

Epidemiology of Complications of Diabetes

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Epidemiology of Complications

Chapter Outline

- Microvascular Complications
- Macrovascular Complications
- Hypertension and Diabetes
- Mortality Associated with Diabetes

INTRODUCTION

The diabetes pandemic is rapidly spreading, and mostly affects developing countries like India. Recent figures have shown that 62.4 million people currently have diabetes in India,¹ and this number is projected to rise to 101.2 million by 2030.² Although by definition, diabetes is characterized by elevated glucose concentrations; the impact of diabetes on both the health of individuals and on the health care systems is almost entirely due to the long term "complications" of diabetes which affect almost every system in the body, but particularly the eyes, kidneys, heart, feet and nerves. In this chapter, we will consider the prevalence of various diabetes related complications with special reference to India.

Diabetes related vascular complications can be broadly classified as:

- *Microvascular complications:* It affects the retina [diabetic retinopathy (DR)], kidney (diabetic nephropathy) and the peripheral nerves (diabetic neuropathy).
- *Macrovascular complications:* It affects the heart (cardiovascular disease), brain (cerebrovascular disease) and the peripheral arteries (peripheral vascular disease).

MICROVASCULAR COMPLICATIONS

People with diabetes have an increased risk of developing microvascular complications, which, if undetected, can have a devastating impact on quality of life and place a substantial burden on health care costs.³

Diabetic Retinopathy

Diabetic retinopathy is considered the most specific complication of diabetes, and indeed one of the hallmarks of the disorder. DR is leading cause of new onset blindness, among adults in developed countries and rapidly becoming so in developing countries also. DR affects the microvasculature in the retina, or the back portion of the eye. The classification of DR has evolved as our understanding of the disease has improved. DR is classified into two major types or stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The sight-threatening forms are PDR and diabetic macular edema (DME, retinal thickening and/or exudates within 500 μ of the macula).⁴ In the early treatment diabetic retinopathy study (ETDRS) classification of DME was (1) focal/multifocal leakage, well-defined focal or multifocal

areas of leakage from microaneurysms; (2) diffuse leakage, defined as the presence of widespread leakage from the retinal capillary bed or any intraretinal microvascular abnormalities (IRMA); (3) diffuse cystoid leakage, where diffuse leakage and the pooling of dye in the cystic spaces of the macula in the late phase of angiogram is seen; and (4) ischemic maculopathy.⁵ All these previous forms can be associated with areas of macular ischemia, which can be seen as areas of capillary loss or an increase in the foveal avascular zone. The presence of macular ischemia is an important finding in deciding the type of treatment needed, and to help in those patients who suffer a loss of visual acuity of unknown origin. In 2003, Wilkinson et al.⁶ proposed a DR severity scale and a DME severity scale, which can be used clinically to accurately grade DR by ophthalmoscopy after dilatation of pupil. A four-stage disease severity classification for DR includes two stages of early to moderate NPDR, a third stage of severe non-proliferative retinopathy, and a fourth stage of PDR. DME has been classified by Wilkinson et al.⁶ as apparently present or apparently absent. Identification of specific severity levels of DME is done according to its relationship to the center of macula (fovea), and this is critical in deciding on laser therapy in DME, since it may or may not cause visual disability in the early stages of the disease. This classification makes clinical documentation, and also communication among physicians easier.

The prevalence of DR in type 2 diabetic individuals have been studied in many populations and racial groups. Table 12.1 summarizes data from various epidemiological studies conducted from 1980 till date.⁷⁻³⁰ The prevalence of DR was reported to be 50.3% in the Wisconsin epidemiological study of diabetic retinopathy, United States,⁷ 33.6% in the Liverpool diabetic eye study, United Kingdom¹⁵ and 29% in the Blue Mountain Eye study, Australia.¹³ Most of the earlier studies on prevalence of DR from India have come from diabetic centers, and there are few population-based studies. At Dr Mohan's Diabetes Specialities Centre, a tertiary diabetes care centre in South India based on a paper published in 1996 in a study of 6,792 type 2 diabetic patients, the prevalence of DR was reported to be 34.1%, which included 30.8% with NPDR, 3.4% with PDR and 6.4% had DME.³¹ Another study was done in 3,010 patients attending a diabetic clinic at Chennai, which reported prevalence of DR to be 23.7%.³² A more recent and much larger study from the same centre looked at data of patients registered in the Diabetes Electronic Medical Record (DEMR) system

between the years 1991 and 2010. The prevalence of DR among 117,359 type 2 diabetic subjects was noted to be 37.9%.³³

There are very few population based studies on complications of diabetes in India but the available data suggests that the prevalence of DR is lower in Indians.³⁴⁻³⁷ To overcome possible referral bias in data collected at tertiary care centers, the CURES (Chennai Urban Rural Epidemiology Study) eye study was conducted. In phase 1, in the urban component of CURES, 26,001 individuals were screened by a systematic sampling technique from 46 out of 155 corporation wards representative of the city of Chennai. Individuals aged more than or equal to 20 years were screened for diabetes using capillary fasting blood glucose.³⁸ In phase 2, detailed retinal evaluation was performed in 1,364 known diabetic (KD) subjects in addition to 354 newly detected diabetic (NDD) subjects. All the subjects underwent four-field stereo color photography and retinopathy was assessed by ETDRS grading of the color fundus photographs.

