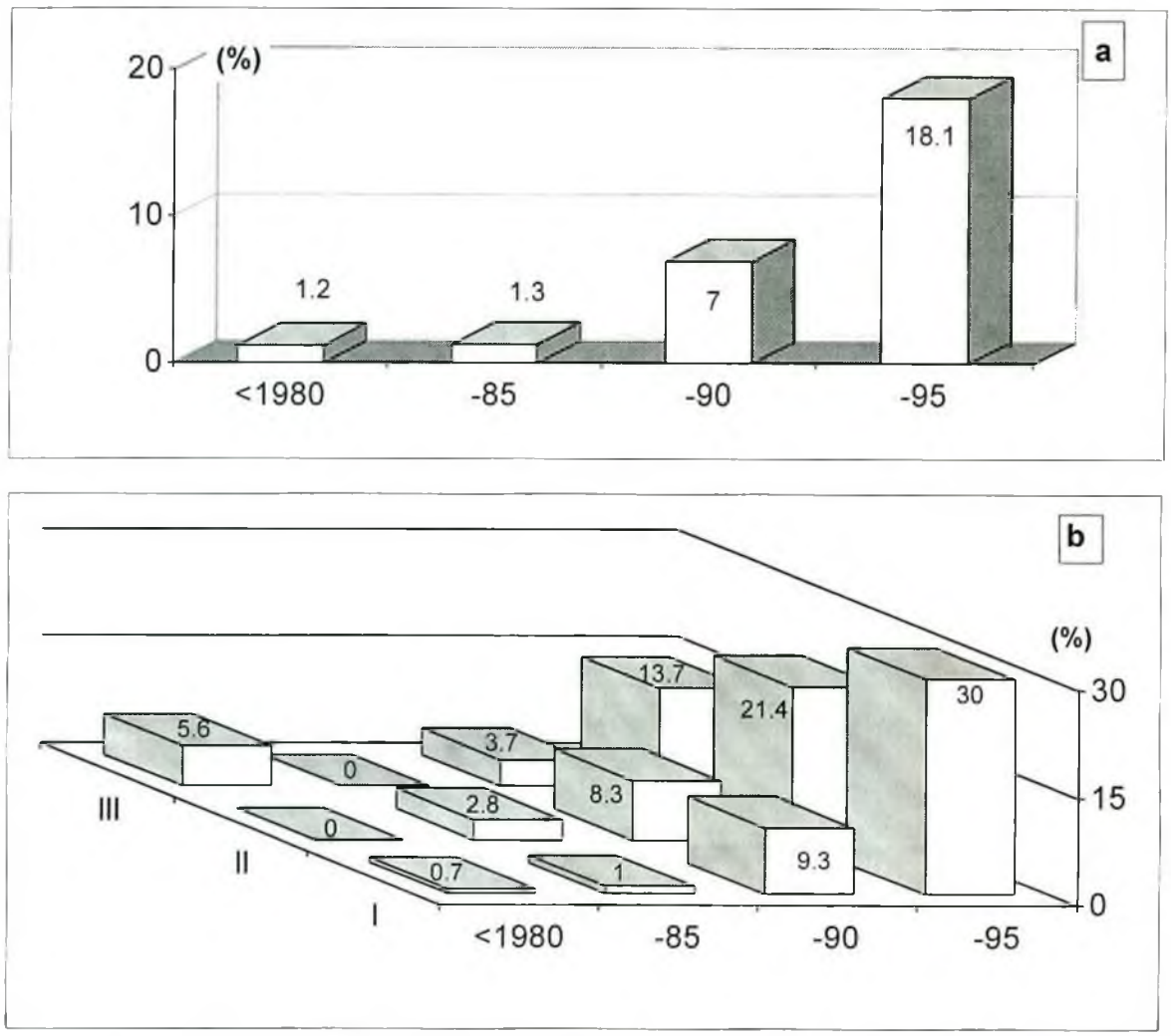


Figure 12a. Prevalence of coronary heart disease (CHD) in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 12b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Strikingly, in the last follow up, CHD prevalence was higher (30%) in the low tertile than in the middle (21.4%) and in the high (13.7%) tertile. But, there was no significant difference among them. For the middle group, there was sharp increase in the last follow up disregarding the grade of glycemia [Figure 13 a & b]. This finding of CHD prevalence indicates that there was little association between macro-vascular complication and glycemic control.

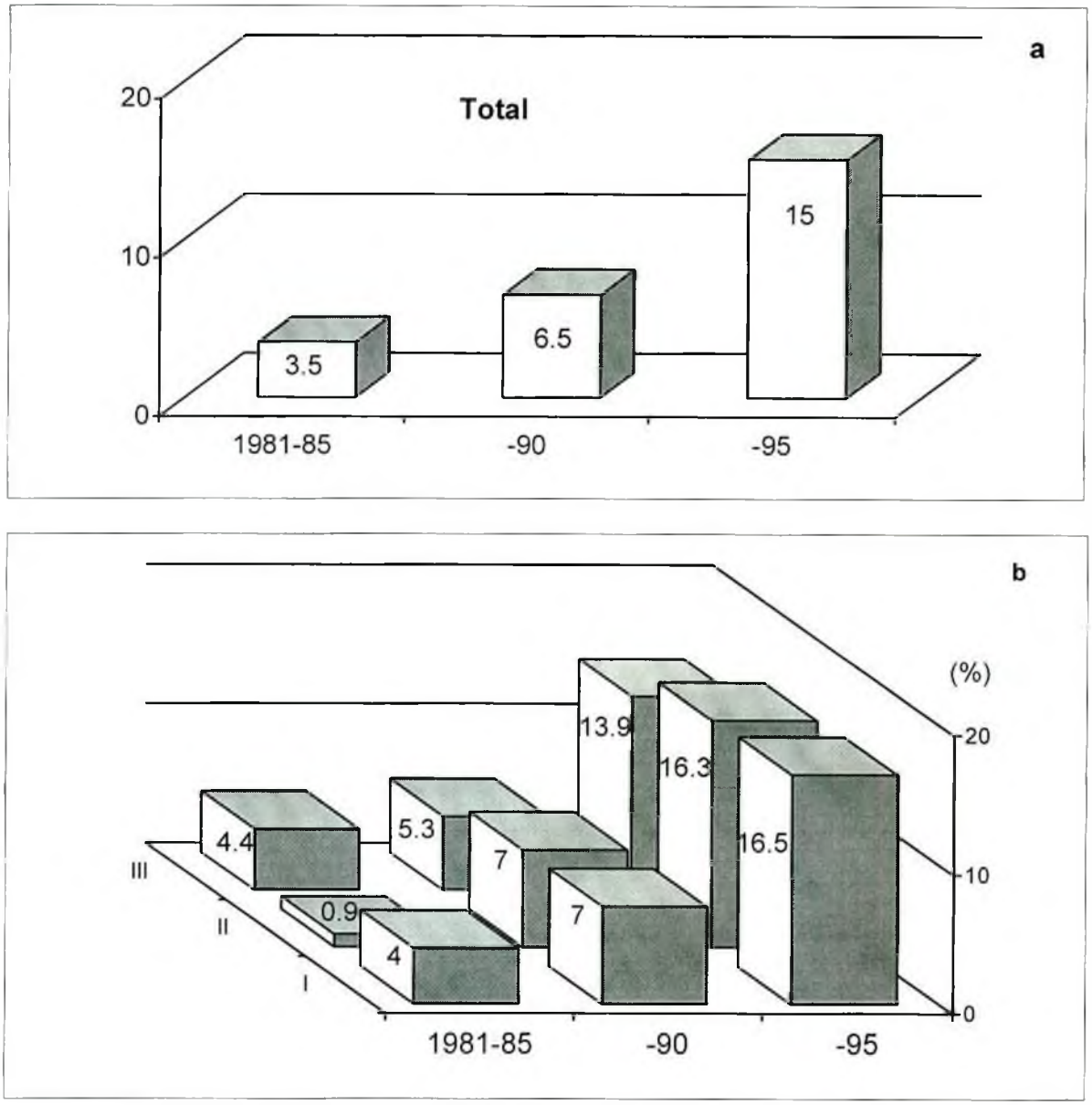
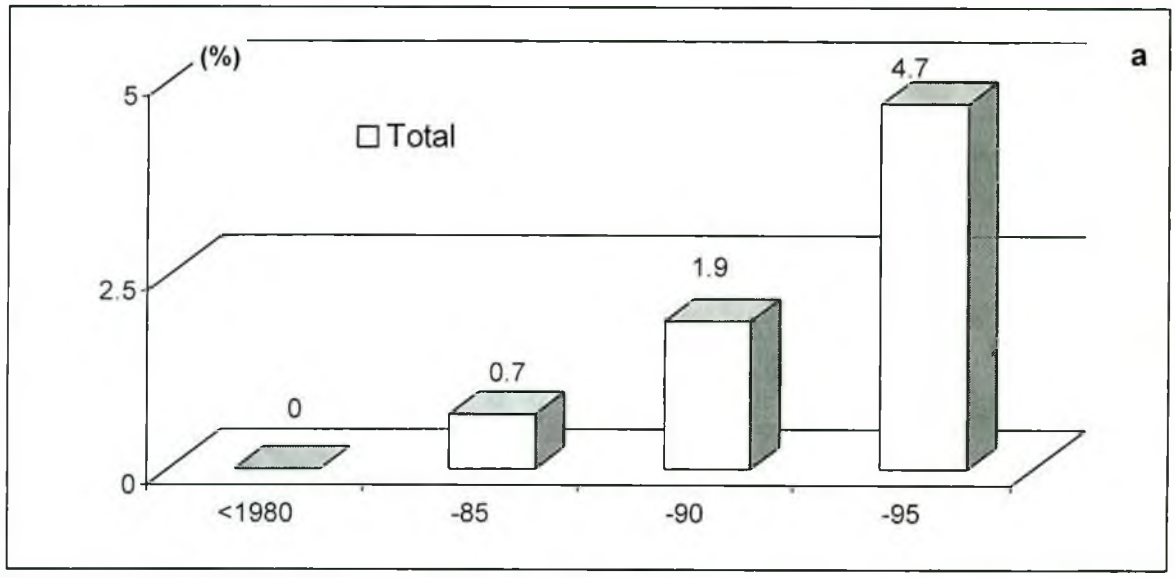


Figure 13a. Prevalence of coronary heart disease (CHD) in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 13b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Prevalence of stroke, in the older group could not be traced back at registration [Figure 14 a & b]. Its prevalence showed a slight increase in the subsequent follow up and the increasing trend was inconsistent and not related to glycemic control.



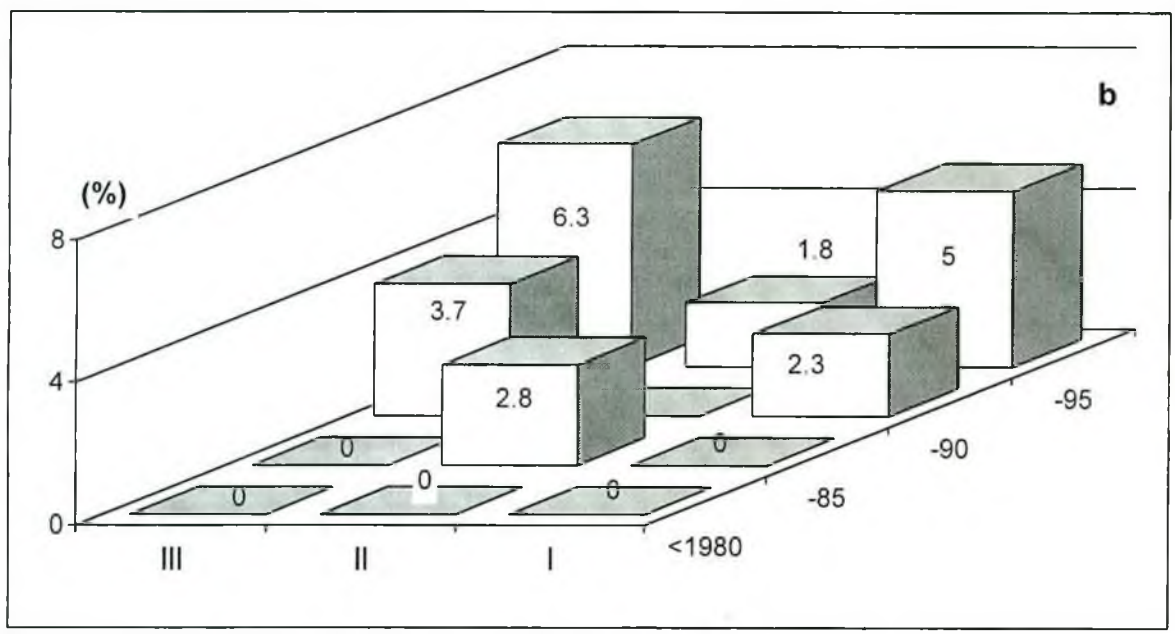
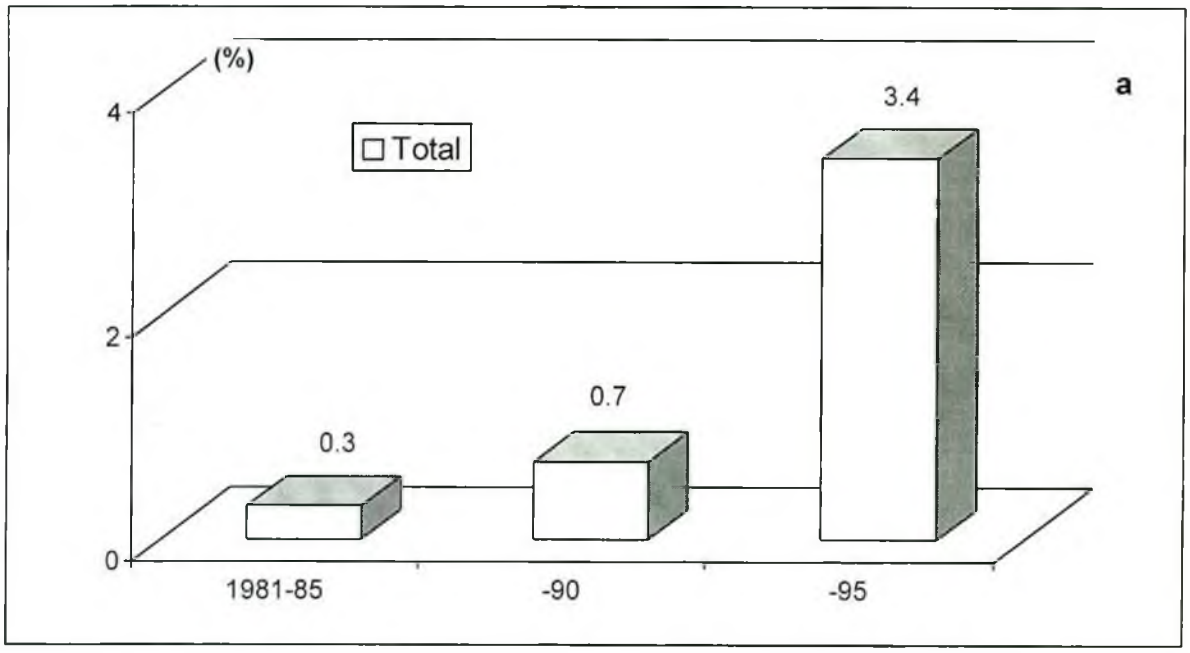


Figure 14a. Prevalence of stroke in diabetic subjects (n= 171) in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 14b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

In the middle group, however, the rising complication was more observed in the higher tertiles than in the low tertile, though there was no significant difference [Figure 15 a & b].



