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RESEARCH ARTICLE

SCREENING TWIN EPIDEMIC IN PAKISTAN; (STEP) STUDY

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ABSTRACT

Objective: The primary objective of the study was to determine the prevalence of diagnosed and undiagnosed diabetes and hypertension in patients from major cities of Pakistan and to identify the associated risk factors.

Method: This cross-sectional STEP study was conducted in seven cities of Pakistan.Diabetes was assessed according to American Diabetes Association 2012 guidelines and hypertension was defined by the Joint National Committee's 7th Report guidelines. Total 884 patients were enrolled from 100 sites. Patient's data including demographics, lifestyle factors, medical history and laboratory diagnostic results were collected by the investigators through study questionnaire.

Result: In this study conducted during November 2013 – January 2015, 884 patients were eligible, of them 55.5% were males and 42.2% were females with a mean age of 48.3 (±12.6) years fromseven sites. However, from those 392 (44.3%) patients had diabetes, out of them 38.3% were known diagnosed cases and 9.7% were newly diagnosed with diabetes. 579 (65.5%) patients were diagnosed with hypertension. Prevalence of hypertension in out-patient was estimated to be 43.9% and the incidence was 38.5%. Prevalence of coexistence diabetes and hypertension was estimated in (40.5%) patients A direct association has been reported among diabetes and hypertension with age, family history of both, cardiovascular risks, along with other co-morbid.

Conclusion: This study suggests that there is a high burden of twin epidemic; Diabetes and hypertension in Pakistan, its coexistence and modifiable cardiovascular risk factors with a poor level of glycemic and blood pressure control.

INTRODUCTION

The burden of chronic diseases including high blood pressure and diabetes is a neglected global health issue worldwide. According to WHO report, in Pakistan mortality rate due to diabetes is approximately 3% whereas 19% deaths are reported due to cardiovascular diseases (World Health Organization, 2016). It has been projected that 422 million adults were identified with diabetes worldwide which shows that the overall prevalence of diabetes has almost folded since 1980, escalating from approximately 4.7% to 8.5% in the adult population (World Health Organization, 2016). This may be due to an increase in associated risk factors such as being overweight or obese. Over the past decade, it is greatly observed that diabetes is highly prevalent in low- and middle-income countries as compared to high-income countries. Diabetes caused four million deaths in 2017 worldwide (IDF Atlas 2017) and surplus 2.2 million deaths were followed due to higher blood glucose levels than the normal optimal range (World Health Organization, 2016). Hypertension being another most important health issue and a leading cause of death in developing countries, it has been estimated that around one-quarter of the world's adult population has hypertension and this is likely to increase to 29% by 2025. Demonstrated forecast points toward an increase to 1.15 billion hypertensive patients by 2025 in developing countries (Mittal, B. V. and Singh, A. K., 2010). Diabetes mellitus and hypertension frequently coexist in many individuals. The possible reason for this may be the common risk factors such as obesity, sedentary lifestyle and poor dietary choices (Opeodu, O. I. and Adeyemi, B. F., 2015). About 75% of diabetic patients are expected to develop hypertension over time because of the activation of the tissue-based renin-angiotensin-aldosterone axis, volume expansion secondary to hyperglycemia, reduced baroreceptor response, loss of circadian rhythm without the normal nighttime depression in blood pressure, endothelial dysfunction and vascular oxidative stress. The proportion at which hypertension co-occurs with diabetes mellitus is such that diabetics are approximately 1.5 - 2 times more likely to develop hypertension as compared to the non-diabetics (Lonati C *et al.,* 2008). Dissimilarity is seen in the co-occurrence of diabetes and hypertension among diverse race, culture and groups of people (Unadike, B. C., *et al.,* 2011; Mansour, A. A., 2012; Akhuemokhan IK, *et al.,* 2008).

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The presence of hypertension in diabetic patients significantly increases the risks of coronary heart disease, stroke, nephropathy, and retinopathy. Mostly hypertension in type 2 diabetic person clusters with other cardiovascular disease risk factors such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulability, increased inflammation and left ventricular hypertrophy. Diabetes mellitus and hypertension are hence referred to as “the bad companions” (Shah and Afzal, 2013). According to local data available, level of awareness at both physicians and patients has been observed to be very low (Hakeem and Fawwad, 2010). Globally diabetes mellitus and hypertension are manageable health conditions and can be controlled by medical intervention and lifestyle modification. Prevention and screening of diabetes and hypertension require a steadfast system not only to collect local data but also to assess and monitor the burden to help design evidence-based local management guidelines (American Diabetes Association, 2012). There is the paucity of current data on the prevalence of diabetes mellitus, hypertension and their coexistence in Pakistan. Although studies have been carried out over the past few decades to estimate the prevalence of diabetes mellitus and hypertension they were often conducted at small-scale and regional or carried out in a particular subset of the Pakistani population (Bahadar *et al.,* 2014). Moreover, in Pakistan, there is a lack of surveillance and timely detection of these epidemics, therefore, need arises to know the representation of diabetes mellitus and hypertension in outpatients setting. Therefore, STEP a nationwide study was conducted to identify the existing prevalence of diagnosed and undiagnosed cases of diabetes mellitus and hypertension visiting primary care physicians and their level of control.