The CURES eye study is the first population-based study, which used four-field stereo retinal photographs and ETDRS grading to document DR in the Indian population. The overall prevalence of DR in urban population in this study was 17.6%.³⁷ Among the KD subjects, 20.8% had DR while 5.1% of NDD subjects had DR. Prevalence of DME in the total diabetic population was 5.0% (KD subjects, 6.3%; NDD subject, 1.1%).³⁷ In another population-based study conducted at Hyderabad, the overall prevalence of DR in self-reported diabetic subjects was 22.4%.³⁴ A marginally higher prevalence of DR (26.8%) was reported among self-reported diabetic subjects aged 50 years and older from Palakkad.³⁶ The Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetic study (SN-DREAMS) conducted in Chennai reported a DR prevalence of 18%.³⁹

A cross-sectional study of 26,519 diabetic subjects who participated in DR screening camps conducted in rural areas in three Southern districts of Tamil Nadu, India, reported the prevalence of DR to be 17.6% among self-reported diabetic subjects.⁴⁰ Another community-based study carried out in a rural setting in Goa reported a DR prevalence of 15.4%.⁴¹ A recent population based study conducted in rural areas⁴² called as the Chunampet rural diabetes prevention project (CRDPP) was conceived with the aim of obtaining epidemiological data in rural Tamil Nadu, in addition to implementing comprehensive diabetes screening, prevention and treatment using a combination of telemedicine and personalized care as a

Table 12.1: Prevalence rates of diabetic retinopathy in type 2 diabetes in different populations

Populations studied	Author/Year	Participants with diabetes (n)	Age (years)	Prevalence of retinopathy (%)
Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), Southern Wisconsin, USA	Klein et al. 1984 ⁷	1,313	≥ 40	50.3
San Antonio Heart Study (SAHS), San Antonio, Texas	Haffner et al. 1988 ⁸	351	≥ 40–74	44.3
San Luis Valley Study (SLVDS), San Luis Valley, Colorado	Hamman et al. 1989 ⁹	360	≥ 40–74	35.3
Beaver Dam Eye Study (BDES), Wisconsin, USA	Klein et al. 1992 ¹⁰	410	43–86	35.1
Taiwan, Republic of China	Chen et al. 1992 ¹¹	527	≥ 40	35.0
Wakefield, UK	Nagi et al. 1997 ¹²	991	≥ 15	37.8
Blue Mountains Eye Study (BMES), Blue Mountain, Australia	Mitchell et al. 1998 ¹³	252	≥ 50	29.0
Barbados Eye Study, Barbados, West Indies	Leske et al. 1999 ¹⁴	615	≥ 40	28.8
The Liverpool Diabetic Eye Study, Liverpool, UK	Broadbent et al. 1999 ¹⁵	395	13–92	33.6
Melbourne Visual Impairment Project (VIP), Melbourne, Australia	McKay et al. 2000 ¹⁶	233	≥ 40	27.5
Proyecto Vision Evaluation Research (VER), Nogales and Tucson, Arizona	West et al. 2001 ¹⁷	899	≥ 40	44.3
Australian Diabetes, Obesity and Lifestyle study (AusDiab), Australia	Tapp et al. 2003 ¹⁸	703	≥ 25	13.7
Los Angeles Latino Eye Study (LALES), Los Angeles, USA	Varma et al. 2004 ¹⁹	1217	≥ 40	46.9
Sandy Lake Diabetes Complications Study, Ontario, Canada	Hanley et al. 2005 ²⁰	133	14–79	23.3
Multi-Ethnic Study of Atherosclerosis (MESA), USA	Wong et al. 2006 ²¹	778	45–85	33.2
USA	Candrilli et al. 2007 ²²	850	≥ 40	27.4
Singapore Malay Eye Study (SIMES)	Wong et al. 2008 ²³	757	≥ 40	35.3
Beijing Eye Study, China	Xie et al. 2009 ²⁴	232	≥ 40	37.1
Fiji	Brian et al. 2010 ²⁵	222	≥ 40	27.2
Taiwan	Huang et al. 2010 ²⁶	356	≥ 65	21.6
USA	Zhang et al. 2010 ²⁷	1006	≥ 40	28.5
Handan Eye Study (HES), Yongnian County, China	Wang et al. 2011 ²⁸	387	≥ 30	43.1
Norway	Kilstad et al. 2012 ²⁹	264	≥ 30	24.0
Laxa, Sweden	Olafsdottir et al. 2013 ³⁰	263	> 50	34.6

model for reaching underserved rural areas in India. This project was undertaken in a cluster of 42 villages in and around Chunampet village in Tamil Nadu in Southern India. A telemedicine van was used to screen for diabetes and its complications. This study reported the prevalence of DR among diabetic subjects to be 18.2%. The population based studies show that approximately 1 in every 5 diabetic individuals may have DR, which is much lower than the figures reported from the west. The exact reasons for this are not clear, but point to the role of genetic factors. Table 12.2 presents studies on the prevalence of

DR in urban India based on clinic-based and population-based reports.^{31–37,39–42} All these studies confirm the lower prevalence of DR among Indians.

