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Original Research Article

Diabetes Mellitus - Comparative Study of Drugs, Comorbidities, Hba1c and Lipid Profile

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Abstract: Diabetes mellitus (DM) is a group of metabolic diseases which manifest as high blood sugar levels over a prolonged period. Long-term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes etc. This comparative study of patients with diabetes mellitus in Karnataka and patients was done to observe the differences and similarities in patterns of disease, HBA1C levels, treatment, and adverse effects of drugs. A total of 330 patients i.e. 230 Karnataka patients and 100 Kerala patients were studied from October 2014 till September 2016. In this prospective observational study, all the patients were observed for detailed history, examination, investigational findings, drug intake, adverse effects, and interactions. The results were analyzed. Patients with Type 1 Diabetes Mellitus were excluded. Males constituted 53.6% of study population, while females constituted 46.4%. 30% of the patients are in age group of 61-70 years followed by 51-60 years group with 28.5. Among Kerala patients 70% have hypertension while 38.7% of Karnataka have hypertension. 14.8% of Karnataka patients have undergone percutaneous coronary intervention (PCI). 9% of Kerala patients had Cerebrovascular accident while only 0.9% of Karnataka patients had Cerebrovascular accident (CVA). Mean Triglycerides, LDL Cholesterol, total cholesterol were higher in Kerala patients compared to Karnataka patients while mean HDL cholesterol is lower in Kerala patients. Patients from Kerala have poorer control of diabetes, higher prevalence of hypertension, heart disease, and cerebrovascular accident. Kerala patients have lesser prevalence of nephropathy and retinopathy but the results are not statistically significant. Adverse effects to drugs were reported commonly by Kerala patients compared to Karnataka patients. Dyslipidemia is more common in Kerala patients. Eventhough patients from both states have more prevalence of comorbidities, Kerala patients are at more risk.

Keywords: Diabetes Mellitus, Hypertension, Ischemic Heart disease, Dyslipidemia, Triglycerides, Cholesterol, Retinopathy, Nephropathy, Neuropathy, Metformin, Glimipiride, Insulin

INTRODUCTION:

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus is probably one of the oldest known diseases to mankind. DM was first recorded in Egyptian manuscript about 3000 years ago [1]. In 1936, the clear distinction between type 1 and type 2 DM was done [2]. Type 2 DM was described as a component of metabolic syndrome for the first time in 1988 [3]. Type 2 DM is the commonest form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [4]. Type 2 DM results due to interaction between genetic, environmental and behavioral risk factors [5, 6].

People living with type 2 DM are more vulnerable to various forms of both short-term and long-term complications, and risk of premature death. As of 2015, an estimated 415 million people are

affected with diabetes worldwide [7] with type 2 DM contributing about 90% of the cases [8, 9]. This number represents 8.3% of the adult population [10] with almost equal rates in both women and men.[11] From 2012 to 2015, an estimate of 1.5 to 5.0 million deaths each year resulted from diabetes. Diabetes at least doubles a person's risk of death. The number of people with diabetes is expected to reach 592 million by 2035.

The global economic cost of diabetes in 2014 was estimated to be $612 billion USD [12]. In the United States, diabetes cost $245 billion in 2012 [13]. Rates of type 2 diabetes have increased drastically since 1960 in parallel with obesity [14]. As of 2013 there were approximately 368 million people diagnosed with the type 2 DM compared to around 30 million in 1985 [15, 16]. This increase is due to aging of the global population, a reduction in exercise, and increasing rates of obesity. The five countries with the highest number of people affected with diabetes as of 2000 are India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million [17]. It is recognized as a global epidemic by the World Health Organization [18].

Usually it begins in middle or older age. Type 2 diabetes is associated with a ten year shorter life expectancy [19]. Diabetes was one of the first diseases described [20]. The importance of insulin in the disease was determined in the 1920s [21]. A number of lifestyle factors are known to be important to the development of type 2 DM [22]. Lifestyle factors include sedentary lifestyle, physical inactivity, cigarette smoking and excessive consumption of alcohol [23]. Obesity contributes to approximately 55% of cases of type 2 DM [24].

The alarmingly increased rate of obesity in childhood between the 1960s and 2000s is thought to have increased type 2 DM in children and adolescents [25]. Environmental toxins are thought to contribute to the increases in the rate of type 2 DM. A weak positive correlation was found between the bisphenol A concentration in the urine, which is a constituent of some plastics, and the incidence of type 2 DM [26]. There is an inheritable genetic connection , having relatives (specifically first degree) with type 2 DM increases the risks of developing type 2 DM.

Concordance among monozygotic twins was found to be almost 100%, and approximately 25% of those have a family history of DM [27]. Genes that are significantly associated with developing type 2 DM, include *TCF7L2*, *KCNJ11*, *NOTCH2*, *PPARG*, *FTO*, *WFS1*, *IGF2BP2*, *SLC30A8*, *CDKAL1*, *JAZF1*, and *HHEX*. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7-like 2) regulates proglucagon gene expression and hence the production of glucagon-like peptide-1 [28].

