ORIGINAL ARTICLE

Association of Impaired Fasting Glucose with Hypertension

Naheed Gul[1], Azra Parveen[3], Neelum Zaka[1] and Mehwish Rafique[2]

ABSTRACT

Objective: To evaluate the association of impaired fasting glucose (IFG) with hypertension in Pakistani population.
Study Design: A cross-sectional, analytical study.
Place and Duration of Study: Shifa Community Health Centre, Islamabad from December 2016 to July 2017.
Methodology: One hundred and eighty-seven hypertensive patients were included in the study, using consecutive sampling technique. Demographic, anthropometric, and laboratory data of the patients were recorded. Continuous variables were expressed as mean + SD and categorical variables as numbers and percentages. Differences among males/females and between hypertensive patients with normal, impaired fasting glucose and diabetes for risk factors were analysed, using independent sample t-test, ANOVA and chi-square test using SPSS version 24.
Results: The mean age of patients was 52.98 $\pm$11.22 years. Females were 69.9% and males 30.1%. The total frequency of IFG in patients with hypertension was 42.6% and new onset diabetes 12.5% showing its close association with hypertension. There was no significant difference between males and females for risk factors (age, BMI, blood pressure, total cholesterol, LDL-cholesterol, and HDL-cholesterol) except for more education, smoking, and high triglyceride in males. There was no significant difference among hypertensive patients with normal, impaired fasting glucose and diabetes for risk factors (gender, BMI, blood pressure, total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol and family history) except for smoking.
Conclusion: The significant association of impaired fasting glucose with hypertension necessitates early screening for impaired fasting glucose.

Key Words: *Hypertension, Impaired fasting glucose, Diabetes, Obesity, Hyperlipidemia.*

INTRODUCTION

Type 2 diabetes is a global health problem and its prevalence is gradually increasing. Worldwide, 415 million people are affected with diabetes and it is estimated that this number will grow to 642 million by year 2040, unless measures are taken to control the disease. In Pakistan 6.9 million people are being affected.[1]

Diabetes mellitus has prolonged intermediate phase known as prediabetes characterised by impaired fasting glucose and impaired glucose tolerance.[2] IFG is an intermediate state of hyperglycemia in which glucose levels are not high enough to meet criteria for diabetes but are too high to be considered normal.[3] WHO criteria for IFG differs from ADA criteria. WHO criteria define IFG as fasting plasma glucose level from 6.1 mmol/l (110 mg/dl) to 6.9 mmol/l (125 mg/dl); while according to the ADA criteria, it is from 5.6 mmol/l (100 mg/dl) to 6.9 mmol/l (125 mg/dl).

IFG is considered among categories of increased risk for diabetes.[4] It is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease.[5] Individuals with IFG levels have a 20-30% chance of developing diabetes over the next 5-10 years.[6] They are at increased risk of developing cardiovascular complications independent of progression to diabetes mellitus.[7] ADA recommends screening of all adults at the age of 45 years to detect diabetes. Those who are overweight or obese (BMI $\geq$25 Kg/m^2) and who have one or more additional risk factors for diabetes, like family history of diabetes (especially in the first degree relatives), race/ethnicity, previous impaired glucose tolerance or IFG, history of gestational diabetes or delivery of baby weighing more than 9 pounds, hypertension, dyslipidemia with HDL cholesterol <35 mg/dl (0.90 mmol/L) or triglyceride level >250 mg/dl (2.82 mmol/l), and polycystic ovarian syndrome should be screened at any age. Either HbA1C, fasting plasma glucose or 2-hour OGTT can be used for screening purposes.[4] Screening targeted to individuals with hypertension has been found to be more cost-effective than universal screening.[8]

Studies published in literature have shown varying degrees of prevalence of IFG in hypertensive patients. In one study, the prevalence of IFG was 13% according to WHO criteria and 33% according to ADA criteria.[9] In another study conducted in China, IFG was found in 26% of hypertensive patients according to ADA criteria and 9.7% according to WHO criteria.[10] However, the data from Pakistan is limited. One study has shown the prevalence of IFG to be 8.7% according to WHO criteria.[11]