Earlier studies have reported on prevalence of DR at the time of diagnosis in clinic population. The prevalence of retinopathy at the time of diagnosis of diabetes in Western populations varies from 20% to 35%^{43,44} compared to 6.7–7.3% in Indians.^{45,46} A familial aggregation study⁴⁷ conducted in 438 consecutive newly diagnosed type 2 diabetic patients reported that 7.3% already had DR, detected by four-field retinal color photography at the

Table 12.2: Prevalence of diabetic retinopathy in urban south India (population and clinic based)

Author/year	City	No. of diabetic subjects	Prevalence of diabetic retinopathy		
			Overall (%)	Among KD subjects (%)	Among NDD subjects (%)
<i>Clinic based studies</i>					
Rema et al. 1996 ³¹	Chennai	6,792	34.1	—	—
Ramachandran et al. 1999 ³²	Chennai	3,010	23.7	—	—
Pradeepa et al. 2011 ³³	Nine clinics in South India	2,26,228	37.9	—	—
<i>Population based studies</i>					
Dandona et al. 1999 ³⁴	Hyderabad	124	—	22.4	—
Rema et al. 2000 ³⁵	Chennai	152	19.0	20.8	5.1
Narendran et al. 2002 ³⁶	Palakkad	260	—	26.2	—
Rema et al. 2005 ³⁷	Chennai	1,715	17.6	23.1	10.9
Raman et al. 2009 ³⁸	Chennai	1,414	18.0	20.6	6.0
Rani et al. 2009 ³⁹	Three Southern districts of Tamil Nadu	26,519	17.6	17.8	10.2
Vaz et al. 2011 ⁴¹	Goa (Rural)	130	15.4	—	—
Mohan et al. 2012 ⁴²	Chunampet (Rural)	1,001	18.2	22.2	6.6

(KD: Known diabetic subjects; NDD: New detected diabetic subjects)

time of diagnosis of diabetes. It also documented that familial clustering of DR was three-times higher in siblings of type 2 diabetic subjects with DR compared to those without DR. In another study done on 249 Mexican-American type 2 diabetic siblings of probands with DR showed that the severity of DR aggregates in families.⁴⁸ A study done in Australia in newly detected diabetes⁴⁹ showed a prevalence rate of 9.9%.

The CRDPP study carried out in rural Tamil Nadu⁴² showed that the prevalence of DR increases significantly with duration of diabetes. Even among diabetic subjects with less than 1 year duration, the prevalence of DR was found to be 6.6%. The onset and progression of DR may be influenced by many systemic factors, including hormonal, immunologic, genetic and ocular factors. There is growing evidence that DR is not only related to hyperglycemia and disorder of diabetes⁵⁰ but also to other risk factors such as systolic blood pressure (SBP), urinary albumin, body mass index (BMI) and serum lipids, although these have not been consistent in all studies.⁵¹⁻⁵⁵ Increased prevalence of retinopathy with increased duration and severity of hyperglycemia is well known. The CURES eye study clearly demonstrated that every 5-year increase in duration of diabetes, increases risk of diabetes retinopathy by 1.89 times and for every 2% increase in HbA_{1c}, risk of DR increases by factor of 1.75 times.³⁷ Hence, to decrease the threat of developing sight-threatening forms of DR,

i.e. PDR and DME, all the risk factors need to be evaluated and managed early and aggressively.

As individuals even with sight-threatening retinopathy may not initially have any symptoms, lifelong evaluation of retinopathy by retinal screening of all diabetic individuals is necessary.⁵⁶ To prevent diabetes related visual impairment, good control of diabetes is essential. Surgical interventions include laser photocoagulation therapy and vitreoretinal surgery. Two large randomized, controlled clinical trials demonstrated that laser photocoagulation therapy decreases visual disability due to DR by 90% if instituted at the correct stages.^{57,58} In a clinic-based study conducted in 261 eyes of 168 type 2 diabetic subjects who underwent Pan Retinal Photocoagulation (PRP) at Chennai, 73% eyes maintained more than or equal to 6/9 vision at 1-year follow-up. Visual acuity at baseline and duration of diabetes played a significant role in determining the post PRP visual acuity.⁵⁹ Vitreous surgery may allow visual rehabilitation in many eyes that are otherwise untreatable.