Obesity is an independent risk factor for type 2 DM, which is strongly inherited [29]. Monogenic forms of type 2 DM like Maturity-onset diabetes of the young (MODY), constitutes up to 5% of cases [30]. The medical conditions which exacerbate type 2 DM include hypertension, obesity, hyperlipidemia, and metabolic syndrome (also known as Syndrome X, Reaven's syndrome) [31]. Other causes contributing include acromegaly, pheochromocytoma, chronic pancreatitis, Cushing's syndrome, cancer, thyrotoxicosis and drugs [32]. Other factors that increase the risk of include aging [33]. high-fat diet, and a less active lifestyle. The diagnostic criteria are included in Table 1 and 2 [34, 35]. Most common symptoms include needing to urinate frequently, feeling thirsty and blurred vision. This prospective study was conducted to study clinical profile, drug usage, adverse effects, lipid profiles and HBA1C levels among Karnataka and Kerala patients.

Many type 2 DM patients are found to have comorbidities including Hypertension, Ischemic Heart disease, dyslipidemia, inadequate or improper drug intake and poor control of blood sugars. Oral hypoglycemic agents and insulin can cause hypoglycemia and other adverse affects such as weight gain, worsening of heart failure, lactic acidosis, liver disease, gastritis etc. Dietary habits in Karnataka and Kerala states vary in the amount of protein consumption, carbohydrate and fat intake. No comparative studies are done regarding the influence of drug discipline in these populations. Hence this study is undertaken.

METHODS:

This observational study was conducted over a period from October 2014 to September 2016. Patients recruited were type 2 diabetics between age more than 18 years and less than 80 years. Type 1 diabetic patients were excluded. Data was pooled from 4 hospitals of which 2 are specialized diabetes centers. Approval from the Institutional Ethics Committee and permission from the respective hospitals were obtained before starting the study.

Out of 330 patients recruited in to study 230 patients were from Karnataka and 100 patients were from Kerala. The demographic data (age, sex), clinical features, co-morbid conditions, investigations, drug usage, results of the treatment and adverse effects were analyzed. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are

presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, and Cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients , Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

+ Suggestive significance (P value: $0.05<P<0.10$)
* Moderately significant (P value: $0.01<P \leq 0.05$)
** Strongly significant (P value: $P \leq 0.01$)

Statistical software:

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

RESULTS:

Out of 330 patients recruited in to study 230 patients were from Karnataka and 100 patients were from Kerala. Males constituted 58.7% of patients in Karnataka, while 42% of patients were male in Kerala. In total males constituted 53.6% of study population, while females constituted 46.4% of study population. 30% of patients are in age group of 61-70 years followed by 51-60 years group with 28.5%.[Table 3] The average height in Karnataka is 161.24±9.38 cm, while in Kerala is 164.1±8.34 cm. Duration of DM and HBA1C distribution were analyzed in Table 4 and 5.

Abnormal Lipid profile was found in 68% of Kerala patients. Regarding lipid profile, 71.7% of Karnataka patients and 33% of Kerala patients have total cholesterol <200mg/dl. 24.3% of Karnataka patients and 22% of Kerala patients have total cholesterol in range of 200-239 mg/dl. While 45% of Kerala patients have total cholesterol> 280mg/dl, only 4% of Karnataka patients have the similar levels. These results are statistically significant and show higher total cholesterol in Kerala patients. [Table 6]

Regarding LDL Cholesterol, 1.3% of Karnataka patients have it >190mg/dl, while 17% of Kerala patients have LDL >190mg/dl. 83.9% of Karnataka patients and 83% of Kerala patients have LDL cholesterol in the range of 70-190mg/dl. [Table 7] Regarding HDL cholesterol 28.1% of Karnataka patients and 31% of Kerala patients have it ≤39 mg/dl. [Table 8] Regarding Triglycerides, 29.5% of Karnataka patients and 40% of Kerala patients have triglycerides ≥200 mg/dl. 70.5 % of Karnataka patients and 60 % of Kerala patients have triglycerides in the range of 30-199 mg/dl. [Table 9] Mean Triglycerides, LDL Cholesterol, Total cholesterol were higher in Kerala patients compared to Karnataka patients while mean HDL Cholesterol is lower in Kerala patients. This is a matter of concern which predisposes to heart disease, stroke and hypertension.

Among Kerala patients 70% have hypertension while 38.7% of Karnataka have hypertension which is statistically significant.[Table 10], 24.4 percent of Karnataka and 32 percent of Kerala patients have Ischemic heart disease(IHD).[Table 11], 14.8% of Karnataka patients have undergone percutaneous coronary intervention(PCI) which is statistically significant compared to Kerala patients. 9% of Kerala patients had Cerebrovascular accident while only 1% of Karnataka patients had Cerebrovascular accident (CVA) [Table 12].