MATERIALS AND METHODS

The STEP study was an observational, cross-sectional, multi-center study carried out in Pakistan during the period of November 2013- January 2015. Data were collected from seven major cities (Faisalabad, Gujranwala, Hyderabad, Karachi, Lahore, Multan, Rawalpindi /Islamabad) of the country. The Aga Khan University Hospital Clinical Laboratory was selected for all investigations. This study was conducted according to the principles laid down by the 18th world medical assembly as per Helsinki, (World Medical Association, 2001) including all subsequent amendments. It was conducted in compliance with all international guidelines and national laws, as well as, any applicable guidelines. A paper-based questionnaire was designed for systematic data collection. Investigators were trained on Good Clinical Practice (GCP) guidelines, protocol and spontaneous adverse event reporting. Each investigator filled the questionnaire for the patient meeting inclusion/exclusion criteria. Consecutive patients visiting clinics were administered screening questionnaires. Eligibility criteria included patient’s age ≥18 years, not pregnant and willing to undergo screening tests. The investigator fully informed the patient about terms and conditions, objectives, constraints, duration, patient’s rights and obtained written and signed informed consent prior to inclusion. The data was forwarded to Sanofi affiliate head office, Karachi for double entry by data punch operator and statistically analyzed using SPSS version 18.0. Categorical variables were reported as percentages, the difference in proportion were assessed using chi-square statistic and continuous variables such as means and standard deviation while the mean differences were assessed using two sample independent "t" test. The prevalence of diagnosed and undiagnosed diabetes was determined according to Standards of medical care in diabetes guidelines (American Diabetes Association. 2012). Patients with previous history of diabetes were considered as “known” diabetic cases and patients who had FBS >126mg/dl on laboratory investigation were considered as “new” diabetic cases. Hypertension was defined by 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian AV., *et al.,* 2003). All hypertensive patients with the previous history were considered as “known” cases, while undiagnosed hypertensive patient without diabetes and/or CKD patients who had BP >140/90mmHg (JNC VII) on clinical examination were considered as “new” cases. Likewise undiagnosed hypertensive patient with diabetes who had BP >130/80mmHg (JNC VII) on clinical examination was also considered as “new” hypertensive cases. BMI was calculated using the weight and height measurements and categorized as: Normal <23 kg/m2, Overweight 23-25 kg/m2 and Obese >25 kg/m2. Waist-hip ratio was calculated using waist and hip circumference measurements according to National Cholesterol Education Program (ATP-III) and Metabolic syndrome was diagnosed on the basis of National Cholesterol Education Program (Grundy, S., et al.,2002).

RESULTS

In this study, 1000 patients were planned as per protocol and after screening total 912 patients were recruited, keeping in view the inclusion/exclusion criteria. While, data on 28 patients were excluded because the fasting plasma glucose (FPG), HbA1c, total cholesterol, microalbuminuria, HDL, LDL, and VDL was not recorded. Therefore, data of 884 patients were analyzed. Off these, 55.8% (n=439) were males and 44.2% (n=391) were females. There mean age was 48.3 (±12.6) years, mean height 163.1 (±12.6 cm), weight 75.4 (±15.1 kg), BMI 28.7 (±9.6 kg/m2), waist circumference 98.5 (±15.2 cm), hip circumference 105.2 (±13.7 cm) and waist-hip ratio (WHR) was 0.93 (±0.1) respectively as shown in Table 1. Almost half of the patients had a family history of diabetes 50.6% (n=447) and hypertension 51.5% (n=455) as shown in Table 2. Overall, 9.5% (n=84) patients had a history of ischemic heart disease (IHD), 4.9% (n=43) patients had a history of myocardial infarction with prevalence being significantly higher in men compared to women, 2.1% (n=19) have a history of stroke and 15.2% (n=134) were either current or past smokers while only 1.2% (n=11) patients had history of alcohol consumption. Prevalence of Diabetes in out-patient settings was estimated as 38.3% (95% CI: 35.2 – 41.6). The incidence of newly diagnosed diabetic patients in the same settings was 9.7% (95% CI: 7.5 – 12.5) as shown in Table 3. There were 44.8% (n=221) male and 43.7% (n=171) female with diabetes and 61.5% (n=303) were male and 70.6% (n=276) female with hypertension in the study population as shown in Table 4. Co-existence of Diabetes and hypertension were more found in females 41.4% (n=162) as compared to males i.e. 39.8% (n=196). Table 5 discussed the burden of hypertension where almost half 43.9%, (95% CI: 40.6 – 47.1) of the study patients were prevalent to hypertension irrespective of any history of diabetes mellitus while many more 38.5% (95% CI: 34.2 – 42.8) were newly added cases. Prevalence of other cardiovascular risk factors along with dyslipidemia are given in table 6.