Identifying IFG in hypertensive patients can have important implications for treatment and resultant

[1] *Department of Medicine / Statistician[2], Shifa College of Medicine, Islamabad, Pakistan.*
[3] *Department of Infectious Diseases, Shaukat Khanum Memorial Hospital, Lahore, Pakistan.*
Correspondence: Dr. Naheed Gul, Department of Medicine, Shifa College of Medicine, Sector H-8/4, 44000, Islamabad, Pakistan.
E-mail: doctornaheed@live.com
Received: February 15, 2018; Accepted: June 20, 2018.

reduction in cardiovascular morbidity.[12] Patients with impaired fasting glucose can reduce the risk of developing diabetes by changing their lifestyle and reducing weight.[13] Hypertensive patients with IFG and those who have other risk factors for diabetes, should also be on metformin in addition to lifestyle modifications.[14] Chances of developing diabetes have been known to decrease by as much as 58% as a result of these interventions.[12]

To identify patients in whom diabetes can be prevented by using lifestyle modifications and medical treatment, will help in reducing the economic burden of diabetes on the patients and on the country as a whole. Furthermore, the effect of confounding factors like obesity, hyperlipidemia, family history, gestational diabetes, and smoking in hypertensive patients with IFG was studied.

The aim of this study was to determine the association of IFG with hypertension in Pakistani patients.

METHODOLOGY

This cross-sectional analytical study was conducted at the Outpatient Department, Shifa Foundation Community Health Centre of Shifa International Hospital, Islamabad, from December 2016 to July 2017. Hypertensive patients aged 30 years and above, with no other comorbidities, were included. Patients with diabetes, Cushing syndrome, acromegaly, pheochromocytoma and those who are pregnant or taking steroids were excluded from the study. Sample size was calculated as 123, considering confidence level of 95%, absolute precision 0.5%, and anticipated population proportion p=8.7%.[11] Consecutive sampling (non-probability) technique was used and out of 187, 136 patients who fulfilled the inclusion criteria, were included in this study which was close to the estimated sample size.

Institutional Review Board approval was obtained before starting data collection. Written informed consent was taken and a proforma was filled for each patient. This included demographic information like patient's medical record number, age, gender, address, and education level. Relevant history was taken regarding smoking, family history of diabetes in first-degree relatives, drug history, and history of gestational diabetes. Blood pressure was measured with a mercurial sphygmomanometer, with the subjects in sitting position. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After an overnight fast of at least eight hours, blood samples were collected in sodium fluoride/ potassium oxalate containers. Blood lipids and glucose were analysed enzymatically on an auto analyser (Selectra Junior, Merck).

IFG was defined as fasting plasma glucose level from 5.6mmol/l (100 mg/dl) to 6.9 mmol/l (125 mg/dl). In patients with glucose level ≥126 mg/dl, the test was repeated on another day. If the test result remained high (≥126 mg/dl), a diagnosis of diabetes was made. Blood pressure <140/90 mmHg was considered as controlled hypertension. Stage 1 hypertension was defined as systolic blood pressure of 140-159/90-99 mmHg. Blood pressure ≥160/100 mmHg was defined as Stage 2 hypertension. Overweight was defined as BMI ≥25 to 29 kg/m^2 and obesity as BMI ≥30 kg/m^2.

Data was analysed using statistical package SPSS version 24. Continuous variables were expressed as mean + SD and categorical variables were expressed as numbers and percentages. Frequency of IFG and newly diagnosed diabetes was calculated according to age groups, gender, smoking, family history of diabetes, history of gestational diabetes in females, stage of hypertension, BMI, and hyperlipidemia. The differences between different groups (Males/Females, those with normal fasting glucose/IFG/diabetes) for risk factors were seen using the independent sample t-test,

Table I: Demographic and anthropometrical characteristics of patients (percentages given out of 100 for each group in parenthesis).