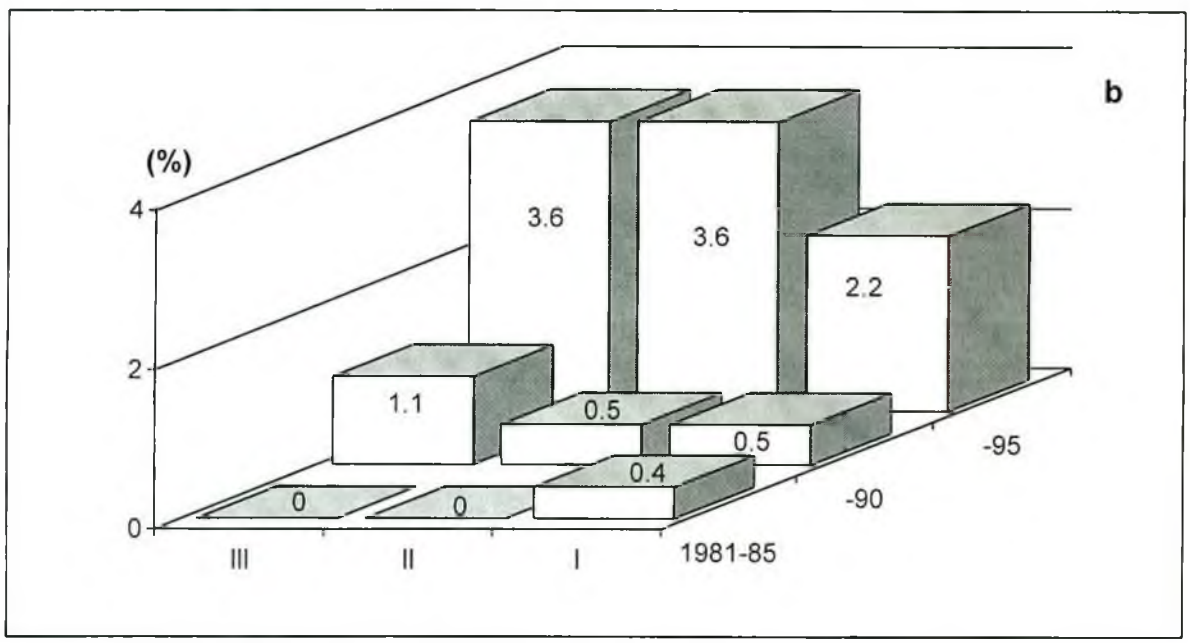
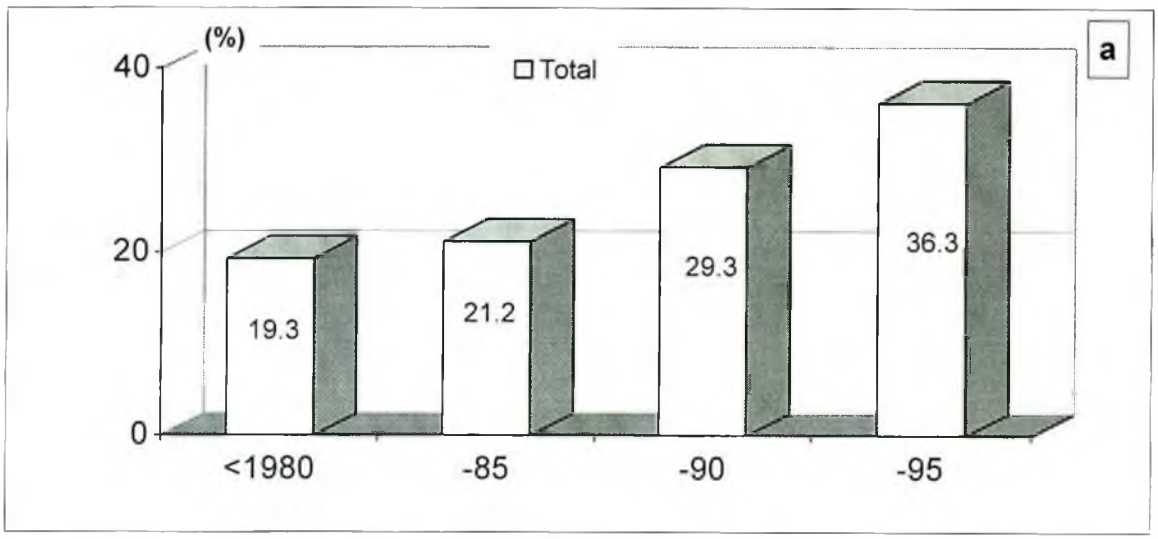


Figure 15a. Prevalence of (cerebrovascular) stroke in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 15b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Hypertension prevalence, in the older diabetic patients, showed gradual and consistent increase starting from the registration throughout their entire follow up period [Figure 16a & b]. The increasing trend was not so consistent when they were stratified according to glycemic status. At the start, highest prevalence of hypertension (44.4%) was found in those who were hyperglycemic (2hPG>12.4 mmol/l). But, within 10 years in the same glycemic group, there was a sharp decline and again rise after 15-year follow up. In the lower tertile groups there was no such striking changes.



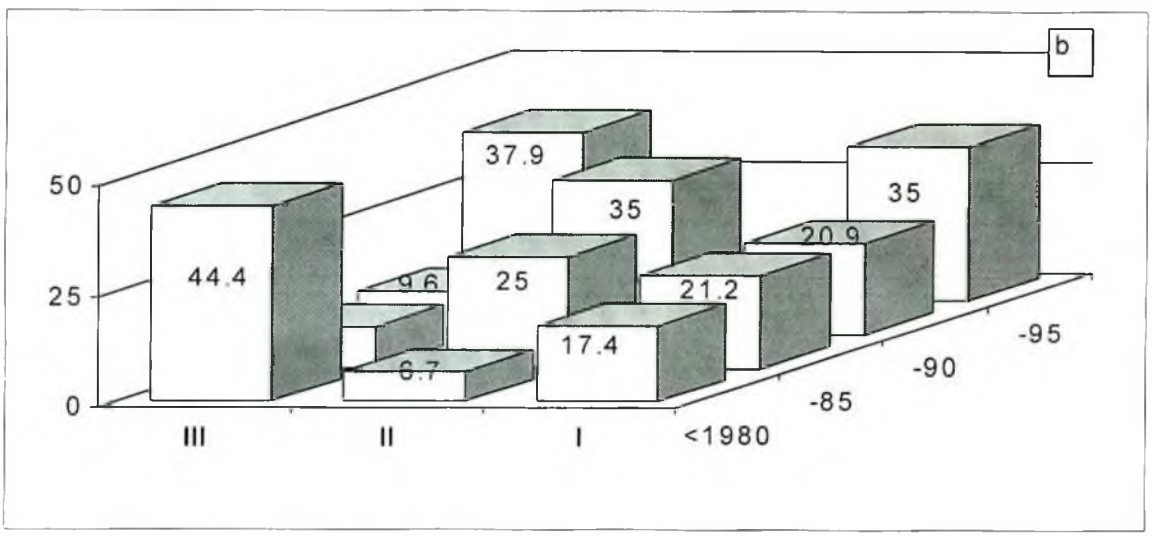


Figure 16a. Prevalence of hypertension (HTN) in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 16b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

For the middle group, hypertension prevalence was very high at registration continued to remain high during their follow up period [Figure 17 a & b]. Strikingly, after 15 year, the prevalence of hypertension was inversely related to plasma glucose level.

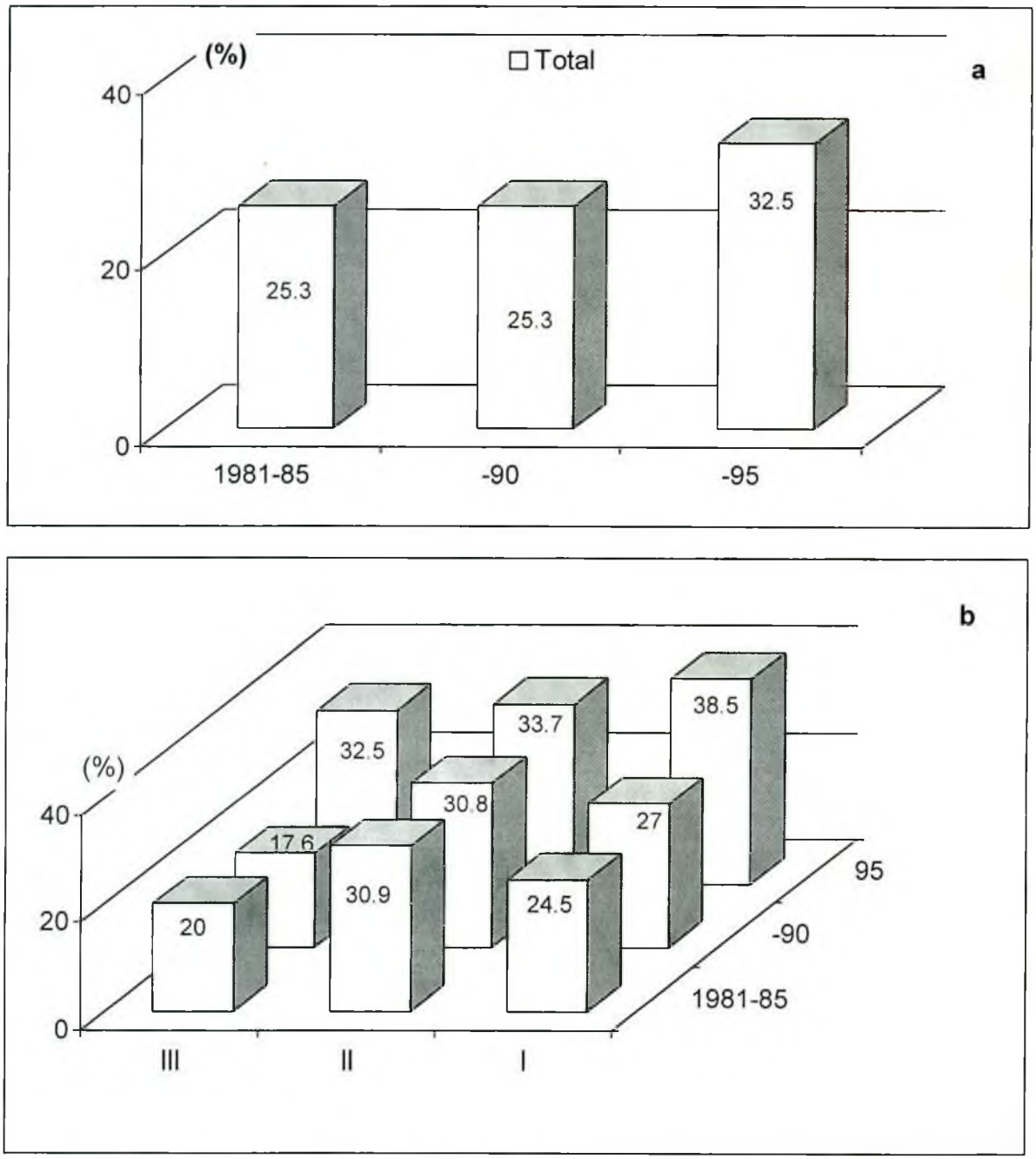


Figure 17a. Prevalence of hypertension in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 17b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Prevalence of diabetic nephropathy, in older patients showed a gradual increase with advancement of duration of illness [Figure 18 a & b]. When they were classified according to 2hPG level it was found that the nephropathy prevalence was very related to glycemia. The higher glycemic tertile groups showed higher prevalence of nephropathy.

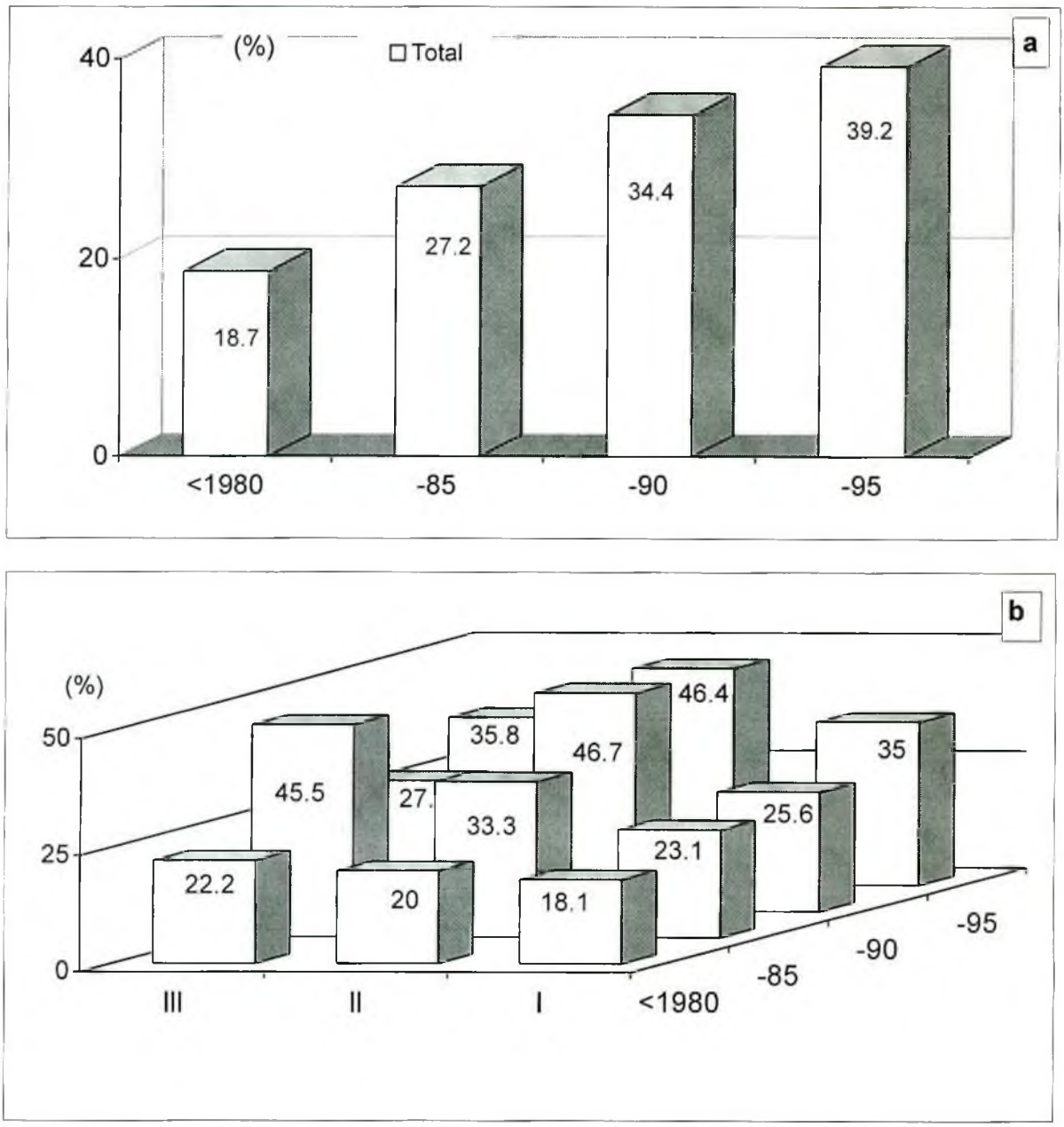


Figure 18a. Prevalence of nephropathy in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 18b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

For the middle group, the observations were not consistent, as glycemic control eventually could not reduce nephropathy [Figure 19 a & b].