Table1. Baseline characteristics by Gender

Parameters	Male (n=493)		Female (n=391)		p-value	All (n=884)	
	Mean	± SD	Mean	± SD		Mean	± SD
Age (years)	48.2	13.1	48.5	12.1	0.687	48.3	12.6
Height (cm)	168.7	10.6	155.9	11.3	<0.01	163.1	12.6
Weight (kg)	79.2	14.6	70.4	14.4	<0.01	75.4	15.1
Body Mass Index (kg/m^2)	28.1	8.1	29.5	11.1	0.027	28.7	9.6
Waist circumference (cm)	98.9	13.6	98.1	17.0	0.450	98.5	15.2
Hip circumference (cm)	104.1	12.4	106.5	15.1	0.010	105.2	13.7
Waist-to-hip Ratio (WHR)	0.95	0.1	0.92	0.1	0.001	0.93	0.1

Table 2. Medical History of Study Population

	Male (n=493)		Female (n=391)		p-value	All(n=884)	
	n	(%)	n	(%)		n	(%)
Ischemic Heart Disease	59	(12.0)	25	(6.4)	0.019	84	(9.5)
Myocardial infarction	32	(6.5)	11	(2.8)	0.012	43	(4.9)
Stroke	10	(2.0)	9	(2.3)	0.527	19	(2.1)
Family history of diabetes	242	(49.1)	205	(52.4)	0.030	447	(50.6)
Family history of hypertension	255	(51.7)	200	(51.2)	0.496	455	(51.5)
Smoking	129	(26.2)	5	(1.3)	<0.01	134	(15.2)
Alcohol consumption	10	(2.0)	1	(0.3)	0.018	11	(1.2)

Table 3. Burden of Diabetes

	N	n *	(%)	(95% C.I)
Prevalence	884	339	38.3	(35.2 – 41.6)
Incidence	545	53	9.7	(7.5- 12.5)

*Subjects with Diabetes irrespective of status of hypertension

Table 4.Prevalence of Diabetes and Hypertension

	Male (n=493)		Female (n=391)		p-value	All(n=884)	
Prevalence	n	(%)	n	(%)		n	(%)
Diabetes (Known + New)	221	(44.8)	171	(43.7)	0.667	392	(44.3)
Hypertension (Known + New)	303	(61.5)	276	(70.6)	0.012	579	(65.5)
Diabetes and Hypertension							
Only Diabetes	25	(5.1)	9	(2.3)	000.7	34	(3.8)
Only Hypertension	107	(21.7)	114	(29.2)		221	(25.0)
Diabetes + Hypertension	196	(39.8)	162	(41.4)		358	(40.5)

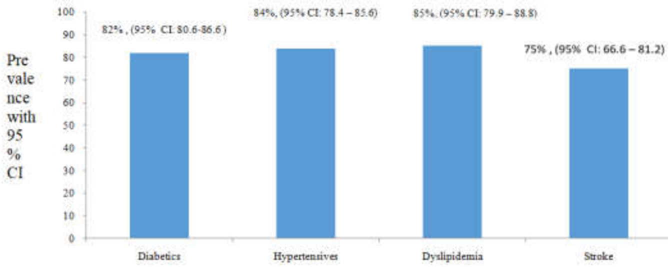
Table 5. Burden of Hypertension

	N	n *	(%)	(95% C.I)
Prevalence	884	388	43.9	(40.6 - 47.1)
Incidence	496	191	38.5	(34.2 – 42.8)