Regarding duration of diabetes 30.9% of total patients are in the group of 6-10 years i.e. 32.6% of Karnataka patients and 27% of Kerala patients. 25.5% of patients have diabetes for a duration of 11-15 years i.e. 27.4% of Karnataka patients and 21% of Kerala patients. 20.1% of Karnataka patients and 11% of Kerala patients had retinopathy.[Table 13] Regarding neuropathy, 45.2% of Karnataka patients and 47% of Kerala patients had it. Nephropathy was found in 27.5% of Karnataka patients and 23% of Kerala patients. Regarding drug usage, 64.8% of Karnataka patients and 78% of Kerala patients used Metformin which is statistically significant. Glimipiride usage was reported in 67.1% of patients from Karnataka and 54% of patients from Kerala. Among Insulins, Glargine usage was found in 3.9% of Karnataka patients and 14% of Kerala patients. Intermediate acting insulin usage was found in 13.9% of Karnataka patients and 25% of Kerala patients. Short acting insulin usage was found in 8.3% of Karnataka and 42% of Kerala patients [Table 14].

Adverse effects to drugs were reported in 20.4% of Karnataka patients and 48% of Kerala patients, which is statistically significant.[Table 15] No statistically significant difference between Karnataka and Kerala patients was found in usage of Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers(38.3% vs. 40%, P value= 0.766). No statistically significant difference between Karnataka and Kerala patients was found in Beta blocker usage (27.4% vs. 30%, P value= 0.628). No statistically significant difference between Karnataka and Kerala patients was found in diuretic usage (30.9% vs. 39%, P value= 0.150) and calcium channel blocker usage (27.5% vs. 34%, P value= 0.235).

Regarding Statin usage, 71% of Kerala patients use Atorvastatin, while only 17.8% of Karnataka patients use Atorvastatin [Table 16] Regarding Rosuvastatin usage, 62.6% of Karnataka patients were using it, while 1% of Kerala patients use it. [Table 17] Regarding Simvastatin usage, 7% of Karnataka patients and 1% of Kerala patients use it. Regarding Fenofibrate usage, 24.8% of Karnataka patients and 13% of Kerala patients use it. Using ANOVA test, we also found significant differences in the quantitative variables of height, weight, age, duration of diabetes in qualitative fasting blood sugar. Table 18 represents the summary of all differences found between Kerala and Karnataka patients.

Table 1: Diagnostic criteria for diagnosis of Diabetes Mellitus (ADA)

Normal — Fasting blood sugar (FBS) less than 100 mg/dL (5.55 mmol/L).
Categories of increased risk
Impaired fasting glucose is defined as a fasting blood sugar level between 100 and 125 mg/dL (5.6 to 6.9 mmol/L).
Impaired glucose tolerance is defined as a blood sugar level of 140 to 199 mg/dL two hours after an oral glucose tolerance test.
A1C – persons with 5.7 to 6.4 percent are at highest risk, although there is a continuum of increasing risk across the entire spectrum of sub diabetic A1C levels.
At least 50 percent of people with impaired glucose tolerance eventually develop type 2 diabetes. Even if they don't develop diabetes, these people are at increased risk of heart disease. Impaired glucose tolerance is very common; about 11 percent of all people between the ages of 20 and 74 have impaired glucose tolerance.
Diabetes mellitus — Considered to be diabetic if he or she has one or more of the following:
Symptoms of diabetes and a random blood sugar of 200 mg/dL (11.1 mmol/L) or higher
A fasting blood sugar level of 126 mg/dL (7.0 mmol/L) or higher
A blood sugar of 200 mg/dL (11.1 mmol/L) or higher two hours after an oral glucose tolerance test
An A1C of 6.5 percent or higher

Table 2: WHO diabetes diagnostic criteria

Condition	2 hour glucose	Fasting glucose	HbA_{1c}	
Units	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycemia	<7.8 (<140)	≥6.1(≥110) & <7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

Table 3: Age distribution of subjects studied

Age in years	Karnataka	Kerala	Total
<20	2(0.9%)	0(0%)	2(0.6%)
20-30	5(2.2%)	2(2%)	7(2.1%)
31-40	13(5.7%)	8(8%)	21(6.4%)
41-50	56(24.3%)	12(12%)	68(20.6%)
51-60	73(31.7%)	21(21%)	94(28.5%)
61-70	65(28.3%)	10(10%)	99(30%)
71-80	14(6.1%)	17(17%)	31(9.4%)
81-90	2(0.9%)	6(6%)	8(2.4%)
Total	230(100%)	100(100%)	330(100%)
Mean ± SD	55.21±11.92	61.17±13.76	57.02±12.78