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide.⁶⁰ This is due to the fact that (1) the prevalence of diabetes is increasing rapidly and (2) diabetic patients now live longer and are hence more likely to develop diabetic kidney complications.⁶¹

Table 12.3: Prevalence of diabetic nephropathy in clinic and population based studies in India

Author	Place	Year	Prevalence
<i>Clinic based studies</i>			
Gupta et al. ⁶⁷	New Delhi	1991	Microalbuminuria: 26.6%
John et al. ⁷⁰	Vellore	1991	Microalbuminuria: 19.7% Diabetic nephropathy: 8.9%
Yajnik et al. ⁷¹	Pune	1992	Microalbuminuria: 23.0%
Vijay et al. ⁷²	Chennai	1994	Proteinuria: 18.7%
Mohan et al. ⁷³	Chennai	2000	Macroproteinuria with retinopathy: 6.9%
Varghese et al. ⁷⁴	Chennai	2001	Microalbuminuria: 36.3%
Pradeepa et al. ³³	Nine sites in India	2011	Microalbuminuria: 25.5%
<i>Population based studies</i>			
Unnikrishnan et al. ⁷⁵	Chennai	2004	Microalbuminuria: 26.9% Overt nephropathy with diabetic retinopathy: 20.2%
Mohan et al. ⁴²	Chunampet (Rural)	2012	Microalbuminuria: 24.3%

Nephropathy affects 20–30% of type 1 and type 2 diabetic patients.⁶² It has been estimated that 20% of type 2 diabetic patients reach ESRD during their lifetime.⁶³ Comparatively, ESRD develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years and in more than 75% by 20 years.⁶² Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria, which progresses to microalbuminuria, macroalbuminuria and eventually to ESRD. Microalbuminuria is the earliest clinically detectable stage of diabetic kidney disease at which appropriate interventions can retard, or reverse the progression of disease.⁶⁴ In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes.⁶²

Earlier studies on migrant Asian Indians had suggested a high prevalence of microalbuminuria and kidney disease compared to native European population.^{65,66} However, studies from India do not support these observations. Gupta et al. in 1991⁶⁷ reported the prevalence of microalbuminuria in North India among type 1 diabetic subjects to be 7.6%. Prevalence of microalbuminuria in type 1 diabetic subjects in South India was reported to be 28.2%.⁶⁸ In a study conducted in Mumbai, among type 1 diabetic patients the prevalence of microalbuminuria was 12.5%.⁶⁹ Data of patients registered in the DEMR system between the years 1991 and 2010 showed that the prevalence of microalbuminuria among 1,633 type 1 diabetic patients was 20%.³³ Table 12.3 presents the prevalence rate of diabetic nephropathy from referral centres in India^{33,42,67,70-75} with persistent proteinuria ranging from

6.9% to 18.7%^{70,72,73} and microalbuminuria ranging between 19.7% and 36.3%.^{33,42,67,70,71,74}

The CURES is perhaps the first population based study from India to report on prevalence of diabetic nephropathy. This study showed that the overall prevalence of overt nephropathy was 2.2% while that of microalbuminuria was 26.9%.⁷⁵ The CRDPP study documented a prevalence of microalbuminuria among rural population in Tamil Nadu to be 24.3%, which is similar to that found among the urban population in CURES.⁴² Table 12.4 compares the prevalence of microalbuminuria and nephropathy in different populations.^{42,75-81} The prevalence of overt nephropathy in Indians appears to be lower, while that of microalbuminuria is comparable to that reported in other populations.

Duration of diabetes and glycemic control along with other risk factors have been reported to be associated with microalbuminuria in clinic based studies.^{73,74} In the CURES population based study, glycosylated hemoglobin, duration of diabetes and SBP were independently associated with diabetic nephropathy.⁷⁵ Timely intervention at this stage can halt or reverse the progression of kidney damage. Development of persistent proteinuria is an ominous sign as glomerular filtration rate progressively declines after that.

There is substantial evidence that good diabetes control is important to prevent diabetic nephropathy; however, some patients develop the disease despite good control and others escape despite poor control. This suggests the role of genetic factors in susceptibility to nephropathy.⁸² Familial clustering of nephropathy has repeatedly been observed in various populations studied and for

Table 12.4: Prevalence of nephropathy and microalbuminuria in type 2 diabetes in different population based studies

Author	Place/Year	No. of diabetic subjects	Prevalence of microalbuminuria (%)	Prevalence of macroalbuminuria (%)
Gatling et al. ⁷⁶	Poole, UK, 1988	450	—	7.0
Klein et al. ⁷⁷	Wisconsin, USA, 1993	798	25.9	16.0
Neil et al. ⁷⁸	Oxford, UK, 1993	246	15	4
Collins et al. ⁷⁹	Western Samoa, 1995	162	22.0* 17.2**	3.9* 6.3**
Wirta et al. ⁸⁰	Finland, 1995	188	29* 27**	4* 7**
Bruno et al. ⁸¹	Italy, 1996	1,574	32.1	17.6
Unnikrishnan et al. ⁷⁵	Chennai, India, 2007	1,716	26.9	2.2
Mohan et al. ⁴²	Chunampet, Rural India, 2012	1,001	24.3	3.2

* NDD: New detected diabetes

** KD: Known diabetes

multiple etiologies of kidney disease.⁸³⁻⁸⁵ A threefold to ninefold greater risk of ESRD is observed in individuals with a family history of ESRD.⁸⁶ In South India, to study whether there was a familial clustering among subjects with or without diabetic kidney disease and their siblings, Vijay et al.⁸⁷ compared sib-pairs, matched for age, duration of diabetes and the level of metabolic control and reported that there was strong familial clustering of diabetic kidney disease in patients with type 2 diabetes, which was independent of the familial clustering of diabetes. This strongly suggests a genetic component, although environmental exposures are still important. It is imperative that nephrologists and primary care physicians recognize that individuals who have relatives with advanced nephropathy are themselves at high risk for subsequent kidney disease, proteinuria and atherosclerotic cardiovascular complications.