Table. 6. Prevalence of Cardiovascular Risk Factors

	Male (n=493)		Female (n=391)		p-value	All(n=884)		(95% CI)
CV Risk Factors	n	(%)	n	(%)		n	(%)	
Obesity								
Normal BMI (<23 kg/m^2)	75	(15.2)	63	(16.1)	0.7	138	(15.6)	(13.3 – 18.1)
Overweight BMI (23 -25 kg/m^2)	63	(12.8)	105	(26.8)	<0.01	168	(19.0)	(16.5 – 21.7)
Obese (>25 kg/m^2)	355	(72.0)	286	(73.1)	0.7	641	(72.5)	(69.4 – 75.3)
Truncal Obesity	365	(74.0)	354	(90.5)	<0.01	719	(81.4)	(78.6 – 83.7)
Dyslipidemia	135	(27.4)	116	(29.7)	<0.01	251	(28.4)	(25.5 – 31.4)
MetabolicSyndrome	170	(34.5)	202	(51.7)	<0.01	372	(42.1)	(38.8 – 45.3)
Microalbuminuria	371	(75.3)	306	(78.3)	0.2	677	(76.6)	(73.6 – 79.2)

Total 72% (n=355) males and 73.1% (n=286) females were obese (BMI > 25 kg/m2), 12.8% (n=63) males and 26.8% (n=105) females were overweight (BMI 23-25 kg/m2). Significantly more women 90.5% (n=354) had abdominal or truncal obesity as compared to males 74% (n=365). Prevalence was significantly higher in women 51.7% (n=202) as compared to men 34.5% (n=170) with metabolic syndrome. There was no significant difference in microalbuminuria among both genders. According to the results given in Figure 1, the prevalence of abdominal obesity in diabetics was {(n=392) 82%, 95% CI: 80.6 – 86.6} , {(n=579) 84%, 95% CI: 78.4 – 85.6} in hypertensive group, {(n=251) 85%, 95% CI: 79.9 – 88.8} with dyslipidemia and {(n=134) 75%, 95% CI: 66.6 – 81.2} patients were observed with smoking history. It was also observed that 29.8% (n=98) of the diabetic patients were on monotherapy, 33.2% (n=109) on dual therapy, 12.5 % (n=41) patients were on insulin and only 8.8% (n=29) patients were on triple therapy for therapeutic management of diabetes as shown in Figure 2. All known hypertensive patients were on anti-hypertensive medication, of them 52.3% (n=203) were on monotherapy, 38.1% (n=148) on dual therapy, 6.7% (n=26) were on triple therapy while only 2.8% (n=11) of the patients were on >3 drugs therapy as shown in figure 3.



CI= Class Interval

Figure1. Prevalence of abdominal obesity in subgroups based on Waist-to-Hip ratio