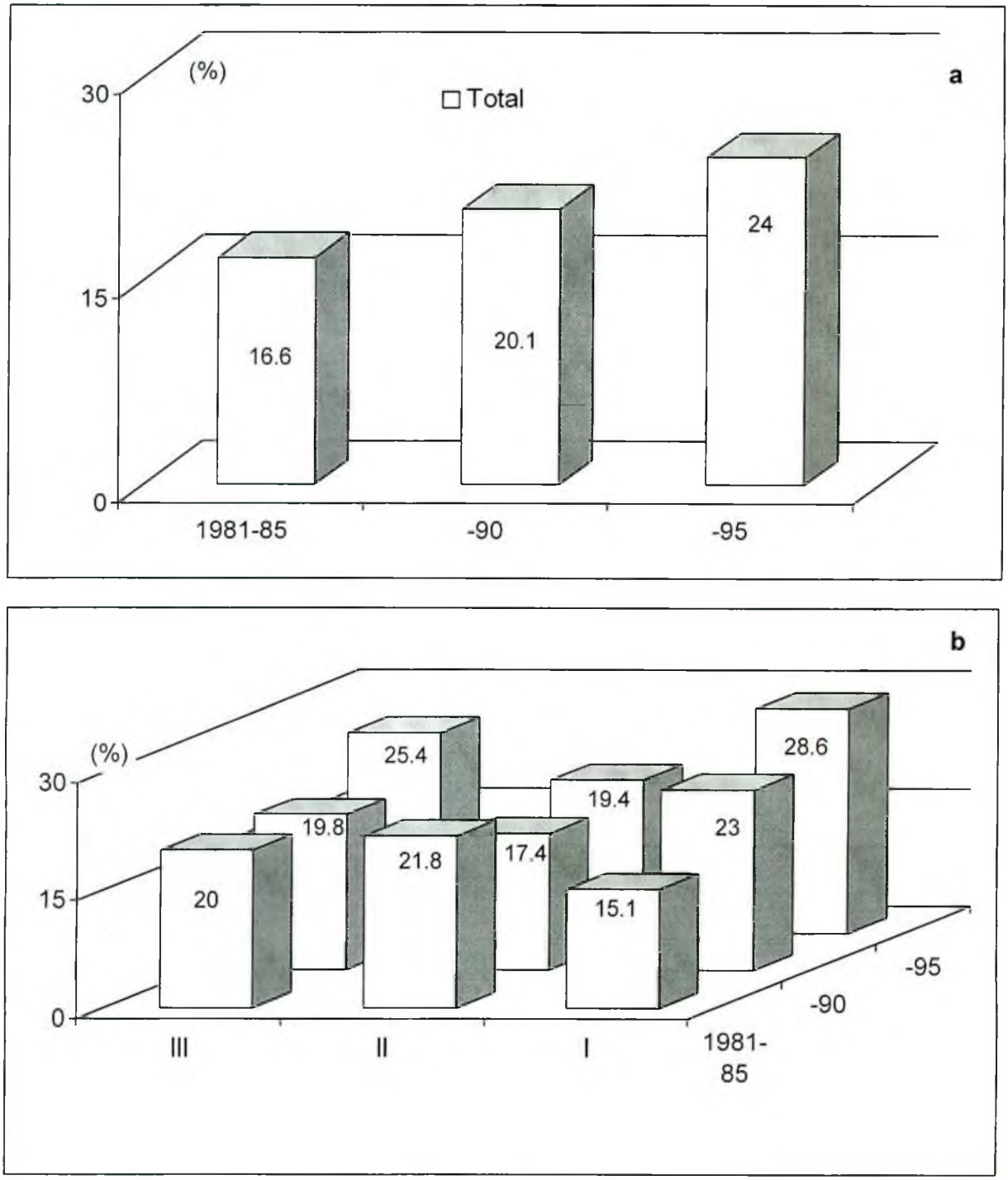


Figure 19a. Prevalence of nephropathy in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 19b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Prevalence of diabetic retinopathy, in the older patients showed a steady increase with advancing duration of diabetes [Figure 20 a & b]. When compared among the low, middle and high tertile, the increase was more marked in the higher tertiles of glycemia and the increase was directly proportional to the plasma glucose level and advancing duration.

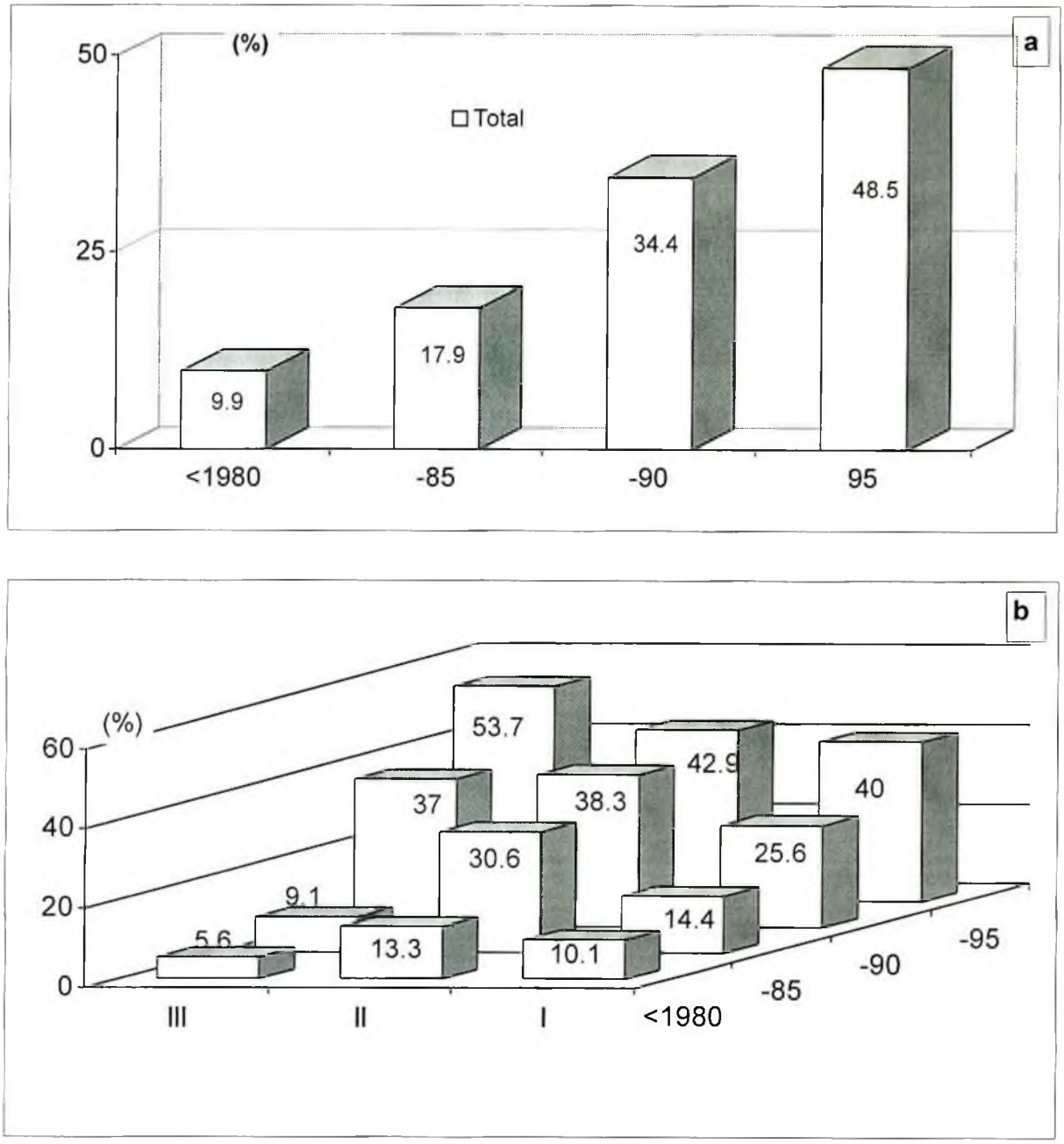


Figure 20a. Prevalence of retinopathy in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 20b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

This observation was also evident in the middle group too [Figure 21 a & b]. Overall finding suggests that glycemic control might have decreased retinopathy in the study group.

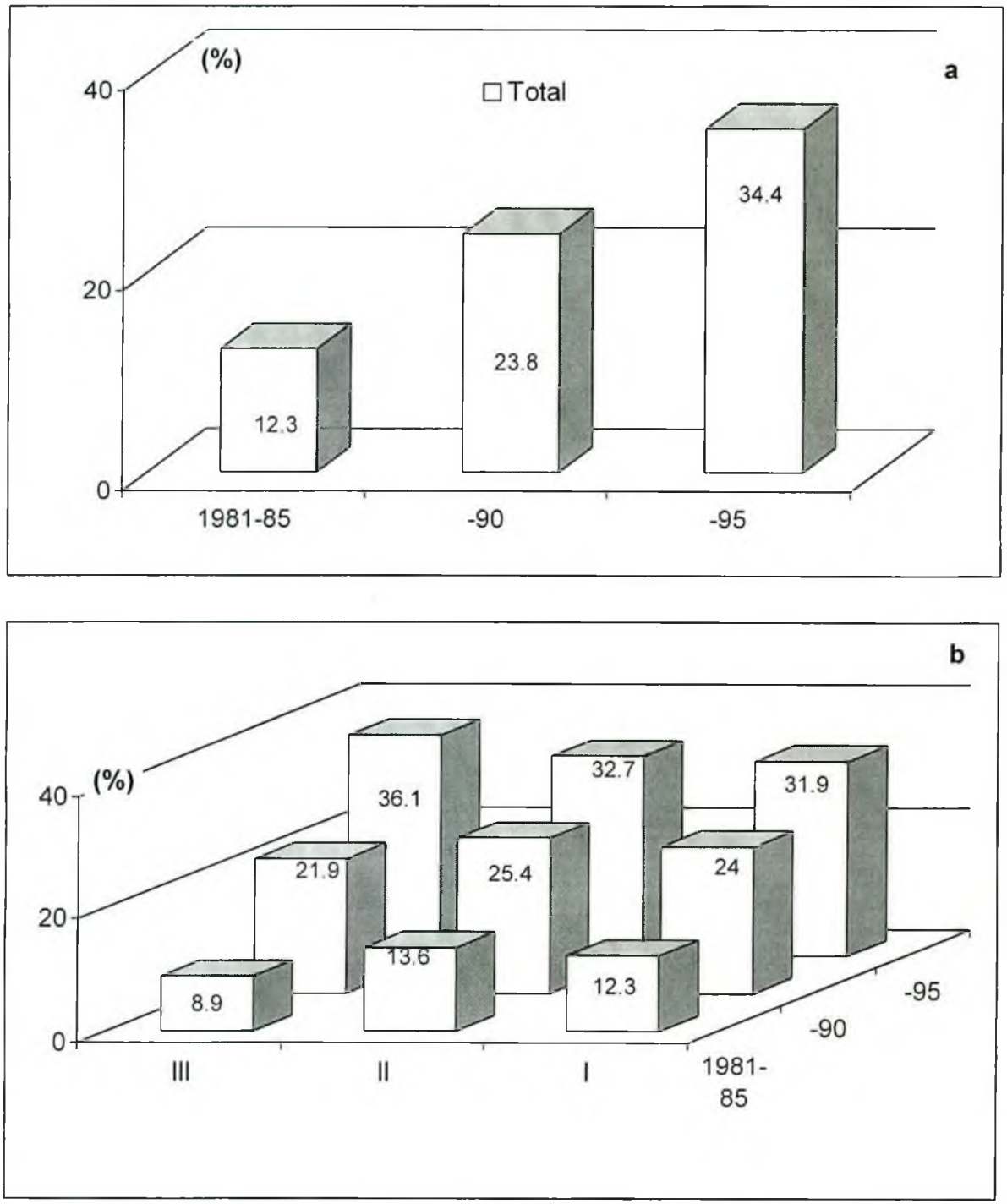


Figure 21a. Prevalence of retinopathy in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 21b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Diabetic skin lesion or dermopathy among the older subjects were recorded only 0.6%, possibly, due to lack of specialized skin-care in BIRDEM outpatient at the time of registration before 1980. In the subsequent follow up period, dermopathy was more frequent with advancing duration and also in the higher hyperglycemic tertiles [Figure 22 a & b].

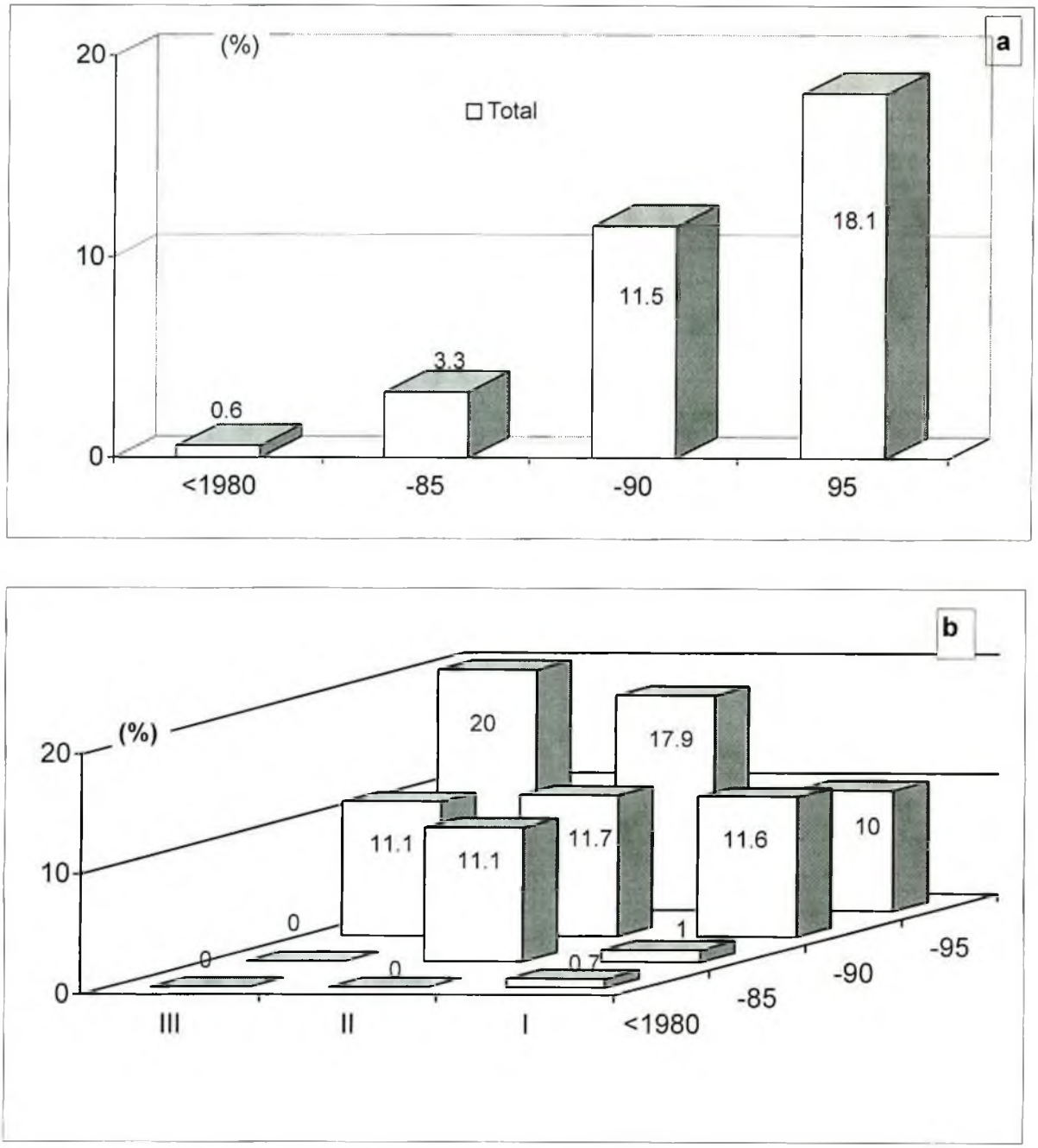
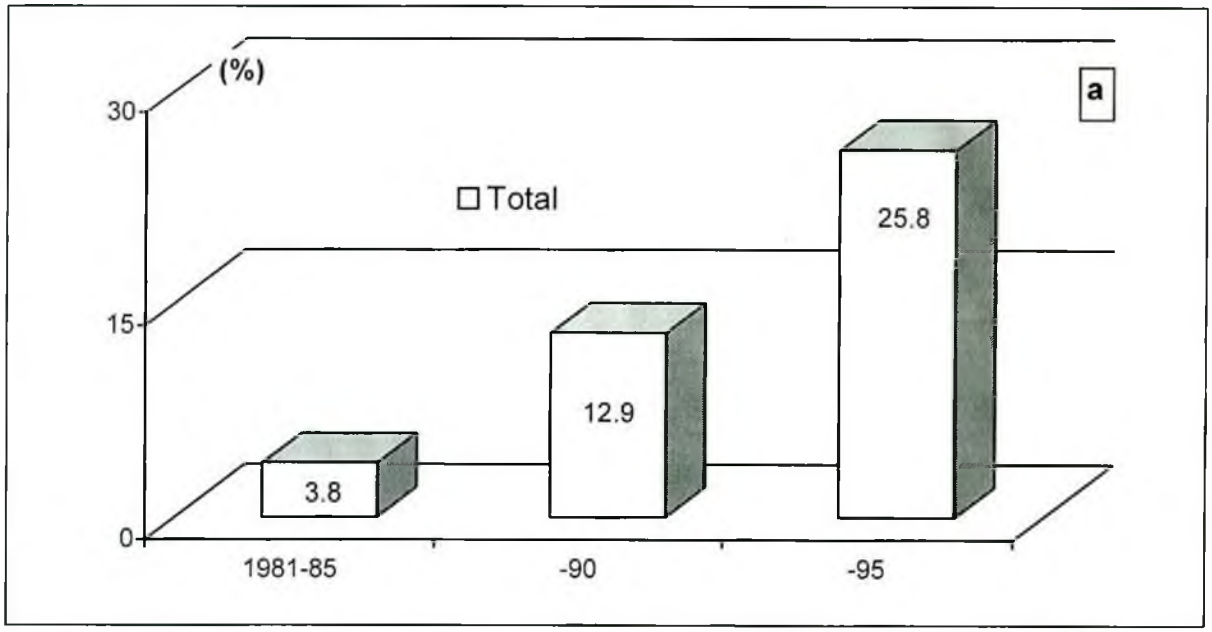