Variables	Men n=41	Women n=95	p-value
Age	54.73 ±12.46	52.23 ±10.62	0.23
Cholesterol mg/dl	171.09 ±42.63	176.27 ±43.99	0.52
TG mg/dl	164.58 ±72.37	137.11 ±63.64	0.02
LDL mg/dl	109.43 ±36.55	113.76 ±37.33	0.53
HDL mg/dl	32.54 ±6.84	36.12 ±11.61	0.06
Educational status			<0.001
Uneducated	12 (29.3)	59 (62.1)	
Educated	29 (70.7)	36 (37.9)	
Smoking status			<0.001
Non-smokers	27 (65.9)	90 (94.7)	
<10 pack year	13 (31.7)	4 (4.2)	
>10 pack year	1 (2.4)	1 (1.1)	
Family history			0.43
Yes	10 (24.4)	32 (33.7)	
No	31 (75.6)	63 (66.4)	
Gestational diabetes			<0.001
Yes	-	2 (2.1)	
No	2 (4.9)	91 (95.8)	
Not applicable	39 (95)	2 (2.1)	
Drug history			0.05
Beta blocker	3 (7.3)	6(6.3)	
ACE inhibitors/ARB	9 (22.0)	42 (44.2)	
Ca. channel blockers	4 (9.8)	15 (15.8)	
Combination	18 (43.9)	24 (25.3)	
No medication	7 (17.1%)	8 (8.5%)	
BSF(mg/dl)			0.22
<100	23 (56.1)	38 (40)	
101-125	14 (34.1)	44 (46.3)	
>126	4 (9.8)	13 (13.7)	
B.P (mmHg)			0.16
<140/90	11 (26.8)	41 (43.2)	
140-159/90-99	17 (41.5)	34 (35.8)	
160/100	13 (31.7)	20 (21.1)	
BMI (kg/m^2)			0.10
<25	19 (46.3)	27 (28.4)	
25-29	12 (29.3)	31 (32.6)	
>30	10 (24.4)	37 (38.9)	

chi square-test, and ANOVA as appropriate. P-values less than 0.05 were considered as statistically significant.

RESULTS

This study initially enrolled 187 patients. One hundred and thirty-six patients, who fulfilled the inclusion criteria, were included. Fifty-one patients were excluded. Females were 95 (69.9%) and males 41 (30.1%). Baseline characteristics of patients are shown in Table I. The mean age of the patients was 52.98 ±11.22 years. The frequency of IFG in patients with hypertension was 58 (42.6%) and that of newly diagnosed diabetes 17 (12.5%), according to the ADA criteria. Patients with normal glucose levels were 61 (44.9%).

Females were less-educated as compared to males. They were non-smokers, had more use of single antihypertensive medication and history of gestational diabetes. However, high triglycerides, use of combination of antihypertensive medication and smoking were more common in males. There was no statistically significant gender difference with respect to IFG, diabetes, total cholesterol, BMI, positive family history, stage of hypertension, LDL-cholesterol and HDL-cholesterol, levels.

Characteristics of patients with IFG and diabetes compared to patients with normal glucose levels are shown in Table II. Hypertensive patients with IFG and diabetes were more likely to be non-smokers. However, no statistically significant difference was found with respect to mean age, gender, education, total cholesterol, LDL-cholesterol, triglycerides, stage of hypertension, BMI, HDL-cholesterol, positive family history, and history of gestational diabetes (in women) showing that hypertension itself was an independent risk factor for IFG in the absence of other confounding risk factors. The frequency of IFG and diabetes by stage of hypertension was analysed (Figure 1). Patients with stage 1 and stage 2 hypertension had no statistically significant high risk of IFG and diabetes compared to those with normal blood pressure (p=0.90). The incidence of both IFG and diabetes increased after age 45. However, after age 60, the incidence gradually decreased.

Most of the patients were using single medicine, mostly an angiotensin converting enzyme inhibitor/angiotensin receptor blockers. Patients using combination therapy were using either angiotensin converting enzyme inhibitor and calcium channel blockers or angiotensin converting enzyme inhibitor and beta blocker. Effect of diuretic medications was not analysed as only 3 patients were using these in combination with other medicines.

Table II: Characteristics of hypertensive patients with normal glucose, IFG and diabetes. (percentages given out of 100 for each group in parenthesis).