P<0.001**, Significant, Student t test

Table 4: Duration of Diabetes in years

Duration of Diabetics	Karnataka	Kerala	Total
≤2 yrs	7(3%)	7(7%)	14(4.2%)
2-5 yrs	32(13.9%)	14(14%)	46(13.9%)
6-10 yrs	75(32.6%)	27(27%)	102(30.9%)
11-15 yrs	63(27.4%)	21(21%)	84(25.5%)
16-20 yrs	32(13.9%)	14(14%)	46(13.9%)
21-25 yrs	15(6.5%)	8(8%)	23(7%)
26-30 yrs	3(1.3%)	2(2%)	5(1.5%)
>30 yrs	3(1.3%)	7(7%)	10(3%)
Total	230(100%)	100(100%)	330(100%)
Mean ± SD	11.60±6.41	12.94±9.25	12.01±7.39

P=0.133, Not significant, Student t test

Table 5: HbA1c distribution

HBA1C Level 1						
			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	4-5.6%	1	.4	.5	.5
		5.7-6.4%	17	7.4	9.2	9.7
		>=6.5%	167	72.6	90.3	100.0
		Total	185	80.4	100.0	
	Missing	System	45	19.6		
	Total		230	100.0		
Kerala	Valid	4-5.6%	1	1.0	1.0	1.0
		5.7-6.4%	9	9.0	9.0	10.0
		>=6.5%	90	90.0	90.0	100.0
		Total	100	100.0	100.0	

HBA1C Level 2						
			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	4-5.6%	1	.4	.4	.4
		5.7-6.4%	15	6.5	6.6	7.1
		>=6.5%	210	91.3	92.9	100.0
		Total	226	98.3	100.0	
	Missing	System	4	1.7		
	Total		230	100.0		
Kerala	Valid	4-5.6%	1	1.0	1.0	1.0
		5.7-6.4%	12	12.0	12.1	13.1
		>=6.5%	86	86.0	86.9	100.0
		Total	99	99.0	100.0	
	Missing	System	1	1.0		
	Total		100	100.0		

Table 6: Cholesterol level

			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	<199 mg/dl	162	70.4	71.7	71.7
		200-239 mg/dl	55	23.9	24.3	96.0
		>=240 mg/dl	9	3.9	4.0	100.0
		Total	226	98.3	100.0	
	Missing	System	4	1.7		
	Total		230	100.0		
Kerala	Valid	<199 mg/dl	33	33.0	33.0	33.0
		200-239 mg/dl	22	22.0	22.0	55.0
		>=240 mg/dl	45	45.0	45.0	100.0
		Total	100	100.0	100.0	

Table 7: LDL Cholesterol levels

Low Density Lipoprotein(LDL)						
			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	<69 mg/dl	33	14.3	14.7	14.7
		70-99 mg/dl	84	36.5	37.5	52.2
		100-129 mg/dl	73	31.7	32.6	84.8
		130-159 mg/dl	26	11.3	11.6	96.4
		160-189 mg/dl	5	2.2	2.2	98.7
		>=190	3	1.3	1.3	100.0
		Total	224	97.4	100.0	
	Missing	System	6	2.6		
	Total		230	100.0		
Kerala	Valid	70-99 mg/dl	24	24.0	24.0	24.0
		100-129 mg/dl	23	23.0	23.0	47.0
		130-159 mg/dl	13	13.0	13.0	60.0
		160-189 mg/dl	23	23.0	23.0	83.0
		>=190	17	17.0	17.0	100.0
		Total	100	100.0	100.0	

Table 8: HDL Cholesterol levels

High Density Lipoprotein(HDL)						
			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	<=39 mg/dl	63	27.4	28.1	28.1
		40-59 mg/dl	134	58.3	59.8	87.9
		>=60 mg/dl	27	11.7	12.1	100.0
		Total	224	97.4	100.0	
	Missing	System	6	2.6		
	Total		230	100.0		
Kerala	Valid	<=39 mg/dl	31	31.0	31.0	31.0
		40-59 mg/dl	64	64.0	64.0	95.0
		>=60 mg/dl	5	5.0	5.0	100.0
		Total	100	100.0	100.0	

Table 9: Triglyceride levels

Triglycerides						
			Frequency	Percent	Valid Percent	Cumulative Percent
Karnataka	Valid	30-199 mg/dl	158	68.7	70.5	70.5
		>=200 mg/dl	66	28.7	29.5	100.0
		Total	224	97.4	100.0	
	Missing	System	6	2.6		
	Total		230	100.0		
Kerala	Valid	30-199 mg/dl	60	60.0	60.0	60.0
		>=200 mg/dl	40	40.0	40.0	100.0
		Total	100	100.0	100.0	

Table 10: Hypertension state wise

			Hypertension		Total
			No	Yes	
	Karnataka	Count	141	89	230
		% within state	61.3%	38.7%	100.0%
		% within Hypertension	82.5%	56.0%	69.7%
		% of Total	42.7%	27.0%	69.7%
	Kerala	Count	30	70	100
		% within state	30.0%	70.0%	100.0%
		% within Hypertension	17.5%	44.0%	30.3%
		% of Total	9.1%	21.2%	30.3%
Total		Count	171	159	330
		% within State	51.8%	48.2%	100.0%
		% within Hypertension	100.0%	100.0%	100.0%
		% of Total	51.8%	48.2%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	27.356[a]	1	.000