Figure 22a. Prevalence of skin lesion in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 22b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

The frequency of skin lesion was more prevalent in the middle group, right from the time of registration, and increased several folds within 10 years follow up. When classified according to severity of glycemia, higher prevalence was observed among the more hyperglycemic group though there was no significant difference [Figure 23 a & b].



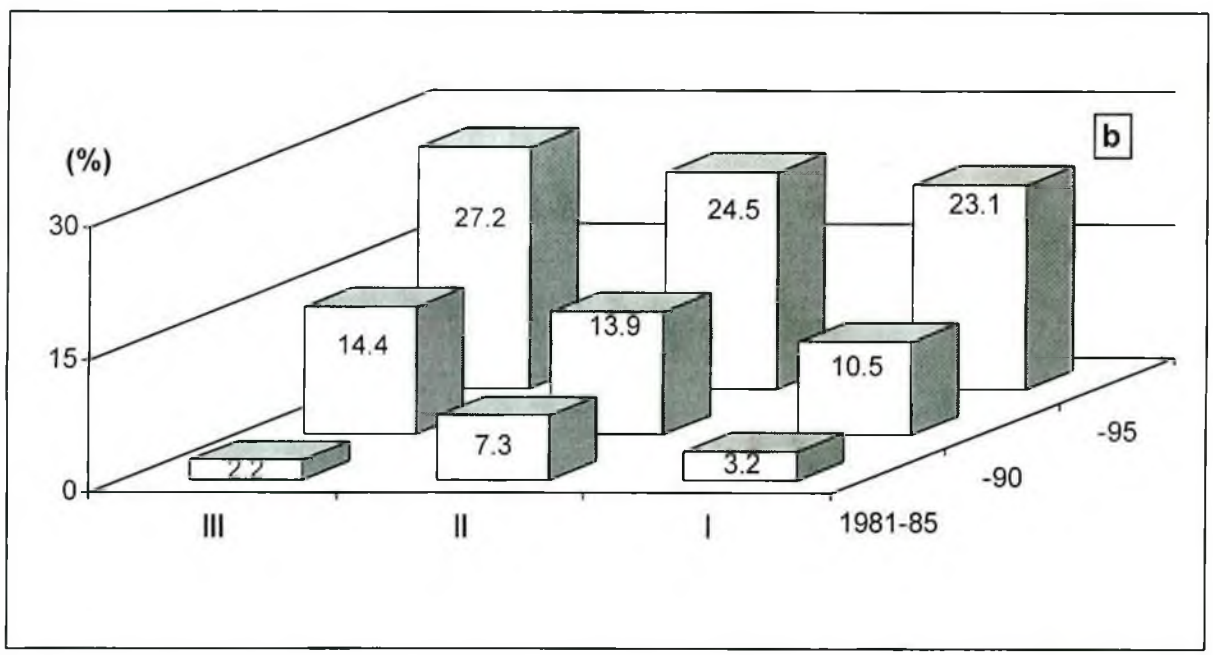
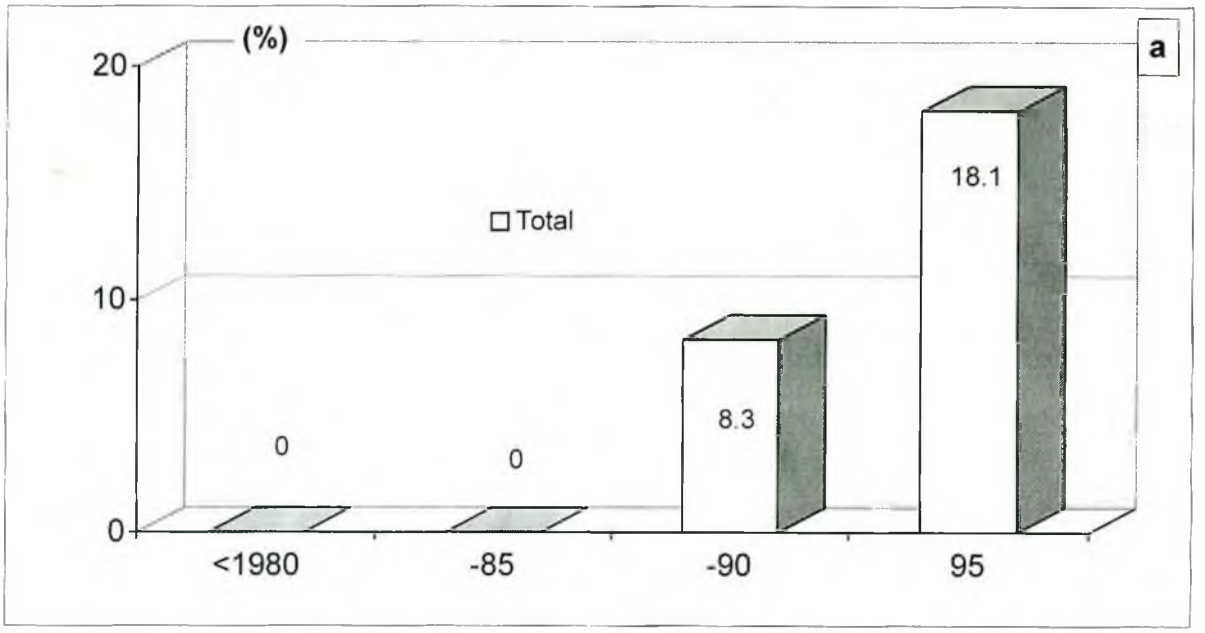


Figure 23a. Prevalence of skin lesion in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 23b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

Orodental diseases in the older subjects could not be traced back at registration and also up to first five year follow up [Figure 24 a]. Only 8.3% orodental complications were recorded in 1990, which increased to more than double in the next five years. Grading of glycemia did not show any association orodental diseases and hyperglycemia [Figure 24 b].



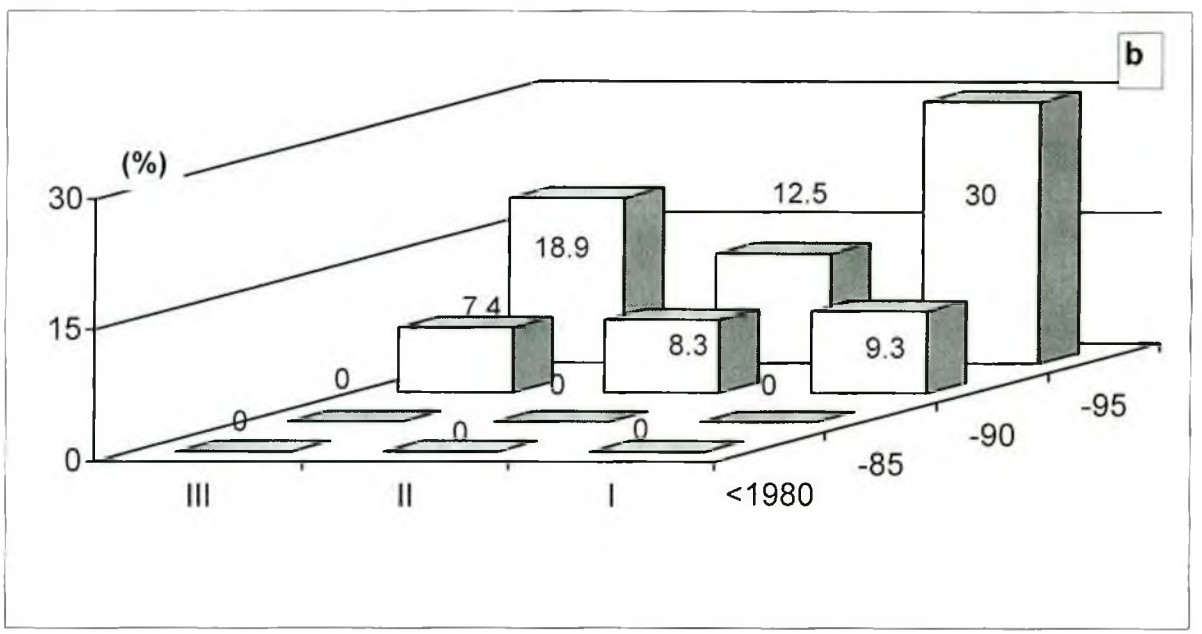


Figure 24a. Prevalence of orodental diseases in the older diabetic subjects (n = 171) at registration up to 1980 and in successive follow-up in 1985, 1990 and 1995.

Figure 24b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

For the middle class, the prevalence increased with duration but not with glycemic level [Figure 25 a & b].

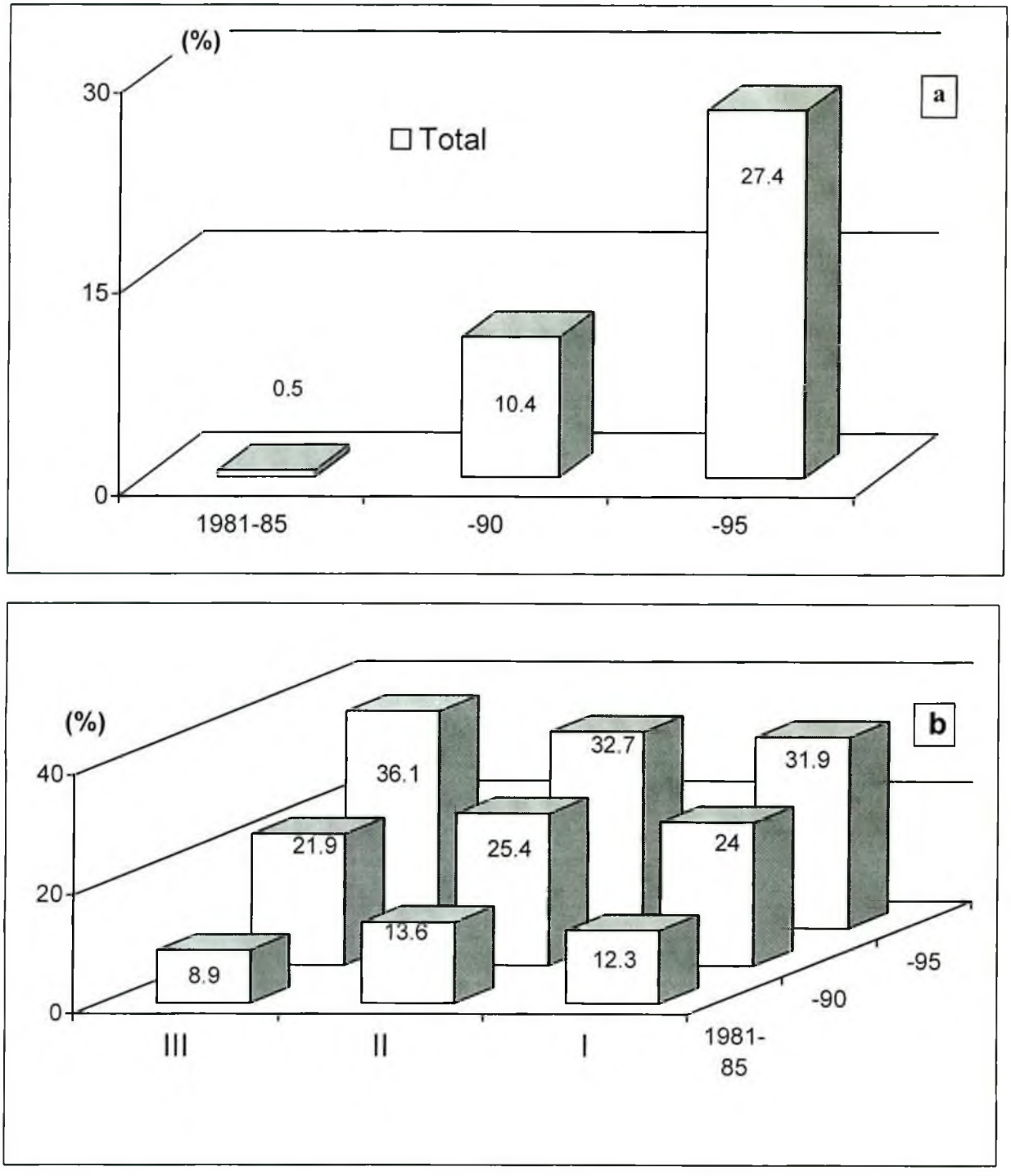


Figure 25a. Prevalence of orodental diseases in diabetic subjects of middle group (n = 625) at registration from 1980 to 1985 and in successive follow-up in 1990 and 1995.

Figure 25b. The same distribution is shown in percentages according to low (I, <10.2), middle (II, 10.3-12.3) and high (III, >12.4) tertile of 2h post-prandial plasma glucose (mmol/L).

3. 2.6 Risk reduction during follow up

The main objectives of the follow up system to reduce obesity, blood pressure (systolic and diastolic) and blood glucose, which in turn help preventing diabetic complications. The mean values of these variables have been shown [Figure 26 - 28]. Regarding obesity, weight could be reduced up to 10 years follow up then it inclined but it was very minimum increase. Both systolic and diastolic blood pressure showed an increment but limited below the accepted target SBP<140 and DBP<90 mmHg. On the contrary, glycemic control below 7.8 mmol/l is one of the main objectives of BIRDEM-OPD follow up that could not be achieved. The mean value of 2hPG at registration was 8.4 and it gradually increased (12.7) and exceeded far above the expected level.