Diabetic Neuropathy

Diabetic neuropathy affects nearly 50% of all diabetic subjects and is considered to be the main cause for morbidity.⁸⁸ The intensity and extent of the functional and anatomical abnormalities of diabetic neuropathy are parallel to the severity and duration of hyperglycemia. Among individuals with diabetes, neuropathy is a common cause of morbidity (painful polyneuropathy, neuropathic ulceration) and mortality (due to autonomic neuropathy) presenting a huge economic burden to society.⁸⁹ Neuropathy occurs with the same frequency in both type 1 and type 2 diabetes, suggesting a common etiologic mechanism based on chronic hyperglycemia.

People with diabetic neuropathy in developing countries incur huge costs largely due to foot complications. It is estimated that in India, diabetic subjects with foot problems incur almost four-times higher costs as compared to diabetic patients without foot problems.⁹⁰

Most studies of diabetic neuropathy have been done in western populations^{91,92} and there is paucity of data in developing countries, particularly from India, where a large proportion of the population walks with bare feet. Most studies published on prevalence of DN in India have been clinic-based^{132,33,93-95} (Fig. 12.1). In a south Indian type 2 diabetic clinic population the prevalence of neuropathy was 27.5% in Chennai in the year 1999.³² In another study conducted in 2002 at Chennai a prevalence of 19.1% was reported.⁹³ A surprisingly high prevalence of 64.1% was reported in a diabetic outpatient clinic at Bangalore in the year 2006.⁹⁵ In a multicentric study from Chennai, Madurai, Vellore and Delhi, conducted in a total of 1,319 type 2 diabetic patients, the total prevalence of neuropathy was reported to be 15%. The prevalence rates in different centers vary from 9% to 17% as shown in Figure 12.1.⁹⁴ At Dr Mohan's Diabetes Specialities Centre, a prevalence of 33.1% was reported among diabetic subjects.³³ This variation could be attributed to the demography of the study population and different diagnostic criteria employed (pinprick perception, clinical signs and symptoms, quantitative sensory tests or electrodiagnostic tests).

The clinical diabetic neuropathies, found at a teaching hospital in Cuttack, were in the following order of frequency: distal symmetrical sensorimotor neuropathy,

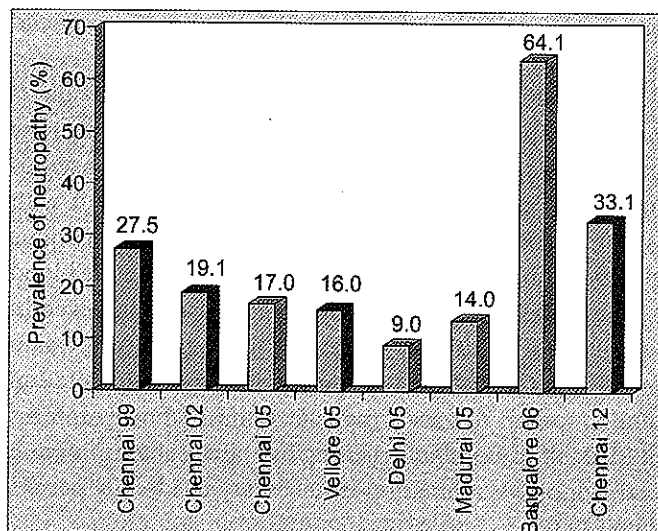


Fig. 12.1: Prevalence of neuropathy in clinic based studies among type 2 diabetes^{32,33,93-95}

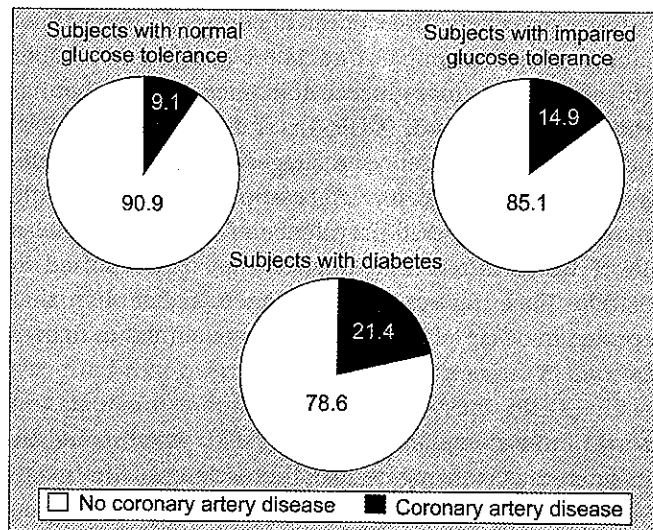


Fig. 12.2: Prevalence of coronary artery disease. The Chennai urban population study¹⁰⁶

cranial mononeuropathy, mononeuropathy multiplex, autonomic neuropathy.⁹⁶ Among the young diabetic patients seen in North-Eastern India, peripheral neuropathy was found to be common (43.5%) in patients with fibrocalculus pancreatic diabetes.⁹⁷