Variables	Normal Glucose n=61	IFG n=58	Diabetes n=17	p-value
Age (years)	53.66 ±12.07	51.39 ±10.28	56.00 ±10.87	0.27
Cholesterol mg/dl	165.73 +34.69	180.00 ±49.54	188.88 +45.64	0.07
LDL mg/dl	105.82 ±29.89	118.64 ±40.31	115.23 ±45.93	0.16
HDL mg/dl	34.47 ±13.71	35.43 ±6.88	35.76 ±7.48	0.84
TG mg/dl	136.42 ±70.43	146.12 ±64.62	175.12 ±59.23	0.11
Gender				0.22
Male	23 (37.7)	14 (24.1)	4 (23.5)	
Female	38 (62.3)	44 (75.9)	13 (76.5)	
Educational status				0.59
Uneducated	29 (47.5)	33 (56.9)	9 (52.9)	
Educated	32 (52.5)	25 (43.1)	8 (47.1)	
Smoking				0.02
Non-smokers	46 (75.4)	55 (94.8)	16 (94.1)	
<10 pack years	13 (21.3)	3 (5.2)	1 (5.9)	
>10 pack years	2 (3.3)			
BP (mmHg)				0.90
<140/90	25 (41)	22 (37.9)	5 (29.4)	
140-160/90-99	23 (37.7)	21 (36.2)	7(41.2)	
>160/100	13 (21.3)	15 (25.9)	5 (29.4)	
Family history				0.22
Yes	16 (26.2)	17 (29.3)	9 (52.9)	
No	45 (73.7)	41 (70.7)	8 (47.1)	
History of gestational diabetes			0.28	
Yes	1 (1.6)	-	1 (5.9)	
No	38 (62.3)	43 (74.1)	12 (70.6)	
Not applicable	22 (36.1)	15 (25.9)	4 (23.5)	
BMI Kg/m^2				0.43
<25	22 (36.1)	21 (36.2)	3 (17.6)	
25-29	20 (32.8)	15 (25.9)	8 (47.1)	
>30	19 (31.1)	22 (37.9)	6 (35.3)	

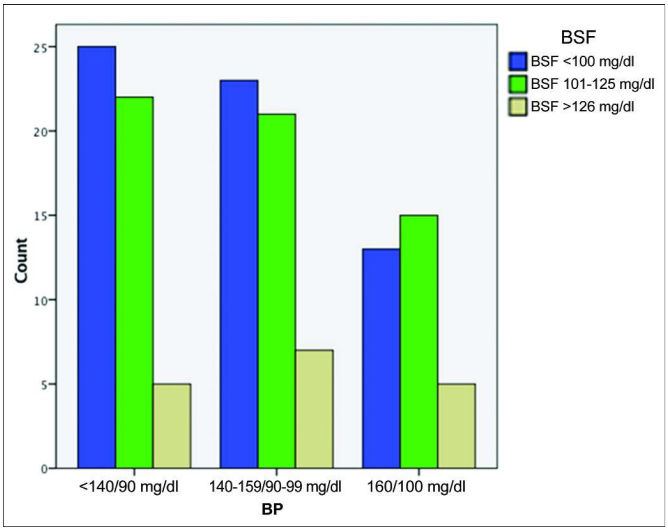

Figure 1: Stage of hypertension and patients with IFG.

DISCUSSION

The frequency of both IFG and newly-diagnosed diabetes is very high in patients with hypertension in Pakistani population. The frequency of IFG was 42.6% and diabetes was 12.5%, according to the ADA criteria. This is very high compared to a previous study which showed prevalence of 8.7 % for IFG and 5% for diabetes in patients with hypertension.[11] This indicates that the frequency of of IFG and diabetes in patents with hypertension has increased tremendously over the last decade. These results are comparable to China, where it is 40.7% for IFG and 15.3% for diabetes in patients with hypertension.[15] This also endorses the IDF estimates which indicate, that 75% of the 8.8% adults with diabetes are in developing countries.[1] In general population, the prevalence of IFG is found to be 5.61% and that of diabetes 13.14% in Pakistan.[16] When considered in patients with hypertension, as shown in our study, the frequency of IFG is 7 to 8 fold higher; while that of diabetes almost the same.