Table 11: Ischemic Heart disease (IHD) distribution state wise

			Ischemic Heart disease		Total
			No	Yes	
State	Karnataka	Count	170	55	225
		% within State	75.6%	24.4%	100.0%
		% within Ischemic Heart disease	71.4%	63.2%	69.2%
		% of Total	52.3%	16.9%	69.2%
	Kerala	Count	68	32	100
		% within State	68.0%	32.0%	100.0%
		% within Ischemic Heart disease	28.6%	36.8%	30.8%
		% of Total	20.9%	9.8%	30.8%
Total		Count	238	87	325
		% within State	73.2%	26.8%	100.0%
		% within Ischemic Heart disease	100.0%	100.0%	100.0%
		% of Total	73.2%	26.8%	100.0%

Chi-Square Tests			
	Value	df	A symp. Sig. (2-sided)
Pearson Chi-Square	2.016[a]	1	.156

Table 12: Cerebrovascular accident (CVA) Distribution State wise

			Cerebrovascular accident		Total
			No	Yes	
State	Karnataka	Count	201	2	203
		% within State	99.0%	1.0%	100.0%
		% within Cerebrovascular accident	68.8%	18.2%	67.0%
		% of Total	66.3%	0.7%	67.0%
	Kerala	Count	91	9	100
		% within State	91.0%	9.0%	100.0%
		% within Cerebrovascular accident	31.2%	81.8%	33.0%
		% of Total	30.0%	3.0%	33.0%
Total		Count	292	11	303
		% within State	96.4%	3.6%	100.0%
		% within Cerebrovascular accident	100.0%	100.0%	100.0%
		% of Total	96.4%	3.6%	100.0%

Chi-Square Tests			
	Value	df	A symp. Sig. (2-sided)
Pearson Chi-Square	12.301[a]	1	.000

Table 13: Retinopathy distribution among patients

			Retinopathy		Total
			No	Yes	
State	Karnataka	Count	183	46	229
		% within State	79.9%	20.1%	100.0%
		% within Retinopathy	67.3%	80.7%	69.6%
		% of Total	55.6%	14.0%	69.6%
	Kerala	Count	89	11	100
		% within State	89.0%	11.0%	100.0%
		% within Retinopathy	32.7%	19.3%	30.4%
		% of Total	27.1%	3.3%	30.4%
Total		Count	272	57	329
		% within State	82.7%	17.3%	100.0%
		% within Retinopathy	100.0%	100.0%	100.0%
		% of Total	82.7%	17.3%	100.0%

Chi-Square Tests			
	Value	df	A symp. Sig. (2-sided)
Pearson Chi-Square	4.013[a]	1	.045

Table 14: Short acting insulin usage State wise

			short acting Insulin usage		Total
			No	Yes	
State	Karnataka	Count	211	19	230
		% within State	91.7%	8.3%	100.0%
		% within short acting Insulin usage	78.4%	31.1%	69.7%
		% of Total	63.9%	5.8%	69.7%
	Kerala	Count	58	42	100
		% within State	58.0%	42.0%	100.0%
		% within short acting Insulin usage	21.6%	68.9%	30.3%
		% of Total	17.6%	12.7%	30.3%
Total		Count	269	61	330
		% within State	81.5%	18.5%	100.0%
		% within short acting Insulin usage	100.0%	100.0%	100.0%
		% of Total	81.5%	18.5%	100.0%

Chi-Square Tests			
	Value	df	A symp. Sig. (2-sided)
Pearson Chi-Square	52.654[a]	1	.000

Table 15: Adverse effects reported- State wise

			Adverse effects		Total
			No	Yes	
State	Karnataka	Count	183	47	230
		% within State	79.6%	20.4%	100.0%
		% within Adverse effects	77.9%	49.5%	69.7%
		% of Total	55.5%	14.2%	69.7%
	Kerala	Count	52	48	100
		% within State	52.0%	48.0%	100.0%
		% within Adverse effects	22.1%	50.5%	30.3%
		% of Total	15.8%	14.5%	30.3%
Total		Count	235	95	330
		% within State	71.2%	28.8%	100.0%
		% within Adverse effects	100.0%	100.0%	100.0%
		% of Total	71.2%	28.8%	100.0%

Chi-Square Tests			
	Value	df	A symp. Sig. (2-sided)
Pearson Chi-Square	25.833[a]	1	.000