There are very few population based studies on diabetic neuropathy in India. Pradeepa et al.⁹⁸ from Chennai in the CURES study reported the age-standardized prevalence of neuropathy to be 13.1% (KD: 13.6% vs NDD 11.2%) whereas the crude prevalence rate was 26.1% (KD: 27.8% vs NDD 19.5%). Vaz et al.⁴¹ reported a prevalence of 60% among diabetic subjects in a rural Goa population. A prevalence of 30.9% was reported in the CRDPP study in rural Tamil Nadu.⁴²

It has been reported that along with the presence of external risk factors, some associations have also been noted between diabetic microvascular complications themselves.^{99,100} Thus the presence of DR itself may reveal patients at risk of diabetic nephropathy,¹⁰¹ and neuropathy.¹⁰² The CURES study identified some common risk factors for all the three microvascular complications of diabetes. These were age, glycated hemoglobin, duration of diabetes and serum triglycerides. This study also reported that the association between DR and nephropathy was stronger than that with neuropathy.¹⁰³ Approaches to prevention of neuropathy include tight control of hyperglycemia and regular foot examination. Most treatments available for diabetic neuropathy focus on relieving pain.

MACROVASCULAR COMPLICATIONS

Macrovascular disease is considered to be a deadly triangle, comprising coronary artery disease (CAD), peripheral vascular disease (PVD) and cerebrovascular disease (CVD) leading to high morbidity and mortality.

Cardiovascular Disease

Diabetes mellitus is an independent risk factor for cardiovascular disease. Unlike type 1 diabetes, type 2 diabetes has a higher risk for cardiovascular disease, the prevalence of which is estimated to be two-fold to four-fold higher compared to non-diabetic subjects.¹⁰⁴ This is because type 2 diabetes is a component of the metabolic cluster, which is associated with other risk factors like insulin resistance, dyslipidemia, hypertension, abdominal obesity and prothrombotic state.¹⁰⁵

In India, the cardiovascular disease epidemic appears to overlap with the epidemic of diabetes. Indeed, of all diabetic complications, the most dangerous and life threatening is cardiovascular disease. Prevalence of CAD is also increasing at an alarming proportion in India. The present prevalence of this disease among Indians ranges from 9% to 14%.^{106,107} In a clinic based study, we showed that 17.8% of diabetic subjects had CAD and that the prevalence increased with age and duration of diabetes. Thus, nearly 40% of the subjects with diabetes duration more than 20 years had CAD.¹⁰⁸

Coronary artery disease was documented in 21.4% of diabetic subjects compared to 14.9% in IGT and 9.1% in subjects with normal glucose tolerance in the Chennai urban population study (CUPS) as shown in Figure 12.2.¹⁰⁶ There is a lot of evidence to suggest that Asian Indians have an increased risk for CAD compared to other ethnic groups.^{109,110} The overall prevalence of CAD in CUPS was 11%,¹⁰⁶ which is ten-times higher than that reported in 1960s.¹¹¹ These figures are also much higher than that reported in other ethnic groups and are similar to figures reported in migrant Indians.^{109,112}

The CUPS has also provided interesting data on carotid intimal medial thickness (IMT), which could be considered as a surrogate for atherosclerosis. The mean IMT of diabetes subjects was significantly higher than those of the non-diabetic subjects.¹¹³ At any age point, the IMT values of diabetic subjects were significantly greater than among non-diabetic subjects. Prevalence of carotid atherosclerosis, defined as carotid IMT more than or equal to 1.1 mm in CUPS, was 1% among non-diabetic subjects, while it was 20% among diabetic subjects.¹¹³ In the same population, arterial stiffness was also greater among diabetic subjects compared to their age and sex matched non-diabetic counterparts, and endothelial function was also severely impaired among diabetic subjects.¹¹⁴ These studies confirm that diabetic subjects are more prone to atherosclerotic changes compared to non-diabetic subjects and that it tends to occur at a younger age.

The various risk factors identified for cardiovascular disease include aging, smoking, strong family history of CAD and diabetes, and lifestyle related factors like physical inactivity and stress. The INTERHEART study conducted in 52 countries demonstrated that over 90% of the population attributable risk of acute myocardial infarction (AMI) was accounted for by nine modifiable risk factors, which included smoking, diabetes, hypertension, abdominal obesity, the ApoB/ApoA1 ratio, psychosocial stress, decreased intake of fruits and vegetables, physical inactivity and regular alcohol consumption.¹¹⁵⁻¹¹⁸ CAD can often be asymptomatic and early screening is therefore beneficial in preventing major events. Since diabetes is considered as a cardiovascular risk equivalent,¹¹⁹ routine screening for CAD in diabetic patients is justified.