Other confounding factors for IFG and diabetes were also analysed. For hyperlipidemia, although the total cholesterol, LDL cholesterol, and triglycerides were more in the IFG and diabetes group compared to normoglycemic group, the results were not statistically significant (Table II). Furthermore, there were more overweight (47.1% *vs*. 32.8%) and obese patients (35.3% *vs*. 31.1%) in the diabetes group compared to normal, but the results were statistically not significant (p=0.43). These findings are not consistent with those of previous studies which showed significantly association of total cholesterol levels, low HDL cholesterol, high levels of triglycerides and obesity (p <0.05) with IFG and diabetes.[15,17] This reflects that hypertension on its own is a major risk factor for impaired glucose levels. Family history and gestation diabetes were more common in patients with diabetes compared to normoglycemic group. However, there was no meaningful difference among the three groups (p=0.22 and 0.28, respectively) compared to studies which showed family history to be significantly associated with diabetes.[17] IFG was present in 10% with family history of diabetes compared to 2% in those with no family history.[13] Although the frequency of IFG and diabetes was very high in patients with hypertension, the patients with high values for BMI, blood pressure, total cholesterol, LDL cholesterol and low HDL cholesterol, high levels of triglycerides and female gender did not correlate well with high risk of having IFG or diabetes. These findings could be due to the relatively small sample size and secondly because only IFG and newly diagnosed cases of diabetes, were included in the study, missing out the impact of already known cases of diabetes, which could have affected the outcome.

There was no significant difference between males and females for risk factors (age, BMI, blood pressure, total cholesterol, LDL-cholesterol and HDL-cholesterol). However, the males were more educated, smokers and had high triglyceride levels. IFG was more common in women compared to men, but the results were not statistically significant. The overall prevalence of cardiovascular risk factor like hypertension, diabetes and hyperlipidemia is high in Pakistan,[16,18] and the same reflected in the present study.

In this study, the different stages of hypertension did not correlate well with IFG and diabetes. These results were clinically significant in concordance to previous study in China,[15] but in contradiction to another study which showed that at high blood pressures there was more risk of IFG and diabetes (37.2% in patients with normal blood pressure, 61.4% in stage 1 hypertension and 63.5% in stage 2 hypertension).[19] The possible reason for this could be the fact that the number of patients in the three groups that is mild, moderate and severe hypertension, were not equal, with more patients being in the mild to moderately controlled group compared to those with severe hypertension in this study.

Smoking was consistent with low prevalence of IFG and diabetes comparable to one study, where smoking was reported as 35.5% in patients with IFG compared to 36.9% in patients with normal glucose levels.[15] Another study reported diabetes in 33.7% nonsmokers as compared to 27.8% smokers.[17] In contradiction, other studies have shown a relative risk of diabetes to be 1.2 and 1.38, respectively. However, these studies are done in general population.[20,21] This finding may be due to the fact that the number of smokers were few (13.97%) in this study and also in another study (13.4%) compared to non-smokers showing less diabetes in non-smokers.[17] Another reason that could explain this observation in this study could be that most of our patients were females and females usually smoke less as compared to males in the local cultural setup.

Effect of diuretics was difficult to establish with IFG and diabetes, compared to previous studies which considered thiazide diuretics as cause of hypertension,[22] as only few patients in our study were on diuretics; so it is difficult to generalise the findings.

This was a small scale hospital-based cross-sectional analytical study with relatively small sample size. Large, community-based studies are required to know the magnitude of the IFG and diabetes in patients with hypertension as the prevalence of pre-diabetes and diabetes is gradually increasing in general population in Pakistan. Patients with known diabetes were not included in the study, which could have led to underestimation of results. HBA1c levels were not checked which could have resulted in overestimation of results.

CONCLUSION

Impaired fasting glucose and undiagnosed diabetes is closely associated with hypertension in the studied population. All patients coming to the outpatient department with high blood pressure should be screened for IFG/diabetes and associated risk factors in order to provide individualised healthcare plan for every patient with hypertension.