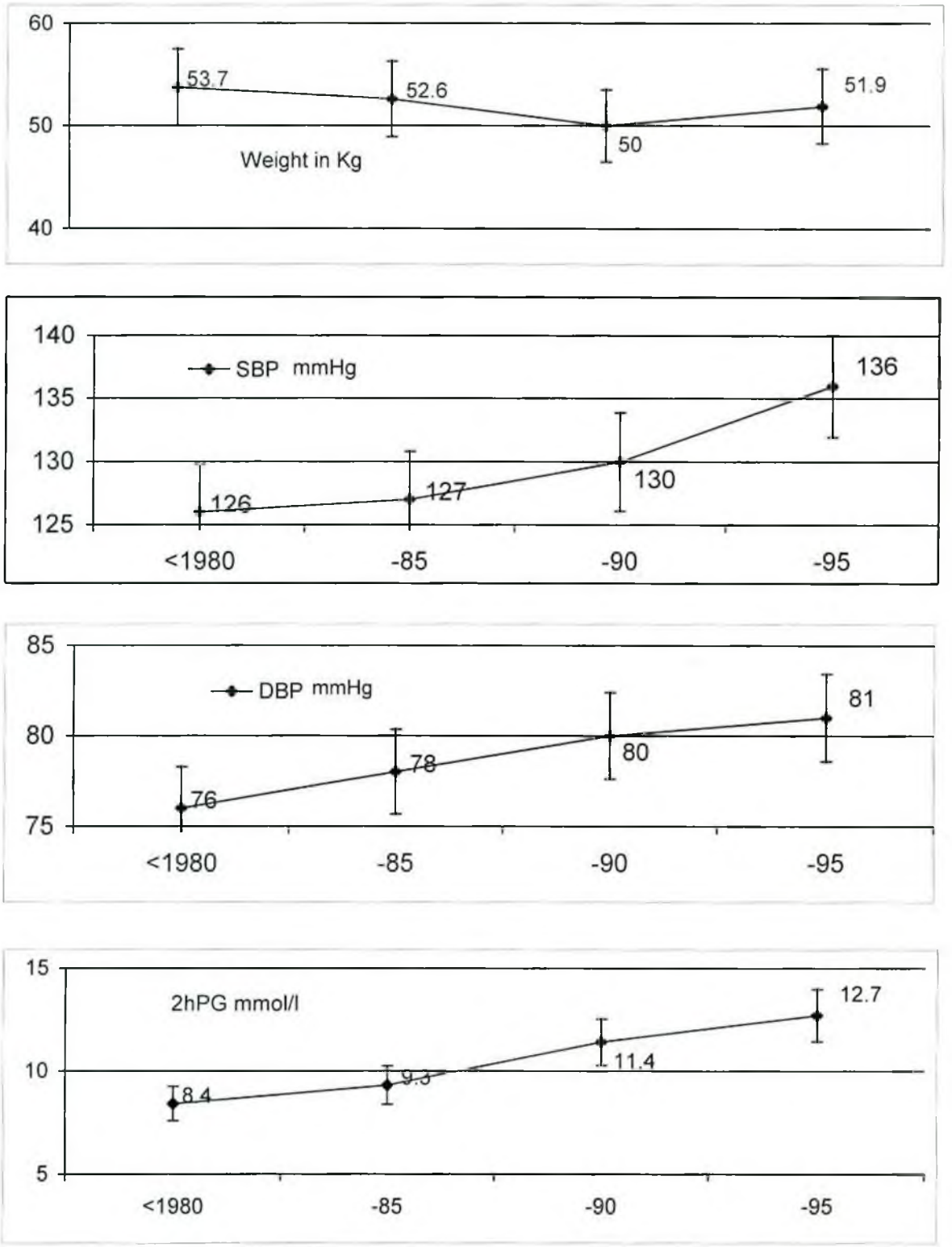
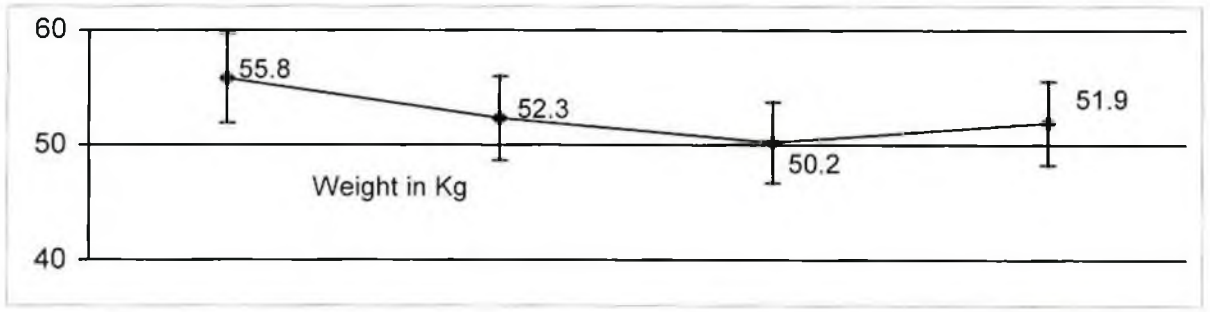
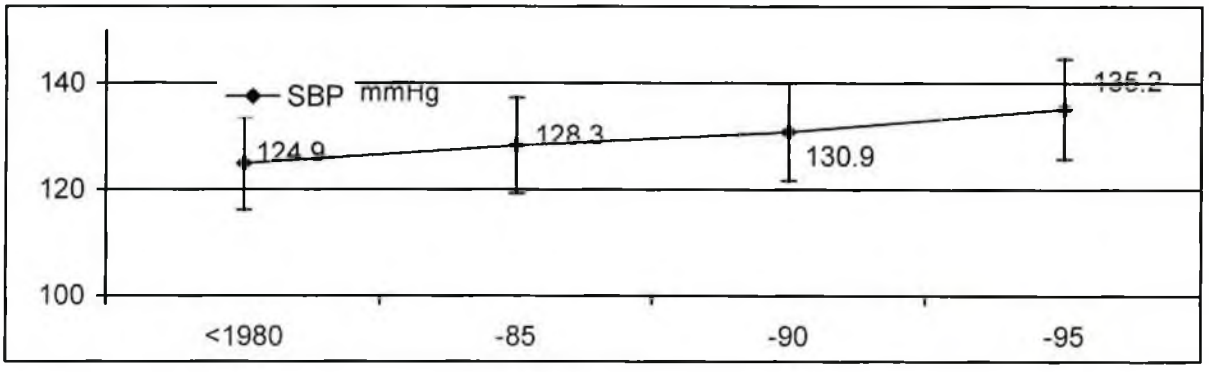
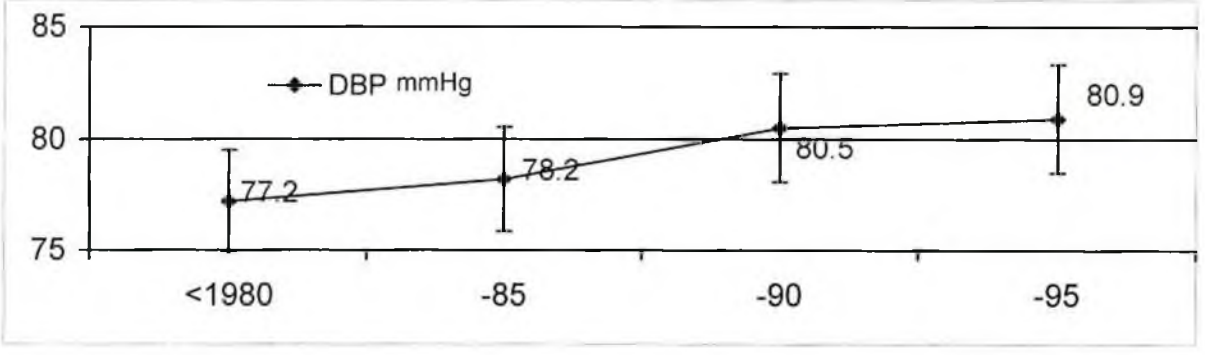


Figure 26. Mean values at registration and in subsequent follow up of all groups (older, middle and recent: n = 906) shown in individual line-graph for weight, systolic BP (SBP), diastolic BP (DBP) and post-load plasma glucose (2hPG).







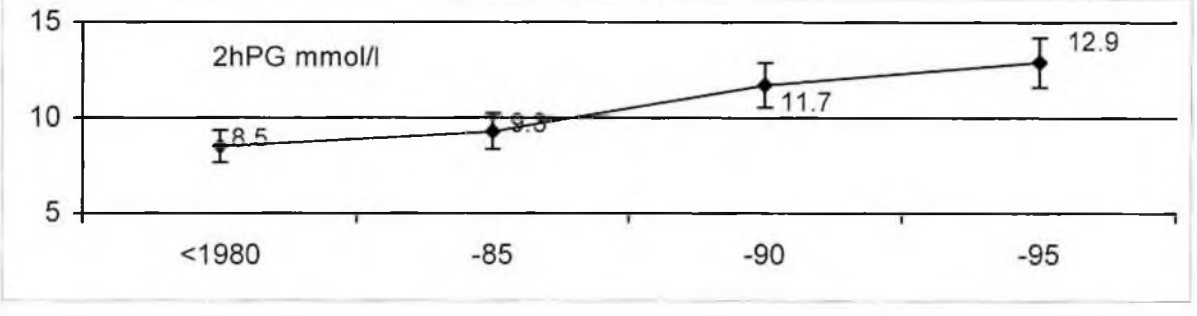


Figure 27. Mean values at registration and in subsequent follow up of the older group (n = 171), shown in individual line-graph for weight, systolic BP (SBP), diastolic BP (DBP) and post-load plasma glucose (2hPG).

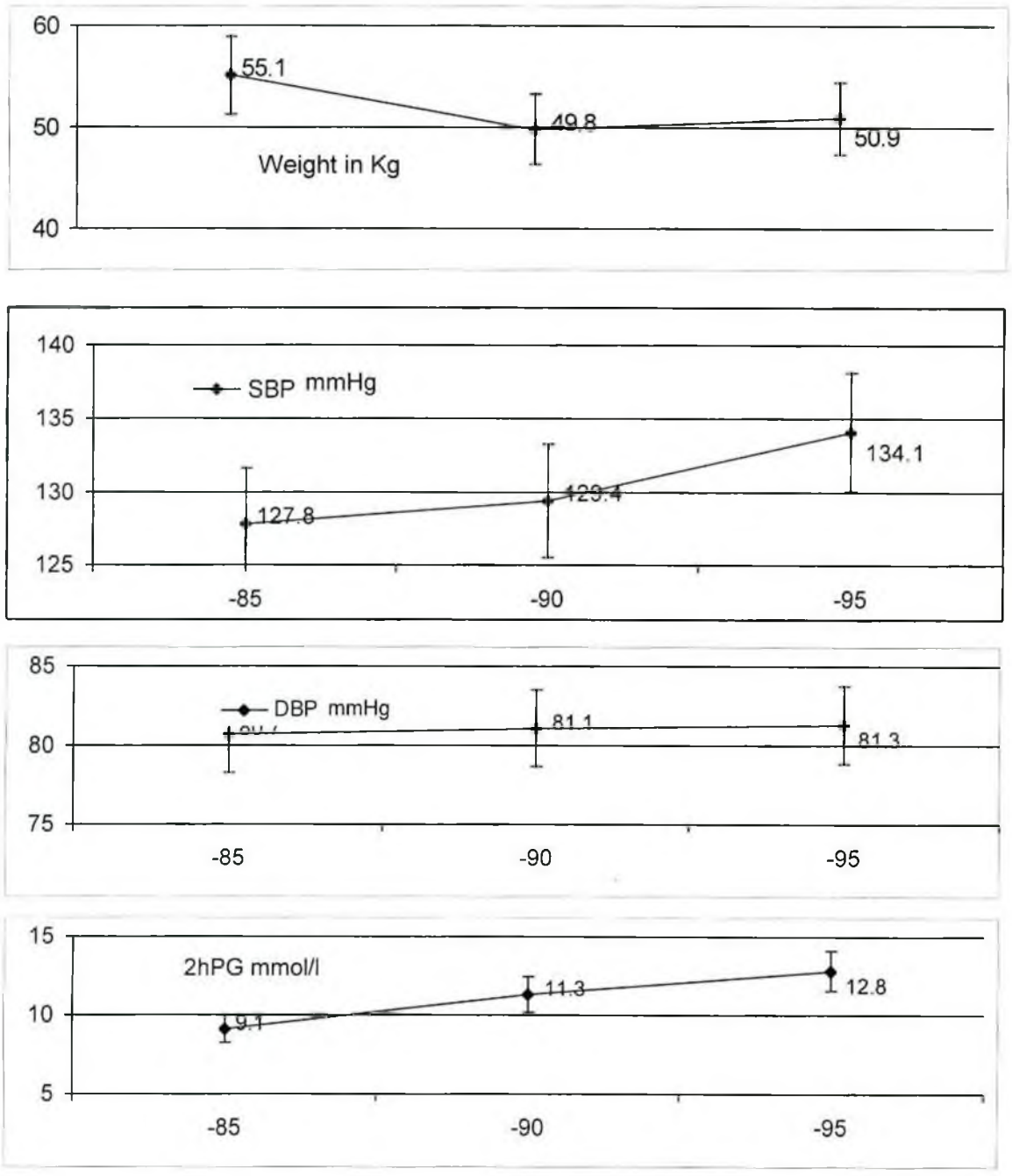


Figure 28. Mean values at registration and in subsequent follow up of middle group (n = 625) shown in individual line-graph for weight, systolic BP (SBP), diastolic BP (DBP) and post-load plasma glucose (2hPG).

3.3 Estimation of predictor (explanatory) for diabetic complications

To explore the effects of explanatory variables (risk factors) on different complication events, the Cox Regression analysis was used. This analysis quantified the individual contribution of combined influence of predictor variables (covariates) in developing complication events. The predictors included biophysical characteristics like age (<40y = 0, ≥40y=1), sex (F = 0, M = 1), body mass index (BMI), blood pressure (BP) and glycemic status (2h post-load plasma glucose = 2hPG). The socio-demographic predictors in the equation were – geographical location (area, rural + suburban = 0 and urban = 1), work (mental =0, physical = 1) and social class (poor =0 and rich =1). Two more variables were taken into consideration – duration of follow up (Duration) and frequency of visits (Visit) during the follow up period.

3.3.1 Predictor variables categorized

Three predictor variables were categorized – two by quartiles (BMI and BP) and one (duration) by tertile. For 'BMI' and 'BP', the first value and for the 'duration' the last value were taken as reference category. The categorization helped in quantifying the reduction of hazard by controlling obesity and blood glucose throughout their entire follow up period. Similarly, the hazard of duration of follow up was estimated by categorizing the 'duration' into recent, middle and older patients. Here, the 'recent' was taken as a reference category to estimate the hazard of 'older' and 'middle' groups.

For easy expression of the hazard of blood pressure, mean arterial blood pressure (MABP) was taken into account to represent both systolic and diastolic blood pressure (MABP = diastolic BP + (systolic BP – diastolic BP). An approximate test of significance for each variable was obtained by dividing the regression estimate by its standard error and comparing the result with the standard Normal distribution.

3.3.2 Complication events influenced by predictor variables

As mentioned, the hazards of predictor variables of complication events were estimated by Cox Regression Analyses. For better estimation of hazards, the variables (or covariates) were quantified in phases or in stepwise fashion. Considering glycemic status (2hPG) in diabetic subjects is the most hazardous predictor, it was estimated as a single predictor and then other covariates were added to the equation for measuring its independent effect and the effect in combination.