Peripheral Vascular Disease

Peripheral vascular disease (PVD) in diabetic patients differs from that seen in non-diabetic individuals. In non-diabetic individuals, the sites of occlusion are more

proximal usually the infra-renal aorta, iliac and superficial femoral arteries with sparing of distal vessels whereas in diabetic patients, occlusive lesions occur in more distal vessels such as the tibialis and peroneals.^{120,121} This may partly explain the fact that PVD is frequently asymptomatic in people with diabetes and may present with ischemic foot ulceration or gangrene with no previous claudication. Distal disease may allow a reasonable blood supply to be maintained to the large muscles involved in walking while critically impairing the supply to the skin of the feet. Coexistent neuropathy and exercise limitation due to other diseases may also mask the symptoms of PVD. Thus, regular screening by physical examination and Doppler examination is necessary to identify people with PVD.

The prevalence of PVD has been reported to be low among Asians ranging between 3% and 6%.^{32,122-125} Earlier clinic-based reports have suggested that PVD is less common among Indian diabetic patients in the United Kingdom¹²⁶ and South Africa.¹²⁷ In a clinic-based study,¹²² we reported the prevalence of PVD in South Indian diabetic patients to be 3.9%. In another study in south Indian type 2 diabetic subjects, PVD was present in 4%, which included 18 subjects with gangrene.¹²⁴ In a large clinic based study, the prevalence of PVD was reported to be 3.9% among 123,563 type 2 diabetic subjects in a tertiary diabetic center southern India.³³

The Chennai urban population study (CUPS) was the first population based study to report on prevalence of PVD, and this study reported that the prevalence of PVD was 6.3% among diabetic subjects compared to 2.7% among non-diabetic subjects¹²³ confirming that the prevalence of PVD is low in our population. Comparative figures in the Western population range from 17.2% to 45%.^{128,129} While the low prevalence of PVD may be attributed to the sample size, selection criteria and other factors; this could also reflect true differences in ethnic susceptibility.¹³⁰ Some of the factors to explain the low prevalence of PVD in Indian diabetic patients could be: (1) the age of onset of type 2 diabetes occurs 10-15 years earlier in Indians (2) the number of patients above the age of 70 years is low (3) duration of diabetes is shorter and (4) the lower prevalence of smoking in Chennai (17.5% in men and 0% in women in this study).¹³¹ The prevalence of PVD rises sharply above 70 years of age,^{122,123} and hence we may see a marked increase in PVD in the next decade or so, with increased longevity of our diabetic patients.

Cerebrovascular Disease

Strokes are the third commonest cause of mortality in diabetic patients after heart disease and cancer, and represents a major health burden in our country.¹³² Strokes are an important cause of morbidity and mortality, and important health and an economic burden. Patients with diabetes have a higher frequency of stroke, and also a poorer prognosis after a stroke.¹³³ A recent study has reported that the prevalence of stroke is more than double among type 2 diabetic subjects compared to the general population.¹³⁴ Prevalence rates of stroke vary from one study to another. However, there has been a definite increase in the prevalence and incidence of strokes in India over the last 30 years. Diabetes is one of the important risk factors for development of stroke.¹³⁵ In a study conducted in Asian Indians living in the United States, prevalence of stroke was significantly associated with systemic hypertension, diabetes CAD, ESRD and family history of stroke, and myocardial infarction.¹³⁶

Although medical and surgical therapies are available for impending or recent onset stroke, prevention is the most effective strategy in reducing the ravages of cerebrovascular disease. To curb the rising trend of stroke in India, the two principal risk factors, i.e. hypertension and diabetes mellitus need to be tightly controlled. Change in dietary habits to reduce intake of fat and salt and a complete cessation of smoking and chewing tobacco needs to be encouraged.

HYPERTENSION AND DIABETES

Hypertension is a common comorbid condition in diabetes and vice-versa. Diabetes and hypertension coexist in approximately 40–60% of patients with type 2 diabetes.¹³⁷ Both type 1 and type 2 diabetic patients are prone to develop hypertension which accelerates cardiac, renal, and cerebral dysfunctions, which are leading causes of death.¹³⁸ Hypertension substantially increases the risk of both macrovascular and microvascular complications in diabetes. The hypertension in diabetes study-I (HDS-I) conducted to determine the prevalence of hypertension in newly diagnosed type 2 diabetic patients reported that 39% of the patients were hypertensive at the time of diagnosis of diabetes.¹³⁹ The HDS-II,¹⁴⁰ which looked at the role of hypertension as a risk factor for macrovascular and microvascular complications in type 2 diabetes, reported that hypertensive patients had a greater incidence of death from diabetes-related, mainly cardiovascular events and a greater incidence of diabetes-related death

and major morbidity combined, including myocardial infarction, angina, strokes and amputation.

Studies from India have shown that diabetes and hypertension coexist in type 2 diabetes. About 50% of diabetic individuals in India have hypertension.^{141,142} The prevalence of hypertension was significantly higher in subjects with diabetes (44.6%) in a study conducted in urban and rural Moradabad in the year 1998.¹⁴³ A study conducted in Srinagar to assess the prevalence of hypertension in newly diagnosed type 2 diabetic patients reported that overall 42% had hypertension.¹⁴⁴ Recently, the screening India's twin epidemic (SITE) cross-sectional study conducted in 10 Indian states¹⁴⁵ reported that diabetes and hypertension were coexistent in 20.6% patients, which demonstrates that the burden of diabetes and hypertension is on the rise in India.