Table 16: Atorvastatin usage State wise

			Atorvastatin		Total
			No	Yes	
State	Karnataka	Count	189	41	230
		% within State	82.2%	17.8%	100.0%
		% within Atorvastatin	86.7%	36.6%	69.7%
		% of Total	57.3%	12.4%	69.7%
	Kerala	Count	29	71	100
		% within State	29.0%	71.0%	100.0%
		% within Atorvastatin	13.3%	63.4%	30.3%
		% of Total	8.8%	21.5%	30.3%
Total		Count	218	112	330
		% within State	66.1%	33.9%	100.0%
		% within Atorvastatin	100.0%	100.0%	100.0%
		% of Total	66.1%	33.9%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	87.895[a]	1	.000

Table 17: Rosuvastatin usage State wise

			Rosuvastatin		Total
			No	Yes	
State	Karnataka	Count	86	144	230
		% within State	37.4%	62.6%	100.0%
		% within Rosuvastatin	46.5%	99.3%	69.7%
		% of Total	26.1%	43.6%	69.7%
	Kerala	Count	99	1	100
		% within State	99.0%	1.0%	100.0%
		% within Rosuvastatin	53.5%	0.7%	30.3%
		% of Total	30.0%	0.3%	30.3%
Total		Count	185	145	330
		% within State	56.1%	43.9%	100.0%
		% within Rosuvastatin	100.0%	100.0%	100.0%
		% of Total	56.1%	43.9%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	107.395	1	.000

Table 18: Summary of differences and statistical significance between Karnataka and Kerala patients

Variables	Value	df	Asymp. Sig. (2-sided)	Conclusion
State * Hypertension	27.356	1	0.000	Rejecting null hypothesis
State * Ischemic Heart disease	2.016	1	0.156	Accept null hypothesis
State * Cerebrovascular accident	12.301	1	0.000	Rejecting null hypothesis
State * sex	7.812	1	0.005	Rejecting null hypothesis
State * Retinopathy	4.013	1	0.045	Rejecting null hypothesis
State * Neuropathy	.093	1	0.760	Accept null hypothesis
State * Nephropathy	.734	1	0.392	Accept null hypothesis
State * Metformin usage	5.671	1	0.017	Rejecting null hypothesis
State * Glimepiride usage	5.128	1	0.024	Rejecting null hypothesis
State * Long acting insulin usage(Glargine)	10.937	1	0.001	Rejecting null hypothesis
State * Intermediate acting insulin usage	5.996	1	0.014	Rejecting null hypothesis
State * short acting Insulin usage	52.654	1	0.000	Rejecting null hypothesis
State * Adverse effects	25.833	1	0.000	Rejecting null hypothesis
State * ACE Inhibitor/ARB Drug usage	.089	1	0.766	Accept null hypothesis
State * Beta blocker usage	.234	1	0.628	Accept null hypothesis
State * Diuretics	2.073	1	0.150	Accept null hypothesis
State * Calcium Channel Blocker	1.410	1	0.235	Accept null hypothesis
State * Atorvastatin	87.895	1	0.000	Rejecting null hypothesis
State * Rosuvastatin	107.395	1	0.000	Rejecting null hypothesis
State * Simvastatin	5.061	1	0.024	Rejecting null hypothesis
State * Fenofibrate	5.790	1	0.016	Rejecting null hypothesis

DISCUSSION:

Data from several epidemiologic studies suggest that the prevalence of hypertension in patients with DM is 1.5-2.0 times greater than in an appropriately matched non-DM population. In patients with type 1 DM, hypertension is usually not present at the time of diagnosis. As renal insufficiency develops, blood pressure increases and may exacerbate the progression to end-stage renal failure. In type 2 DM, many patients are hypertensive at the time of diagnosis. The incidence of hypertension in type 2 DM is related to the degree of obesity/overweight, advanced age and extensive atherosclerosis that is usually present, and it also probably includes patients with essential hypertension.

Several pathophysiologic mechanisms contribute to the genesis and maintenance of hypertension in the patient with DM. Hyperglycemia and increased total-body exchangeable sodium leads to extracellular fluid accumulation and plasma volume expansion. In some patients, alterations in the renin-angiotensin-aldosterone system function and vascular sensitivity to vasoactive hormones may also play a role [36]. In our study Hypertension was found in 70% of Kerala patients and only 38.7% of Karnataka patients.

Our study correlates with other studies of prevalence in total but Kerala patients have more than optimal prevalence of hypertension which is a matter of serious concern.

According to one study published in 1993, Thirty-nine per cent of the patients (35% of the males, 46% of the females) were hypertensive (mean blood pressure > or = 160 systolic and/or > or = 90 mmHg diastolic between 2 and 9 months after the diagnosis of diabetes, or taking antihypertensive therapy). The hypertensive patients had a greater mean body mass index (30.1 versus 28.0 kg/m2, P < 0.0001) than the normotensive patients [37].