3.3.3 The hazard of glycemia and other covariates for diabetic complications

The independent effect of glycemia (2hPG) was shown in model-1, combined with obesity (BMI quartile) in model-2, with obesity and blood pressure (MABP quartile) in model-3 and with socio-demographic plus other predictor variables in model-4. All these models predicting the hazard ratio of glycemia and other variables attributed to the development of complications (outcome or dependent variables) were shown in separate tables. These are - for nephropathy [Table 16], retinopathy [Table 17], coronary heart disease [Table 18], dermopathy or skin lesion [Table 19], hypertension [Table 20], foot-ulcer or peripheral vascular disease [Table 21], cerbrovascular accidents (stroke) [Table 22] and orodental diseases [Table 23]. All these tables showed the hazard of covariates in different models for specific complication.

Nephropathy

The hazards of 2hPG, BMI, MABP and other covariates were shown for developing nephropathy in model 1 through 4 [Table 16]. When glycemic status (mean 2hPG, mmol/l: $<10 = 0$, $\geq 10 = 1$) was estimated as an independent factor, the hazard with 2hPG ≥ 10 mmol/l was 140% higher than those with 2hPG ≥ 10 mmol/l (model –1). This effect of glycemia remained significant when BMI and MABP were included in the model (model-2 &3). However, the hazard with glycemia was no more significant when age, sex, social class,

duration and follow up visits were entered in the equation (model 4). In contrast, the hazards with female gender, urban area, older and middle group and decreased visit-frequency were proved significant for developing nephropathy.

Table 16. Predictors of diabetic nephropathy quantified by different models using Cox Regression analysis

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.40*	1.13 – 1.74	1.38*	1.11 – 1.72	1.38*	1.10 – 1.73	1.10	0.86 – 1.39
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			1.10	0.64 – 1.90	1.10	0.63– 1.87	1.17	0.67– 2.03
III - 25.7			1.36	0.80 – 2.33	1.29	0.75 – 2.21	1.33	0.77 – 2.31
IV ≥ 25.7			1.58	0.95 – 2.65	1.43	0.84 – 2.43	1.25	0.72 – 2.18
MABP								
I <93					1	-	1	-
II – 97					0.97	0.56 – 1.69	0.97	0.55 – 1.71
III – 102					1.18	0.69 – 2.03	1.31	0.75 – 2.26
IV ≥ 102					1.57	0.92 – 2.67	1.61	0.94 – 2.76
Age: <40 = 0, ≥40 = 1							1.20	0.81 – 1.78
Sex: women = 0,men = 1							0.39*	0.26 – 0.59
Area: rural + suburban = 0, urban = 1							2.45*	1.11 – 5.41
Social class: poor = 0, rich = 1							0.57	0.30 – 1.10
Duration								
Recent							1.00	-
Old							29.04*	3.95 – 213
Middle							14.24*	1.96 – 103
Follow up visit							0.95*	0.94 – 0.96

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other variables were included.

Retinopathy

The estimation of hazards of plasma glucose (2hPG) and other predictor variables were shown for retinopathy in model 1 through 4 [Table 17]. When glycemic status (mean 2hPG, mmol/l: <10 = 0, ≥10 = 1) was estimated as an independent factor, the hazard with 2hPG ≥10 mmol/l was 124% higher than those with 2hPG ≥10 mmol/l (model –1). This effect of plasma glucose remained significant even when BMI (obesity) and MABP were included in the model (model-2 &3). However, the estimated risk of plasma glucose was no longer significant when other covariates (age, sex, area, social class, and duration and visit frequency) were entered in the equation (model 4). The hazards with older and middle groups and decreased visit-frequency were proved significant for developing retinopathy. The urban area and female sex as found significant for nephropathy were proved to have no significant effect for retinopathy.

Table 17. Predictors of diabetic retinopathy quantified by different models using Cox Regression analysis

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.24	1.07 – 1.43	1.22	1.05 – 1.42	1.22	1.05 – 1.42	1.13	0.93 – 1.37
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			0.98	0.68 – 1.44	0.98	0.67– 1.43	1.05	0.72– 1.54
III - 25.7			1.17	0.80 – 1.71	1.15	0.78 – 1.69	1.27	0.86 – 1.88
IV ≥ 25.7			0.96	0.66 – 1.40	0.93	0.63 – 1.38	0.97	0.764– 1.46
MABP								
I <93					1.00	-	1.00	-
II – 97					1.03	0.71 – 1.51	0.92	0.63 – 1.35
III – 102					1.02	0.70 – 1.49	0.92	0.63 – 1.35
IV ≥ 102					1.11	0.75 – 1.65	0.99	0.66 – 1.47
Age: <40 = 0, ≥40 = 1							0.93	0.70 – 1.23
Sex: women = 0, men = 1							0.62	0.46 – 0.83
Area: rural + suburban = 0, urban = 1							1.41	0.87 – 2.28
Social class: poor = 0, rich = 1							0.93	0.56 – 1.54
Duration								
Recent							1.00	-
Old							2.28	0.88 – 5.88
Middle							2.19	0.88 – 5.47
Follow up visit							0.97	0.96 – 0.97

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Coronary heart disease (CHD)

The hazard ratio of post-load plasma glucose (2hPG) was estimated as an independent predictor variable (model 1) and in combination with other covariates (model 2-4) for CHD [Table 18]. The effect of glycemia in developing CHD was not at all significant, neither independently nor in any combination. However, obesity (BMI) of higher quartiles was found to have significant hazards for CHD even after inclusion of other covariates (model 2- 4). Among the other significant covariates showed increased hazards were mean arterial blood pressure (MABP, 192%), age (>40y, 257%) and sex (F, 61%). For CHD, duration of diabetes did not differ between older and recent patients. However, the frequency of visit still remained significant protective effect against developing CHD [Table 18: model-4].

Table 18. Predictors of coronary heart disease quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.01	0.71 – 1.45	0.95	0.65 – 1.39	0.93	0.62 – 1.41	0.97	0.68 – 1.39
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			1.60	0.86 – 2.99	1.62	0.86 – 3.05	1.56	0.83– 2.96
III - 25.7			2.55	1.40 – 4.62	2.43	1.33 – 4.46	2.34	1.26 – 4.33
IV ≥ 25.7			2.11	1.16 – 3.86	1.86	1.00 – 3.46	1.82	0.96 – 3.44
MABP								
I <93					1.00	-	1.00	-
II – 97					0.70	0.38 – 1.29	0.53	0.29 – 1.00
III – 102					0.75	0.41 – 1.37	0.63	0.34 – 1.16
IV ≥ 102					1.92	1.14 – 3.24	1.36	0.80 – 2.32
Age: <40 = 0, ≥40 = 1							2.57	1.56 – 4.21
Sex: women = 0, men = 1							0.61	0.40 – 0.93
Area: rural + suburban = 0, urban = 1							1.58	0.75 – 3.29
Social class: poor = 0, rich = 1							1.19	0.52 – 2.77
Duration								
Recent							1.00	-
Old							0.88	0.23 – 3.36
Middle							1.36	0.40 – 4.62
Follow up visit							0.98	0.97 – 0.99

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Skin lesion

The relative risk (hazards) of plasma glucose (2hPG) and other predictor variables were shown for diabetic dermopathy in model 1 through 4 [Table 19]. When glycemic status (mean 2hPG, mmol/l: <10 = 0, ≥10 = 1) was estimated as an independent factor, the hazard with 2hPG ≥10 mmol/l was 139% higher than those with 2hPG ≥10 mmol/l (model –1). This hazard with higher plasma glucose remained significant after inclusion of BMI (obesity) and MABP in the model (model-2 &3). The estimated hazard of plasma glucose was not significant when other covariates (age, sex, area, social class, and duration and visit frequency) were entered in the equation (model 4). The hazard with female gender was higher and remained significant despite inclusion of all other covariates. The increased frequency of visit was found to reduce the hazard in developing dermopathy.

Table 19. Predictors of diabetic dermopathy (skin lesion) quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.39	1.16 – 1.67	1.40	1.16 – 1.69	1.39	1.15 – 1.68	1.16	0.96 – 1.41
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			0.98	0.66 – 1.45	0.98	0.66 – 1.45	0.83	0.56 – 1.23
III - 25.7			0.92	0.62 – 1.38	0.92	0.61 – 1.38	0.83	0.55 – 1.25
IV ≥ 25.7			1.22	0.84 – 1.77	1.21	0.82 – 1.77	0.93	0.63 – 1.40
MABP								
I <93					1.00	-	1.00	-
II – 97					1.02	0.68 – 1.52	0.99	0.66 – 1.48
III – 102					1.13	0.76 – 1.67	1.06	0.71 – 1.58
IV ≥ 102					1.05	0.69 – 1.58	0.95	0.63 – 1.45
Age: <40 = 0, ≥40 = 1							1.18	0.88 – 1.59
Sex: women = 0, men = 1							0.32	0.23 – 0.43
Area: rural + suburban = 0, urban = 1							1.64	0.97 – 2.79
Social class: poor = 0, rich = 1							0.99	0.56 – 1.73
Duration								
Recent							1.00	-
Old							0.34	0.18 – 0.65
Middle							0.65	0.40 – 1.05
Follow up visit							0.96	0.95 – 0.97

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Hypertension

The hazard ratio of post-load plasma glucose (2hPG) was estimated as an independent predictor variable (model 1) and in combination with other covariates (model 2-4) for hypertension [Table 20]. The hazard with 2hPG >10 mmol/l for hypertension was significantly higher than those with 2hPG >10 mmol/l. This hazard was not reduced after inclusion of obesity (BMI). Rather, the highest quartile of BMI showed relative risk (174%) for hypertension. Among the other covariates that had significant hazards were age over 40 years (199%), sex (female, 41%), area (urban, 142%) and frequency visit (5% reduction of every visit) [Table 20, model 4].

Table 20. Predictors of hypertension quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.26	1.06 – 1.50	1.27	1.05 – 1.54			1.11	0.85 – 1.44
BMI I <21.7			1	-	MABP was not included in the equation		1.00	-
II - 23.6			0.90	0.58 – 1.40			1.04	0.67 – 1.63
III - 25.7			1.46	0.96 – 2.20			1.42	0.92 – 2.16
IV ≥ 25.7			1.74	1.17 – 2.57			1.20	0.79 – 1.83
MABP I <93								
II – 97								
III – 102								
IV ≥ 102								
Age: <40 = 0, ≥40 = 1							1.99	1.28 – 2.48
Sex: women = 0, men = 1							0.41	0.35 – 0.66
Area: rural + suburban = 0, urban = 1							1.42	1.08 – 3.21
Social class: poor = 0, rich = 1							1.23	0.47 – 1.98
Duration Recent							1.00	-
Old							1.45	0.77 – 2.72
Middle							1.01	0.57 – 1.81
Follow up visit							0.94	0.93 – 0.95

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Diabetic foot ulcer

The estimation of hazards of plasma glucose (2hPG) and other predictor variables were shown for diabetic foot ulcer in model 1 through 4 [Table 21]. The effect of 2hPG was not found significant when quantified independently or even with obesity of all grades [Table 21, model 1 &2]. Glycemic effect was significant when entered with MABP, though the latter did not show any hazard. This hazard ratio was removed when other covariates were included in the Cox Regression model (model 4). Duration of older patients had significant risk for developing diabetic foot ulcer. Very consistently, as for the other complication events, the increased follow-up visits reduced the hazards for foot ulcer.

Table 21. Predictors of diabetic foot ulcer quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.26	0.85 – 1.88	1.31	0.88 – 1.95	1.39	1.15 – 1.68	1.16	0.96 – 1.41
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			0.72	0.25 – 2.09	0.98	0.66 – 1.45	0.83	0.56 – 1.23
III - 25.7			0.50	0.15 – 1.70	0.92	0.61 – 1.38	0.83	0.55 – 1.25
IV ≥ 25.7			0.89	0.32 – 2.46	1.21	0.82 – 1.77	0.93	0.63 – 1.40
MABP								
I <93					1	-	1.00	-
II – 97					1.02	0.68 – 1.52	0.99	0.66 – 1.48
III – 102					1.13	0.76 – 1.67	1.06	0.71 – 1.58
IV ≥ 102					1.05	0.69 – 1.58	0.95	0.63 – 1.45
Age: <40 = 0, ≥40 = 1							1.18	0.88 – 1.59
Sex: women = 0, men = 1							0.32	0.23 – 0.43
Area: rural + suburban = 0, urban = 1							1.64	0.97 – 2.79
Social class: poor = 0, rich = 1							0.99	0.56 – 1.73
Duration								
Recent							1.00	-
Middle							0.34	0.18 – 0..65
Old							0.65	0.40 – 1.05
Follow up visit							0.96	0.95 – 0.97

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Cerebro-vascular accidents (CVA or stroke)

All predictor variables were investigated in different models of Cox Regression analyses to determine the hazard for stroke [Table 22, model 1- 4]. Plasma glucose, obesity, blood pressure and other socio-demographic factors were found to have no effect on stroke. Only increased frequency of follow up visits could effectively reduce the hazard of this complication.

Table 22. Predictors of cerebrovascular accidents (stroke) quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1	1.13	0.62 – 2.07	1.17	0.64 – 2.13	1.14	0.60 – 2.15	1.01	0.53 – 1.95
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			0.88	0.34 – 2.29	0.88	0.34 – 2.31	0.74	0.28 – 1.95
III - 25.7			0.60	0.20 – 1.80	0.59	0.19 – 1.79	0.55	0.18 – 1.69
IV ≥ 25.7			0.89	0.34 – 2.32	0.86	0.32 – 2.29	0.70	0.25 – 1.95
MABP								
I <93					1.00	-	1.00	-
II – 97					0.78	0.26 – 2.35	0.83	0.27 – 2.55
III – 102					1.25	0.46 – 3.43	1.27	0.46 – 3.51
IV ≥ 102					1.23	0.43 – 2.53	1.27	0.43 – 3.74
Age: <40 = 0, ≥40 = 1							0.70	0.88 – 1.49
Sex: women = 0, men = 1							0.53	0.24 – 1.17
Area: rural + suburban = 0, urban = 1							4.29	0.54 – 34.33
Social class: poor = 0, rich = 1							1.83	0.23 – 14.27
Duration								
Recent							1.00	-
Middle							0.15	0.02 – 1.17
Old							0.29	0.05 – 1.73
Follow up visit							0.98	0.96 – 0.99

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

Orodental diseases

The relative risk of post-load plasma glucose (2hPG) was quantified independently (model 1) and in combination with other covariates (model 2-4) for orodental diseases [Table 23]. The hazard of glycemia for orodental diseases was found significant as an independent factor and in combination with other covariates. Though obesity and MABP had significant hazard; but the findings were not consistent with the severity of obesity and hypertension. As observed with other complication events, females showed increased risk as with paucity of visit frequency.

Table 23. Predictors of orodental diseases quantified by different models using Cox Regression analysis.

Variables	Model 1		Model 2		Model 3		Model 4	
	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI	Exp (B)	95% CI
2-hPG								
Mean (mmol/l)	1.23	1.02 – 1.50	1.22	1.00 – 1.48	1.23	1.00 – 1.50	1.16	0.96 – 1.41
<10 = 0, ≥ 10 = 1								
BMI								
I <21.7			1.00	-	1.00	-	1.00	-
II - 23.6			1.43	0.99 – 2.08	1.48	1.02 – 2.15	0.83	0.56 – 1.23
III - 25.7			1.21	0.82 – 1.79	1.24	0.84 – 1.84	0.83	0.55 – 1.25
IV ≥ 25.7			1.15	0.78 – 1.69	1.19	0.80 – 1.78	0.93	0.63 – 1.40
MABP								
I - <93					1.00	-	1.00	-
II – 97					0.66	0.45 – 0.97	0.99	0.66 – 1.48
III – 102					0.90	0.76 – 1.67	1.06	0.71 – 1.58
IV ≥ 102					0.88	0.69 – 1.58	0.95	0.63 – 1.45
Age: <40 = 0, ≥40 = 1							1.18	0.88 – 1.59
Sex: women = 0, men = 1							0.32	0.23 – 0.43
Area: rural + suburban = 0, urban = 1							1.64	0.97 – 2.79
Social class: poor = 0, rich = 1							0.99	0.56 – 1.73
Duration								
Recent							1.00	-
Middle							0.34	0.18 – 0..65
Old							0.65	0.40 – 1.05
Follow up visit							0.96	0.95 – 0.97

Model 1 through 4 quantified the predictor variables. In model 1 only 2hPG was entered and in the next two steps in model 2 and 3, quartiles of BMI and mean arterial blood pressure (MABP) were included. In the last model, all other socio-demographic variables were included.