It has been demonstrated that lowering blood pressure in high-risk patients with diabetes can reduce complications and progression of disease.¹⁴⁶ The United Kingdom prospective diabetes study (UKPDS) showed that each 10 mm Hg decrease in mean SBP was associated with 12% reduction in the risk for any complication related to diabetes, 15% reduction in deaths related to diabetes, 11% reduction in myocardial infarction and 13% reduction in microvascular complications.¹⁴⁷

MORTALITY ASSOCIATED WITH DIABETES

There are as yet no large scale Indian studies on mortality in patients with type 2 diabetes and most available studies are from clinical settings, and therefore have shown different results.

A retrospective study from Srinagar¹⁴⁸ reviewed medical records of 133,374 patients admitted from January 1987 to December 1996. Of the 9,627 individuals who died, 269 had diabetes. Infections contributed to over 30% of the deaths, which was followed by chronic renal failure (30%) and CAD (16%). In another study done by the same group,¹⁴⁹ of the 234,776 admissions to the centre, 16,690 (7.11%) died, of whom 741 had diabetes mellitus as mentioned in the death certificate. The causes contributing to death were infections (40.9%), chronic renal failure (33.6%), CAD (16.9%), cerebrovascular disease (13.2%), chronic obstructive pulmonary disease (6.9%), acute renal failure (6.2%), malignancy (4.2%), hypoglycemia (3.5%) and diabetic ketoacidosis (3.4%). Another study of 440 patients with diabetes related mortality seen at a tertiary care centre in North India also revealed the most common cause of death to be infections (46.5%) followed

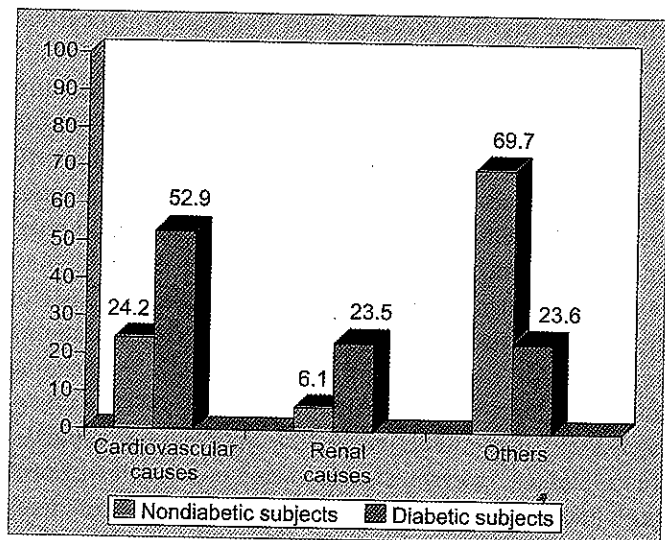


Fig. 12.3: Causes of mortality rates in diabetic and non-diabetic individuals. The Chennai urban population study¹⁵¹

by CAD (17.4%), chronic renal failure (9.7%), stroke (6.0%), diabetic ketoacidosis (3%), hyperosmolar coma (2.2%) and hypoglycemia (2.1%). Analysis of the causes of death in diabetic versus non-diabetic hospital inpatients showed infection, CAD and chronic renal failure to be more frequent in diabetic subjects.¹⁵⁰

A follow-up of the original CUPS cohort in Chennai showed that the overall mortality rates were nearly threefold higher (18.9 per 1,000 person-years) in people with diabetes compared to non-diabetic subjects (5.3 per 1,000 person-years, $p = 0.004$).¹⁵¹ The hazard ratio (HR) for all cause mortality for diabetes was found to be 3.6 compared to non-diabetic subjects. This study also showed that mortality due to cardiovascular (diabetic subjects: 52.9% vs non-diabetic subjects 24.2%, $p = 0.042$) and renal (diabetic subjects 23.5% vs non-diabetic subjects 6.1%, $p = 0.072$) causes were higher among diabetic subjects (Fig. 12.3).

SUMMARY

Diabetes related complications pose a huge economic burden and with decreased quality of life. Three landmark studies on glycemic control in diabetes namely the diabetes complications and control trial (DCCT), the UKPDS and Kumamoto study¹⁵²⁻¹⁵⁴ have clearly documented the beneficial effects of glycemic control in preventing microvascular complications. Hence, clinicians should aim to achieve as tight a control of diabetes as possible without compromising the safety. Life style measures to prevent

complications include dietary modification, which includes substituting: (1) saturated fat, dietary cholesterol and transfatty acids with non-hydrogenated mono and polyunsaturated fats (2) high glycemic foods with low glycemic foods, increasing fiber intake and reducing salt intake. In addition to tight diabetes control, good control of blood pressure and dyslipidemia and other measures such as tobacco cessation and increasing physical activity would also help to prevent macrovascular complications.

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