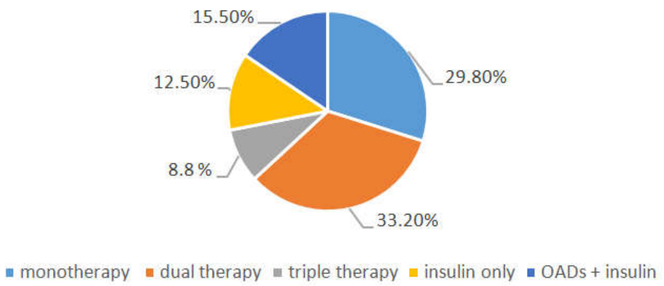


Figure 2. Therapeutic management of known Diabetes

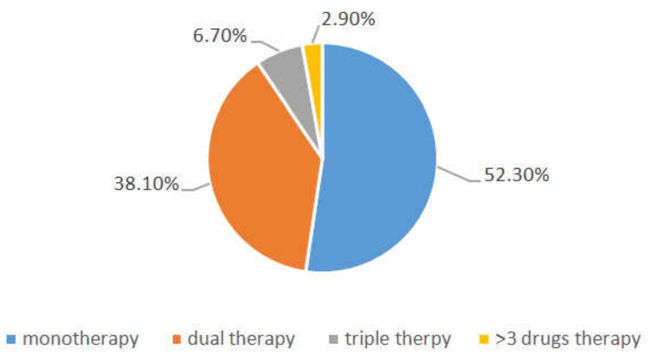


Figure 3. Therapeutic management of known Hypertensive

DISCUSSION

The STEP study was conducted to estimate the prevalence of diabetes mellitus and hypertension (diagnosed and undiagnosed). The study was conducted in seven different cities of Pakistan and the pooled analyses are from a representative sample of the Pakistani population. Diabetes mellitus is a major problem relating public health with multiple complications and increasing prevalence (Meo *et al.,* 2016). According to the World Health Organization (WHO), Diabetes will be the seventh leading cause of mortality by the year 2030(World Health Organization, 2011). According to this study, the prevalence of diabetes in Pakistani population was approximately 38.3%, it was found more prevalent in males as compared to females as given in table 4. However, these findings are also supported by other epidemiologic studies which show the increased prevalence of diabetes in males 11.20% as compared to females 9.19% (Meo *et al.,* 2016). A higher proportion of the study population was diagnosed with hypertension as compared to diabetes as given in table 4. Moreover, the prevalence of hypertension is found to be significantly higher in the patients with non-insulin-dependent diabetes mellitus (NIDDM or type II DM). The two diseases diabetes mellitus and hypertension coexist in 40.5% patients. However, it was quite visible that more patients had both diabetes and hypertension as compared to diabetes or hypertension alone as shown in table 4. A number of reasons for this association may be insulin resistance, aging, obesity and increased use of thiazide diuretics in subjects with hypertension (Aziz 2015; Shah and Afzal, 2013). Cardiovascular risk factors that were prevalent in the study population as shown in table 6, a high prevalence of obesity was observed in diabetic patients. There was a significantly greater proportion of obese patients amongst known hypertensive as compared to normotensive patients. Prevalence of obesity among different populations worldwide is increasing each year which makes obesity an important risk factor for diabetes (Wild *et al.,* 2004).

In diabetic patients control of hyperglycemia is an important aspect, but the morbidity and mortality rate may further decline by controlling other cardiovascular risk factors rather than controlling glucose only. In this cross-sectional study higher study population receiving treatment of diabetes, were on monotherapy as compared to dual and triple therapy. Initially, monotherapy is used for treatment purposes but it may be worth initiating treatment with a combination therapy since disease recovery rate is less with the use of monotherapy. However, combination of drugs like Dipeptidyl peptidase-4 (DPP 4) inhibitor and Biguanides is known to be associated with an improved glycemic control in patients with type 2 Diabetes Mellitus (Khardori and Griffing, 2011). All patients with hypertension were on anti-hypertensive medication out of which majority were on monotherapy, while few were on dual and triple therapy as shown in figure 3. Monotherapy effectively reduces BP in most patients with mild hypertension (Egan *et al.,* 2012). Combination therapy is a mainstay of hypertension treatment and for adequate BP control, a substantial proportion of patients require triple-combination therapy. In recent years, several single-pill, triple-combination therapies have become available but these combinations are not effective for all cases (Neutel and Smith, 2013; Beckett *et al.,* 2008).

The risk factors like congestive heart failure (CHF), end-stage renal disease (ESRD), stroke and coronary artery disease are known to be associated with hypertension. The outbreak of a number of microvascular and macrovascular diseases is usually in response to the co-existence of hypertension and diabetes mellitus. However, hypertension markedly increases the risk for cardiovascular diseases (CVD) and mortality especially in patients with type 2 diabetes mellitus. Previous family history of either diabetes mellitus or hypertension is one of the most important cause for the increased disease susceptibility among these patient. Recently a prompt rise in the prevalence of diabetes mellitus and hypertension is observed in Pakistan that may be due to genetic predisposition, environmental factors like gender, urbanization, obesity and sedentary lifestyles particularly in middle age or cultural practices promoting sedentary lifestyle especially in females (Aziz, 2015). This STEP study suggests that there is a high burden of twin epidemic; diabetes mellitus and hypertension in Pakistan. Cardiovascular risk factors leading to diabetes mellitus and hypertension are highly prevalent and are modifiable with lifestyle changes (Chobanian *et al.,* 2003).

Control of these cardiovascular risk factors is essential to minimize the burden of diabetes mellitus and hypertension and their complications in the local population.

Limitations

The study was limited to outpatient clinics in urban cities of Pakistan. Hence, the observations and conclusions of this study may not be extrapolated to the rural population. Nevertheless, two-thirds of the investigators were physicians with the general practice which would reflect the first point of care. Accordingly, the results are a reflection of the patients in the urban community.

CONCLUSION

The STEP study demonstrated a high burden of diabetes mellitus, hypertension, its coexistence and modifiable cardiovascular risk factors with a poor level of glycemic and blood pressure control. Despite the limitations mentioned above, the study provides valuable information from a large population representative of Pakistan. This can be useful in improvement of management of diabetes and hypertension as well as in the formulation of strategies and guidelines for the control of such health risks globally.

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