3.3.4 Summary of predictable variables estimated against each complication

All the covariates investigated for the complication events undertaken in this study were shown in a summary table [Table 24]. This table was prepared on the basis of strictly quantifying the hazard ratio (forward stepwise entry) of the predictor variables. This model enables the equation to include only those covariates with significant hazard ratio and also to remove those without. Among the significant covariates, female gender and decreased frequency of follow-up visit were found most significant and also most consistent. The next important factor proved important was the duration of diabetes or more correctly, the duration of follow up. Mean arterial blood pressure was found important only for CHD and nephropathy. The increasing age over 40 years showed significant risk for CHD and hypertension. Reduced physical work had the hazard for developing retinopathy.

Table 24. Predictor variables proved to have significant effect either positive or negative effect for the contribution to develop complication events in the diabetic patients after Cox Regression analysis.

	CHD	HTN†	DNP§	DRP§	Foot-Ulcer	Stroke	Skin ‡‡ Lesion	Oro-dental‡
Age	2.48 *	1.99 *						
Sex: F = 0, M = 1	0.55 *	0.39 *	0.35 *	0.54 *	0.40 *	0.47 *	0.32 *	0.46 *
BMI								
MABP††	1.05*		1.03*					
2-hPG Mean (mmol/l) <10 = 0, ≥ 10 = 1								
Social class; poor = 0, rich = 1								
Area: rural+suburban=0, urban=1								
Physical work: No = 0, yes = 1				0.69 *				
Follow up period:								
>15y			30.6*		13.2 *		2.86 *	6.64 *
10 – 15y			15.6*		6.6 *		1.96 *	2.55 *
Follow up visits	0.98 *	0.94 *	0.95 *	0.97 *	0.98 *	0.98 *	0.96 *	0.98 *

All the predictor variables (covariates) were included in the Cox Regression analysis using forward stepwise method. The covariates not having any significant effect were excluded from the analysis in the final model. Only the results of final analyses are shown in the table.

§ - DNP, diabetic nephropathy; DRP, diabetic retinopathy.
† - HTN, hypertension: systolic blood pressure ≥ 140 or, diastolic blood pressure ≥90 mmHg
†† - MABP, mean arterial blood pressure
‡ - Orodental dis: periodonditis, gingivitis, glossitis and other orodental infection.
‡‡ - Skin lesion: all types of infected lesion in the skin, shin spots, necrobiosis lipoidica diabetocorium

Chapter 4

DISCUSSION

DISCUSSION

Databases and registers of chronic ailments are indispensable in decision making for quality care of patients. An excellent system and environment has been developed in BIRDEM for follow up of diabetic patients. In each working day, more than twelve hundred diabetic patients visits BIRDEM-OPD for follow up and more than sixty newly referred cases are registered. Regular registry becomes increasingly difficult as there are increasing referral cases.

Once registered, they are entitled to visit BIRDEM-OPD for follow up. The aims of the follow up care to prevent diabetes morbidity and mortality. However, it was not known how much the aims were achieved. Nor even known what and which types of morbidity and mortality among the attending subjects were prevalent.

The objective of this study was to find out the prevalence of complications in a Bangladeshi diabetic population attending BIRDEM and to determine the type of complications among them. In addition, the study-design aimed to evaluate the effectiveness of BIRDEM-outpatient follow-up care in achieving glycemic control of the diabetic patients. So the duration of sample collection was maintained for twelve months with a view to increase the sample size.

As already mentioned, 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 it has been very useful to determine the types of complications among those who were still visiting the center.

The main limitation of the study is that the expected number of patients was not found after 10 years of follow up. Five percent (n=2475) of a total of 49,510 registered were expected after 10 years follow up, but, we got only 1065 patients at end-point.

After stratification of the historical cohort (longitudinal follow up since 1985) there were very few patients for comparative (older vs. younger age group, men vs. women) analysis. We got follow -up data of only 172 patients for a duration of 10 years or more. So, further stratification for comparison was not possible, at least to confirm the statistical significance.

Some valuable data related to renal function tests and HbA1c could not be retrieved from the guidebook. In the past, HbA1c was not the routine test for assessment of long-term glycemic status. Lipid profiles were not included as regular risk assessment. In addition, a substantial number of facts were mis sing because of damaged or lost guidebook inflicted by flood. Thus, any conclusion on these risk factors for developing individual complication could not be confirmatory.

Diabetic patients classified according to duration of follow up

Despite the sample size was small the retrospective cohort for longer duration was reasonable. Follow-up information of 1065 diabetic patients was retrieved throughout the year 1995. Of them, only 906 patients could provide complete follow up data. As already noted, they were stratified into three groups according to the duration of follow up. They were **older** (up to December 1980), **middle** (1 January 1981 to 31 December 1985) and **recent** (1 January 1986 to 31 December 1990) with duration of ≥ 15 years, ≥ 10 years and 5-10 years follow up, respectively. The older (n=171), middle (n=625) and recent (110) groups constituted 0.7, 2.7 and 0.3% of the total registered patients of those specified periods. Thus, the duration strata could assess the proportion of attending patients after 15 and 10 years follow up. The complication events in the recent group could be used as reference. Thus, the

stratification was helpful for comparison of complication events according to duration and frequency of follow up visits.

Three remarkable prospective studies compares two groups based on glycemic control [2,3,8]. All these three compares strictly controlled with traditionally controlled diabetic patients. As this study is not a prospective one it could observe the natural course of the disease for a long period. In this regard, it is invaluable and unique for a Descriptive Epidemiology of diabetes.

Analysis of follow-up-visit events

It was expected that the visit events written in the guidebook would provide all relevant information. But, it was observed that for some patients the information was incomplete though majority was available. Somehow, 46,694 visits were retrieved for analysis. The mean (±SD) of visit frequency was 32.3 ± 24.9; and the quintiles of visit events from low to high were 12, 27 and 47. It was observed that the median of visit frequency was 27. Thus, it indicates that the data for visit-events were substantial for analysis though some biophysical information were missing

Area and sex distribution of study population

The study revealed that almost two-thirds were male both at registration and also throughout the follow up period for older group, whereas, for the middle and recent groups the female patients predominated over male counterpart. It appears that as the time passes the female subjects are detected, referred and registered more, and they also maintain more strictly follow up.

Though not very unusual the predominance of urban subjects, the study observed that the drop off from rural population was more marked. The cause of non-adherence to follow up by the rural people is not known. Possibly, they had to face different types of difficulties like

transport, night-halt and also to get access to the follow up care. Therefore, some special care for rural diabetic patients may be ensured.

It might also be true that the rural people had more complications, as indicated by recent study [98]; and they developed more disabling condition and most of them can not reach BIRDEM-OPD. They might have also lost interest or confidence or both in follow up system rendered by BIRDEM.

Glycemia continued to increase despite follow up irrespective of sex and area

The mean plasma glucose levels, in either sex, increased significantly from the time of registration to last 5-year follow up in men (95% CI 7.9 – 9.2 to 12.4 – 13.5 mmol/l) and in women (95% CI 6.9 – 8.8 to 12.1 – 13.3 mmol/l) [Table-4]. This finding is consistent with other longitudinal studies [2,3,8, 99-101]. In type 2 diabetes, there is always an increasing failure of secretory capacity of B-cell that virtually leads an insulin dependent state and optimum control necessitates insulin injection [99]. This is also considered as B-cell decompensation and is observed irrespective of area and sex. Thus, increasing trend of plasma glucose level with increasing duration of follow up was observed in both urban and rural-plus-suburban patients.

Prevalence of complications

Overall in combined (old + middle + recent) diabetic population, the prevalence of retinopathy was the highest followed by hypertension and nephropathy. In the fifteen-year follow 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 [101-103].

Micro- versus macrovascular complications - older and middle group

This study showed that macrovascular complications (foot ulcer, stroke and coronary heart disease) were lower than microvascular (nephropathy and retinopathy) and also mixed-type

(HTN, skin-lesion and periodondal diseases) complications in both the older and middle groups. In addition, compared with the middle group, nephropathy and retinopathy were significantly higher in the older subjects (for both, $p < 0.001$).

Here two findings are noteworthy. Firstly, the microvascular events were found more prevalent than the macrovascular ones irrespective of registration time. Thus it may appear that these patients had less macrovascular 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 subjects with macrovascular events were either incapable of coming for follow up or simply, they had increased mortality. Macrovascular events always had high mortality [56-67]. So, this finding is not inconsistent to other investigations.

Prevalence of complications increased with duration of follow-up

For older patients, the increasing trend of stroke and coronary heart disease (CHD) was significant ($p<0.01$ and $p<0.001$); whereas, the trend in peripheral vascular disease with foot-ulcer was not significant [Table 6]. It is not clear, however, why there was no increase in foot ulcer incidence with the duration of diabetes. Possibly, increased awareness of foot care among the diabetic patients could prevent foot ulcer. A significant reduction of foot ulcer and lower extremity amputation (LEA) has been reported by many a centers [112,113]. In this regard, like many other standard centers, BIRDEM could successfully prevent the increasing incidence of lower leg amputation as informed by personal communication from the department Surgery, BIRDEM.

This success was not true for microvascular complications like nephropathy and retinopathy. These events showed a significant increasing trend. The mixed-type-complication events like hypertension, dermopathy and orodental diseases were no exception to this finding. More importantly, these were not confined in any group (older or middle). All these findings were

suggestive of newly developing complication events. These complications among the study subjects were either inevitable or the follow up visits were not effective. Here, 'effective' we mean the target aimed by BIRDEM.

To estimate the effective measures with regard to glycemic control it was found that the mean values of plasma glucose found at registration increased significantly at different times of follow up [Table 15]. So, overall control of glycemia was not effective as desired. As other biochemical variables like microalbuminuria and dyslipidemia were not consistently monitored no further comment on effectiveness of follow up could not given. As found in other longitudinal studies [104,106], it was evident that glycemic control becomes increasingly difficult as time passes on.

This study showed that all types of complications equally affect male and female subjects. This finding is consistent to other longitudinal studies that no gender is immune to diabetic complication [2,3,105].

Effect of glycemic status on the prevalence of diabetic complication

It was observed at the time of registration that there was more than half of the population (56%) had blood glucose <8.mmol/l. As the duration of diabetes increased the severity of glycemia also increased. 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 till 1995 [Figure 11]. This indicates that glycemic control was poor among the subjects. The question is, whether the subjects with poor control had more complications than those with better control

This study addressed whether this different grade of glycemia influenced any specific type of complication. The glycemic status was graded into low, middle and high tertile with 2hPG values <10.2, 10.3 – 12.3 and >12.3 mmol/l, respectively. The prevalence of complications

was shown according to the tertile of 2hPG right from the registration up to the last visit recorded in 1995.

For all study population, glycemia of any degree did not increase macrovascular and mixed type complications. As the glycemic control was not achieved for more than 90% patients this study was finding could not be compared to other longitudinal studies [2,3,8,104,105]. However, in those studies also the glycemic control could not significantly reduce the coronary events.

Strikingly, after 15 year, the prevalence of hypertension was inversely related to plasma glucose level. This finding has not been so far reported in other population. In our previous study, we found the same inverse relation between glycemia and blood pressure [114]. Possibly, advanced diabetes with persistent glycemia may contribute to the impaired sympathetic innervation together with diastolic dysfunction preventing hypertension.

Unlike macrovascular events, the microvascular complications were significantly related to hyperglycemia. The diabetic patients with poor control developed retinopathy and nephropathy. This was also observed in other longitudinal studies [104,105]. However, in our patients, none maintain the strictly control level nor even the traditionally controlled value.

Risk reduction during follow up

It has already been mentioned that the main objectives of the follow up system to reduce obesity, to control blood glucose and to control blood pressure (systolic and diastolic). The mean values of these variables have been shown in Figure 26 - 28. Regarding obesity, weight could be reduced from 53.7 kg at registration to 50.9 kg at last follow up ($p<0.001$). This could be the major achievement of BIRDEM follow up. The comparable studies like UKPDS and DCCT reported a higher weight at the end point [3,40,99-101].

Both systolic and diastolic blood pressure showed an increment but eventually controlled (at last follow up mean SBP was 131 and DBP was 81mmHg) well below the accepted target

SBP<140 and DBP<90 mmHg. On the other hand, glycemic control could not be achieved. Our target was to maintain post challenge glucose below 7.8 mmol/l and still is one of the main objectives of BIRDEM-OPD follow up. The mean value of 2hPG at registration was 8.4 and it gradually increased (12.7) and exceeded far above the expected level. Thus this study revealed that the glycemic control could not be achieved. Therefore, the risk reduction with regard to glycemic control among them was not attained.

Predictor (explanatory) variables for microvascular complications

Cox Regression Model helped quantifying the individual contribution of combined influence of predictor variables (covariates) in developing complication events. The predictors included age, sex, BMI, BP, 2hPG, area, physical work, social class, duration and frequency of visit. For easy expression of the hazard function of blood pressure, mean arterial blood pressure (MABP) was taken to avoid separate tests for systolic and diastolic blood pressure. An approximate test of significance for each variable was obtained by dividing the regression estimate by its standard error and comparing the result with the standard Normal distribution.

The hazard function of glycemia and other covariates for microvascular events

For nephropathy and retinopathy, the hazard with glycemia was not significant when age, sex, social class, duration and follow up visits were entered in the Cox Regression Model (model 4). This finding is not consistent with the famous prospective studies like DCCT, UKPDS, Kumamoto, Oslo and others [2,3,8, 104, 105]. All these studies showed a significant reduction of microvascular complications among the strictly controlled than non-strictly controlled group. Then, why these microvascular events in our population could not be related to hyperglycemia. Possibly, the strict glycemic control that could prevent the microvascular events was not achieved in the study population. In fact, post-load plasma glucose was found significantly elevated at different points of follow up. But the question

remains still unclear why the subjects with severe hyperglycemia did not show more complications than those did with less or moderate hyperglycemia [Table 15].

It is a retrospective study. It gives us a natural course of the disease as very few could maintain glycemic control. Different glycemic status of uncontrolled patients showed no variation in complications. This makes us to hypothesize that to prevent complication there might be a cut-point (or threshold) of glycemic control, beyond that point, control of glycemia is no more effective. This cut-point may be considered as 'all or none law'. If one desires to control he or she must have to maintain below the threshold. Otherwise, the outcome of control is ineffective for prevention of complications.

We may recall here that "the Kumamoto study on optimal diabetes control" opined in favor of glycemic threshold to prevent the onset of progression of diabetic microvascular complication [8]. They reported that worsening of complications correlated significantly with glycemic status and no further worsening below the threshold levels of FPG <6.1 and 2hPG <10.0; and for HbA1c <6.5%. However, it was not known whether microvascular complications differed among the uncontrolled glycemia of different level. The Kumamoto study reported the 6-year follow up period; whereas, this study subjects had 10-15 year follow up. Possibly, in the long continued persistent hyperglycemia of any degree could lead to the same sequels.