REFERENCES

1. International Diabetes Federation. Diabetes Atlas 2015, 7th ed. Available online: https://www.idf.org/e-library/diabetes-atlas/13-diabetes-atlas-seventh-edition.html
2. Ranlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes: implications for clinical practice. *Prim Care* 1999; **26**: 771-89.
3. Nicholas GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes Care* 2007; **30**:228-33.
4. American Diabetes Association. Standard of medical care in diabetes-2011. *Diabetes Care* 2011; **34** Suppl 1: S11.
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005; **28**: S37-S42.
6. Bock G, Dalla Man C, Campioni M, Chitttilapilly E, Basu R, Yoffolo G, *et al*. Mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 2006; **55**: S3536-49.
7. Robinson SJ, Gordon SA, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. *Diabetes* 2003; **52**:2867-73.
8. Hoerger TJ, Harris R, Hicks KA. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. *Ann Intern Med* 2004; **140**:689.
9. Dellomo G, Penno G, Prato SD, Mariani M, Pedrinelli R. Dysglycemia in non-diabetic hypertensive patients: comparison of the impact of two different classifications of impaired fasting glucose on the cardiovascular risk profile. *J Hum Hypertens* 2009; **23**:332-8.
10. Sun Z, Zheng L, Xu C, Zhang X, Li J. Prevalence of diabetes and impaired fasting glucose in hypertensive adults in rural China. *Acta Cardiol* 2009; **64**:351-6.
11. Ram K, Masroor M, Qamar R, Ahmed I, Sattar A, Imran K, *et al*. Frequency of impaired glucose tolerance in hypertensive patients. *Pak Heart J* 2005; **38**:46-51.
12. Obgu I, Neboh CI. The prevalence of prediabetes among hypertensive patients in Enugu, southeast Nigeria. *Niger Med J* 2009; **50**: 14-7.
13. Shaikh MA, Kumar R, Ghori RA. Comparison of impaired fasting glucose in young healthy individuals with diabetic and non-diabetic first degree relatives. *J Coll Physcians Surg Pak* 2010; **20**:499-501.
14. American College of Endocrinology Consensus statement on the diagnosis and management of Prediabetes. *Endocr Pract* 2008; **14**:933-46.
15. Yu S, Sun Z, Zheng L, Guo X, Yang H, Sun Y. Prevalence of diabetes and impaired fasting glucose in hypertensive adults in rural China: Far from leveling-off. *Int J Environ Res Public Health* 2015; **12**:14764-79.
16. Zafar J, Bhatti F, Akhter N, Rasheed U, Bashir R, Humayun S, *et al*. Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. *JPMA* 2011; **60**:40-7.
17. Zafar J, Nadeem D, Khan SA, Jawad Abbasi MM, Aziz F, Saeed S. Prevalence of diabetes and its correlates in urban population of Pakistan: A cross-sectional survey. *JPMA* 2016; **66**:922-7.
18. Ahsan S, Ahmed SD, Jamali SN, Imran M, Saifulhaq M, Qasim R. Frequency and risk of metabolic syndrome in prediabetics versus normal glucose tolerant subjects – a comparative study. *JPMA* 2015; **65**: 496-500.
19. Nayak B.S, Sobrian A, Latiff K, Pope D, Rampersad A, Lourenço K, *et al.* The association of age, gender, ethnicity, family history, obesity and hypertension with type 2 diabetes mellitus in Trinidad. *Diabetes Metab Syndr* 2014; **8**:91-5.
20. Sun K, Liu D, Wang C, Ren M, Yang C, Yan L. Passive smoke exposure and risk of diabetes: A meta-analysis of prospective studies. *Endocrine* 2014; **47**:421-7.
21. Akhter S, Goto A, Mizoue T. Smoking and risk of type 2 diabetes in Japan: a systematic review and meta-analysis. *J Epidemiol* 2017; **27**; 553-61.
22. Zillich AJ, Garg J, Basu S, Bakris G.L, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: A quantitative review. *Hypertension* 2006; **48**:219-24.