Chances of developing a stroke in diabetic patients are 1.5 times higher than in people who don't have DM. When considering age-adjusted incidence rates, patients with DM are 2.9 times as more likely to have a stroke compared with nondiabetic patients, a disparity that is seen in many racial/geographic groups [38, 39]. Although stroke is more common among diabetics, many studies report a significantly reduced rate of transient ischemic attacks (TIAs) in diabetics compared with nondiabetic patients. Diabetic patients are more likely to present with cerebral infarct, indicating that ischemia in DM patients is less likely to be reversible [40, 41]. Our study reports 9% of Kerala patients but only 1% of Karnataka patients have history of Cerebrovascular accident. This shows that risk of higher CVA in Kerala diabetic patients compared to Karnataka patients.

The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. Among younger-onset patients with diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years. The prevalence of PDR was 0% at 3 years and increased to 25% at 15 years.[42] Our study reports 20% of Karnataka patients and 11% of Kerala patients have retinopathy which is above normal ranges. Duration of diabetes is related to incidence of retinopathy.

Diabetic neuropathy (DN) is a common disorder and is defined as signs and symptoms of peripheral nerve dysfunction in a patient with DM in whom other causes of peripheral nerve dysfunction have been excluded. There is a higher prevalence of DM in India (4.3%) [43]. Compared with the West (1%–2%) [44]. probably Asian Indians are more prone for insulin resistance and cardiovascular mortality [45]. The incidence of DN in India is not well known but in a study from South India 19.1% type II diabetic patients had peripheral neuropathy. Our study reports 44.8% of Karnataka patients and 47% of Kerala patients have neuropathy which is higher than normally expected prevalence.

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide, and it is estimated that ~20% of type 2 diabetic patients reach ESRD during their lifetime [46]. Kidney disease in diabetic patients is 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 progress of the disease. The results of one study suggested that in urban Indians, the prevalence of overt nephropathy and microalbuminuria was 2.2 and 26.9%, respectively. Duration of diabetes, A1C, and systolic blood pressure were the common risk factors for overt nephropathy and microalbuminuria [47].

In the United Kingdom prospective diabetes study (UKPDS), after 15 years of follow-up, 28% had developed an eGFR <60 ml/min and 14% had no albuminuria, [48] while similar data were reported from the US [49]. A 7.5-year prospective study showed that the presence of cerebral micro infarcts, documented by magnetic resonance of brain imaging, predicted subsequent doubling of serum creatinine or dialysis dependency in diabetic patients with no microalbuminuria [49]. This suggested that this nonproteinuric type of renal malfunction is the result of arteriolopathy. Our study shows that nephropathy is much higher than expected number. 27.5% of Karnataka patients and 23% of Kerala patients had nephropathy which is a matter of concern.

Drug usage in Diabetics is important in management along with diet, lifestyle changes and exercise. Metformin is an old and widely accepted first line agent, stands out not only for its antihyperglycemic properties but also for its effects beyond glycemic control such as improvements in endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution. Metformin acts primarily at the liver by reducing glucose output and, secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle. These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), which in turn regulates the downstream kinase adenosine monophosphatase protein kinase (AMPK). AMPK phosphorylates a transcriptional co-activator, transducer of regulated CREB protein 2 (TORC2), resulting in its inactivation which consequently down regulates transcriptional events that promote synthesis of gluconeogenic enzymes [50].

The best evidence for a potential role for metformin in the prevention of type 2 diabetes comes from The Diabetes Prevention Program (DPP) trial. Lifestyle intervention and metformin according to DPP trial reduced diabetes incidence by 58% and 31%, respectively, compared to placebo [51]. Metformin's first-line position was supported by the United Kingdom Prospective Diabetes Study (UKPDS) observation that the metformin-treated group had risk reductions of 32% ($p = 0.002$) for any diabetes-related endpoint, 42% for diabetes-related death ($p = 0.017$), and 36% for all-cause mortality ($p = 0.011$) compared with the control group. The UKPDS demonstrated that metformin is as effective as sulfonylurea in controlling blood glucose levels of obese patients with type 2 diabetes mellitus [52]. Metformin was shown to be effective in normal weight patients also [53].

Glimepiride is a sulphonylurea that stimulates insulin release from beta-cells of pancreas and may also act via extra pancreatic mechanisms. It is administered once daily to patients with type 2 (non-insulin-dependent) DM in whom glycemia is not controlled by diet and exercise alone, and may be combined with insulin in patients with secondary sulphonylurea failure. The greatest lowering effects in blood glucose by glimepiride occur in the first 4 hours after taking the medication. Glimepiride has fewer and less severe effects on cardiovascular variables compared to glibenclamide (glyburide). Pharmacokinetics is mainly unaltered in elderly patients or in patients with renal or liver disease.

Only few drug interactions with glimepiride were documented. In patients with type 2 DM, glimepiride has an effective dosage range of 0.5 to 8 mg/day, although there is little difference in efficacy between dosages of 4 and 8 mg/day. Glimepiride was similar in efficacy to glibenclamide and glipizide in 1-year studies. However, glimepiride appears to reduce blood glucose faster than gliplizide over the first few weeks of treatment. Glimepiride and gliclazide were comparable with good glycaemic control at baseline in a 14-week study that noted no differences between their effects. Glimepiride plus insulin was almost equally effective as insulin plus placebo in helping patients with secondary sulphonylurea failure to reach a fasting blood glucose target level of < or = 7.8 mmol/L, although lower insulin dosages and more rapid effects on glycemia were seen with glimepiride.