The effect of visit frequency in outpatient department (OPD)

One striking observation of this study is that increased frequency of visit reduced almost all types of diabetic complication significantly. Neither the visit frequency nor its effects have so far been reported. This variable is a new one and taken for the estimate of behavioral change in modifying lifestyle. Each visit in BIRDEM-OPD enriches one with increasing awareness about good and bad practice in daily life. So, it is likely that the lifestyle modification was largely influenced by the interaction among the health educators, physicians and diabetic

patients. Any single visit to OPD might have given the opportunity to visualize and to experience different types of diabetic complications. Thus, increased frequency of visits helped them to be motivated for disciplined life which in turn might have prevented diabetic complications.

The hazard function of glycemia and other risk factors for macrovascular events

For coronary heart disease (CHD), glycemic status did not show any significant effect, neither independently nor in any combination. Though other prospective studies inclined to prove that strict control group had less CHD compared with less controlled group their findings could not reach significant level [2,3,104]. In this study population, obesity (BMI) of higher quartiles was found to have significant hazards for CHD even after inclusion of other covariates (model 2- 4). Among the other significant covariates showed increased hazards were mean arterial blood pressure (MABP, 192%), age (>40y, 257%) and sex (F, 61%).

As there was no other risk factors like cholesterol, TG, HDL and LDL for investigation we could not find their role in developing CHD in our population. Here again, the frequency of visit still remained significant protective effect against developing CHD [Table 18: model-4]. Possibly, lifestyle change is the key to avoid CHD. The quantification of risk variables for foot ulcer and cerebrovascular accidents almost simulates the findings as stated in the coronary events.

The hazard function of glycemia and other risk factors for mixed lesions

We took hypertension, dermopathy and orodental diseases as combined effect of micro- and macrovascular lesion together with immune incompetence in the later two events. The risk factors or hazard functions were shown in Table 19, 20 and 23. The findings were almost the same as found for other diabetic complications. Hyperglycemia showed no hazard for these events and visit frequency significantly reduced the risks. It may be mentioned that there were very few patients with foot ulcer and dermopathy and orodental diseases to be followed

up for more than 10 years due to lack of specialized services in the past. So, there is some limitation to conclude in these regards.

In summary, all the covariates investigated for the complication events undertaken in this study were shown in a summary table [Table 24]. Among the significant covariates, female gender and decreased frequency of follow-up visit were found most significant and also most consistent. The next important factor proved important was the duration of diabetes or more correctly, the duration of follow up. Mean arterial blood pressure was found important only for CHD and nephropathy. The increasing age over 40 years showed significant risk for CHD and hypertension. Reduced physical work had the hazard for developing retinopathy.

Conclusion

Of the total 1065 diabetic patients, only 906 patients could provide complete follow up data. They were classified into older, middle and recent group with duration of ≥15 years, ≥10 years and 5-10 years follow up, respectively. The older and middle groups constituted 0.7, 2.7% of the total registered patients still attending BIRDEM-OPD after 15 and 10 years, respectively. As this study is not a prospective one, it could observe the natural course of the disease for a long period. In this regard, it is invaluable and unique for a Descriptive Epidemiology of diabetes.

Prevalence of all complications showed increasing trend with duration of diabetes irrespective of vascular pathology (micro- or macro-). The effect glycemic control (comparison of plasma glucose: high, middle and low tertile) was found not significant for macrovascular events e.g. CHD and stroke. In contrast, microvascular complications (nephropathy and retinopathy) were found higher in higher tertiles of plasma glucose compared to the low tertile.

Quantifying all the covariates for hazard ratio (forward stepwise entry) of the predictor variables it was found that among the significant covariates, female gender and decreased

frequency of follow-up visit were found most significant and also most consistent. The next important factor proved important was the duration of diabetes or more correctly, the duration of follow up. Mean arterial blood pressure was found important only for CHD and nephropathy. 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 completely disabled for long-term follow up or in early death.

This study revealed that very few patients were found to maintain blood glucose within desired level. The complication events followed 'all or none law' of blood glucose control. If one is to control blood glucose needs strict and persistent control. Irregular control, possibly, does not help preventing complications. However, the frequency of follow up visit significantly reduced most of the complication events. Only blood glucose control is not the predictor of diabetic complications. Repeated visits to BIRDEM helped the patients modifying lifestyle, like diet, physical exercise, and control of hypertension. Self-learning by interaction with physicians and other patients seems to be extremely important.

Chapter 5

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

Backgrounds

Diabetes mellitus, hypertension and coronary heart disease are emerging as a major health problem in Bangladesh. World Health Organization alarmed that diabetes has posed a serious threat to developing and South East Asian countries in respect to their existing health care service. Diabetes, hyperinsulinemia and coronary risk factors are more prevalent in Bangladeshis compared with other South Asian migrants (Indian, Pakistani) settled in United Kingdom and with the native population. It has also been reported that Bangladeshis among the entire South Asians immigrant had highest mortality and attack rate from diabetes and coronary heart disease. And we all know that most disabling complications of diabetes are modifiable and even preventable.

The most disabling complications of diabetes mellitus mainly refer to micro- and macro-vascular complications. The microvascular lesions encompass retinopathy, nephropathy and neuropathy. The macrovascular complications are related to atherosclerosis and include mainly coronary artery disease, peripheral vascular disease and cerebrovascular disease (stroke). Two most world-famous prospective studies – Diabetes Complication Control Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) concluded that strict monitoring and maintenance of normal blood glucose certainly prevents micro-angiopathy or microvascular complications. For macrovascular complications, glycemic control could not confirm such prevention.

Prevention of diabetic complication through continued lifelong follow-up was endeavored in Bangladesh. BIRDEM is a unique referral center for diabetes health care. This center was established in 1956 for the follow up care of diabetic patients. Since its birth it has been maintaining diabetes health care and preserving the follow up data. Thus, it happens to be a privilege to retrieve and examine the follow up data of registered diabetic patients in this

center. The goal of BIRDEM is to control glycemia, triglyceridemia and hypertension through lifelong follow up.

Objectives

This study addresses to determine the prevalence of micro- and macro-vascular complications among the Bangladeshi diabetic patients attending BIRDEM-outpatient for more than 10 years. More over, it attempts to determine the association(s) between individual type of complication and the known biophysical risk factors like obesity, hypertension, hyperglycemia and dyslipidemia. It also evaluates the effectiveness of BIRDEM-outpatient follow-up care in achieving glycemic control of the diabetic patients.

Methodology

BIRDEM-outpatient department (OPD) was selected for recruitment of the study subjects who were once registered in BIRDEM-OPD. Almost all patients throughout the country after being detected as diabetic, are usually referred to this Institute for – a) confirmation of diagnosis and b) subsequent follow up. More than fifty new patients are registered and more than a thousand patients visit the OPD for follow-up in each working day.

During registration, each patient is given a *'Reference Number'* chronologically. It is used as ID Number for follow up in BIRDEM and remains valid for life. Moreover, each patient is also provided with a '*Guide-Book*'. This book printed with specific ID number that contains basic information and necessary advises related to diabetes management, and blank pages for subsequent follow-up information. For determining the duration of registration or detection of diabetes the date and ID number is used.

To select the diabetic patients with at least duration of ten years it was decided to identify the patients according to the date and ID number, to select the patients registered up to 31 December 1985 and to continue data collection from the '*Guide-book*' throughout the year 1995. So, it was planned to retrieve all those patients who were registered before

31December, 1985 still attending BIRDEM-OPD for follow up in 1995. All of them will be divided into three groups according to the duration of follow up - '*the older*', '*the middle*' and '*the recent*' with ≥ 15 years, ≥ 10 years and 5-10 years follow up, respectively.

Results

Up to December 1980, 26,349 diabetic patients were registered in BIRDEM and they constituted the older group. Of them, after 15 years, 171 (0.7%) were found attending BIRDEM-OPD during the study period of 12 months in 1995. The middle group constituted those who were registered from 1 January 1981 to 31 December 1985. Of them, 625 (2.7%) were available during the same period. They had a follow up period of ≥10 years. The data of older and middle group were analyzed separately. The recent group consisted of only 110 diabetic patients, supposedly, with fewer complications. They were registered from January 1986 through December 1990 and were included in the study as the reference cases for comparative analysis between the groups - older versus recent and middle versus recent. Overall, the follow-up information of 1065 diabetic patients of different groups was retrieved throughout the year 1995. Of them, only 906 patients could provide complete follow up data.

Regarding men to women ratio, among the older patients, about two-thirds were male at registration and that proportion continued throughout 15-y follow-up period. In contrast, for the middle group, the female outnumbered male subjects and it was consistently observed throughout their follow up period. The recent group (1986 – 90) also showed the same distribution as for middle. As regards the rural-urban proportion, more than four-fifths of the study subjects were from the urban; and in the second 5-year follow up, the rural subjects attended only one-tenth of study subjects.

Glycemic status at registration showed an increase at subsequent follow up visits. The mean 2hPG at registration was 8.3 mmol/l that gradually and consistently increased to each successive 5-year follow up and reached to 12.9 mmol/l at third 5-year. There was a

significant difference between the mean 2hPG values of registration and subsequent follow up visits as tested by ANOVA. The mean plasma glucose levels, in either sex, increased significantly from the time of registration to last 5-year follow up in men (95% CI 7.9 – 9.2 to 12.4 – 13.5 mmol/l) and in women (95% CI 6.9 – 8.8 to 12.1 – 13.3 mmol/l). The increasing trend of plasma glucose level with increasing duration of follow up was observed in both urban and rural patients. The trend was more consistent and more significant in urban subjects than their rural counterparts.

Prevalence of macro-vascular complications (foot ulcer, stroke and coronary heart disease) were lower than micro-vascular (nephropathy and retinopathy) and also mixed type (hypertension, skin-lesion and periodondal diseases) complications

The prevalence of both types of vasculopathy (micro- and macro-vascular lesion) and mixed type were compared between older and middle groups. Micro-vascular complications (retinopathy and nephropathy) were the highest among both the older and middle groups. Compared with the middle group, retinopathy was significantly higher in the older subjects (34.4 vs. 48.5 %: χ^2 =11.5, p <0.001). Similarly, nephropathy was also significantly higher in the older patients (24.0 vs. 39.2 %: χ^2 = 15.6, p<0.001).

In contrast, mixed type of diabetic complications were significantly higher in the middle than in the older group. Thus, compared with the older group, the middle group showed higher prevalence of orodental (18.1 vs. 27.4%: χ^2 = 6.0, p<0.02) and skin infections (18.1 vs. 25.8%: χ^2 = 4.3, p<0.05) and the differences were significant.

For macrovascular complications (CHD, stroke and foot-ulcer) in both groups (older vs. middle) were less prevalent and there was no significant difference between them.

All types of complications were found increasing with the duration of follow up. For older patients, the increasing trend of cerebrovascular accident (stroke) and coronary heart disease (CHD) was significant (p<0.01 and p<0.001); whereas, the trend in peripheral vascular

disease with foot-ulcer was not significant. Similarly, micro-vascular complications like nephropathy and retinopathy showed also a significant increasing trend. The mixed-type-complication events like hypertension, skin-lesion and orodental diseases were no exception to this finding. Middle group patients also had the similar increasing trend of complications.

The increasing trend with duration of follow up was persistently observed. It was observed that none of the study patient maintained desired glycemic control (FBG <6.1 and / or 2hBG <7.8 mmol/l) when taken the mean blood glucose of total follow up visits. Thus, all of them had moderate to severe hyperglycemia. The comparison between subjects with and without severe hyperglycemia (2hPG: <10.0 vs. ≥10.0 mmol/l) showed very little difference of complication.

Hypertension prevalence is shown according to registration and subsequent follow -up by sex for older and middle group. For the older patients, though the difference of hypertension prevalence between men and women was negligible at registration, the female diabetic patients had increasingly higher frequency after 5- and 10- year follow up. This gender difference of prevalence reduced to minimal after 15-year. In contrast, in the middle group, the women showed higher prevalence of hypertension than their male counterpart and almost maintained the same difference throughout their follow up period.

The prevalence of coronary heart disease (CHD), in older and middle group, showed no difference between men and women at registration. Both the gender had similar CHD event throughout their follow up period except only after 15 years, a slight increase in men than women, though the difference was not significant.

Compared with the female the male patients had higher prevalence of cerebro-vascular complications and the difference was significant (χ^2: 4.4, $p<0.05$). For middle group, in contrast, the female patients had stroke almost twice the men (4.3 vs. 2.3%), though the difference was not significant.

Comparison of foot ulcer between men and women showed that the prevalence was higher in women; but the difference was not significant. Similarly, for the middle group, the female diabetic patients had more foot ulcer than the men did. But here again, there was no significant difference between men and women.

Diabetic nephropathy, in older diabetic patients, was observed in about 20% of them at registration in either sex. 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, $p<0.05$). There was almost similar observation encountered in the middle group that the female patients developed significantly higher nephropathy than their male counterpart (14.3 vs. 26.5%; χ^2 =14.0, $p<0.001$). Thus, the findings indicates a long standing diabetes leads to development of nephropathy more in female than in male patients.

Prevalence of diabetic retinopathy was about 10% in either sex of older group at registration. The subsequent follow up showed greater increase in women than men, but the difference was not significant. For the middle group, retinopathy prevalence was found affecting men and women equally (35.3 vs. 32.3%).

Prevalence of skin lesion and orodental diseases was almost similar to those described for macrovascular complications.

Considering the different grade of glycemic status maintained by study population it was observed that more than half of the population (56%) had blood glucose <8.mmol/l. at registration. 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 till 1995.

Conclusions

Prevalence of all complications showed increasing trend with duration of diabetes irrespective of vascular pathology (micro- or macro-). The effect glycemic control (comparison of plasma glucose: high, middle and low tertile) was found not significant for macrovascular events e.g. CHD and stroke. In contrast, microvascular complications (nephropathy and retinopathy) were found higher in higher tertiles of plasma glucose compared to the low tertile.

Quantifying all the covariates for hazard ratio (forward stepwise entry) of the predictor variables it was found that among the significant covariates, female gender and decreased frequency of follow-up visit were found most significant and also most consistent. The next important factor proved important was the duration of diabetes or more correctly, the duration of follow up. Mean arterial blood pressure was found important only for CHD and nephropathy. 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 completely disabled for long-term follow up or in early death.

This study revealed that very few patients were found to maintain blood glucose within desired level. The complication events followed 'all or none law' of blood glucose control. If one is to control blood glucose needs strict and persistent control. Irregular control, possibly, does not help preventing complications. However, the frequency of follow up visit significantly reduced most of the complication events. Only blood glucose control is not the predictor of diabetic complications. Repeated visits to BIRDEM helped the patients

modifying lifestyle, like diet, physical exercise, and control of hypertension. Self-learning by interaction with physicians and other patients seems to be extremely important.

Chapter 6

LESSONS FROM THE STUDY

LESSONS FROM THE STUDY

1. Very few patients were found to maintain blood glucose within desired level. So, for the first time, the study revealed that the follow up care was not adequate.
2. This study revealed that the complication events followed 'all or none law' of blood glucose control. If one is to control blood glucose one needs strict control to the targeted value for prevention of complications. Partial control was not found to be effective for achieving desired goal.
3. The frequency of follow up visit significantly reduced most of the complication events. Interestingly, the association between visit frequency and blood glucose level was not significant. Blood glucose control is not the only parameter for prevention of diabetic complications.
4. Repeated visits to BIRDEM helped the patients modifying lifestyle, like diet, physical exercise, and control of hypertension. Self-learning by interaction with health care predictors and other patients seems to be extremely important and would encourage the patient to be exposed to a suitable environment for self-education.
5. More emphasis should be given to improve the follow up care. Health care providers and policy makers should use the study results. All these modifiable behavioral changes, possibly, help preventing complications.

Chapter 7

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