In our study 64.8% of Karnataka patients and 78% of Kerala patients were using metformin, while 67.1% of Karnataka patients and 54% of Kerala patients were using Glimepiride. Glimepiride is a relatively safer drug in cases of renal disorders; still the use is less in India. Long acting insulin usage was reported in 3.9% of Karnataka patients and 14% of Kerala patients. Intermediate acting insulin usage was reported in 13.9% of Karnataka and 25% of Kerala patients. Short acting insulin usage was reported in 8.3% of Karnataka and 42% of Kerala patients. Adverse effects due to drugs were reported in 20.4% of Karnataka and 48% of Kerala patients. All the above show statistically significant difference between Karnataka and Kerala patients. No statistically significant difference was observed in antihypertensive usage.

Dyslipidemia is a common problem in diabetics which predisposes to heart disease and vascular complications. The most common pattern of dyslipidemia in type 2 diabetic patients is elevated triglyceride (TG) levels and decreased HDL cholesterol levels. The concentration of LDL cholesterol in type 2 diabetic patients is usually not significantly different from nondiabetic individuals. Diabetic patients may have elevated levels of non-HDL cholesterol (LDL plus VLDL). However, type 2 diabetic patients typically have a preponderance of smaller, denser LDL particles, possibly increasing atherogenicity even if the absolute concentration of LDL cholesterol is not significantly increased. In a technical review of a study [54], the median triglyceride level in type 2 diabetic patients is <200 mg/dl (2.30 mmol/l), and 85–95% of patients have triglyceride levels below 400 mg/dl (4.5 mmol/l).

As in nondiabetic individuals, lipid levels may be affected by factors unrelated to glycemia or insulin resistance, such as hypothyroidism, renal disease, and the genetically determined lipoprotein disorders (e.g., familial combined hyperlipidemia and familial hypertriglyceridemia). These genetic disorders may contribute to the severe hypertriglyceridemia in some patients with diabetes. Use of alcohol and estrogen may also contribute to hypertriglyceridemia. Our study shows that Kerala patients have higher degree of dyslipidemia compared to Karnataka patients. 71.3% of Karnataka patients and 33% of Kerala patients have total cholesterol <200mg/dl. 27.4% of Karnataka patients and 39% of Kerala patients have total cholesterol in range of 200-280 mg/dl, while 28% of Kerala patients have total cholesterol> 280mg/dl, only 1.3% of Karnataka patients have the similar levels. Regarding LDL Cholesterol, 1.3% of Karnataka patients have it >190mg/dl, while 15% of Kerala patients have LDL >190mg/dl. 84.3% of Karnataka patients and 85% of Kerala patients have LDL cholesterol in the range of 70-190mg/dl. Regarding Triglycerides, 43.9% of Karnataka patients and 26% of Kerala patients have triglycerides <150mg/dl. 56.1% of Karnataka patients and 71% of Kerala patients have triglycerides in the range of 150-500mg/dl. Even regarding statin and fibrate usage there are statistically significant differences between Karnataka and Kerala patients.

CONCLUSION:

Our study correlates with other studies of prevalence of hypertension in total but Kerala patients have more than optimal prevalence of hypertension which is a matter of serious concern. Our study shows that risk of higher CVA in Kerala diabetic patients compared to Karnataka patients. Our study reports 20% of Karnataka patients and 11% of Kerala patients have retinopathy which is above normal ranges. Duration of diabetes is related to incidence of retinopathy. Our study shows that nephropathy is much higher than expected number. 27.4% of Karnataka patients and 23% of Kerala patients had nephropathy which is a matter of concern.

Glimepiride is a relatively safer drug in cases of renal disorders; still the use is less in India. Statistically significant differences were observed in antidiabetic drug usage. Adverse effects due to drugs were reported in 20.4% of Karnataka and 48% of Kerala patients. All the above show statistically significant difference between Karnataka and Kerala patients. No statistically significant difference was observed in antihypertensive usage. Kerala patients have more prevalence of dyslipidemia compared to Karnataka patients. Even regarding statin and fibrate usage there are statistically significant differences between Karnataka and Kerala patients. More education regarding comorbidities and encouragement for optimal usage of anti-diabetic medication, antihypertensives and Statins should be done.

LIMITATIONS OF STUDY:

1. The number of patients studied was 330 which is an optimal number. But, large study sample may be required for more statistically significant data and accurate estimation of prevalence.
2. As it is an observational study, no active intervention was done.
3. Patients may be subjected to selection bias as all the patients are diabetic.
4. Recall bias regarding comorbidities, procedures and drugs. The sample would have been prone to non-response bias.
5. The sample was prone to volunteer bias.

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