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Hypertension in type 2 diabetes mellitus in Isfahan, Iran: Incidence and risk factors

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Abstract

Background: Evidence on the long-term incidence of and risk factors of hypertension in diabetic patients is scarce and mainly derived from studies in developed countries. Evidence from developing countries is required for planning a well-co-ordinated approach to this public health problem in these countries.
Objective: The objectives of present study were to estimate the incidence of and risk factors for the development of hypertension in people with type 2 diabetes mellitus using routinely collected data from a clinical information system at Isfahan Endocrinology and Metabolism Research Centre, Iran.
Method: During the mean (standard deviation (S.D.)) follow-up period of 2.9 (2.5) (range 1–11) years, 3202 diabetic patients (1315 male and 1887 female) from Isfahan Endocrinology and Metabolism Research Centre out patient clinics, Iran have been examined. The mean (S.D.) age of participants was 48.3 (10.6) years with a mean (S.D.) duration of diabetes of 6.5 (6.7) years at initial registration. Blood pressure was measured by standardised protocols, and hypertension was defined as at least in two consecutive measurements within 2 months a systolic and/or diastolic blood pressure of $\geq$130 and/or $\geq$80 mmHg and/or taking anti-hypertensive medication.
Results: Among the 3202 patients free of hypertension at initial registration who attended the clinic at least twice in the period 1992–2004, the incidence of hypertension was 20.8 (20.6 male and 20.9 female)) per 100 person-years based on 9403 person-years of follow-up. The age-adjusted incidence rate of hypertension was 22% lower among insulin-treated than non-insulin-treated type 2 diabetes mellitus clinic attenders and it was greater with older age. Using a Cox's Proportional Hazards Model, male gender, and treatment regimen were significant independent predictors of hypertension. Smoking, duration of diabetes, age at diagnosis of diabetes, fasting blood glucose, glycosylated haemoglobin, BMI, proteinuria and creatinine, had no significant independent association with hypertension when other covariates were considered.

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Conclusion: These findings will help the identification of those patients at particular risk of hypertension and strongly support the case for vigorous control of blood pressure on type 2 diabetic patients.

Keywords: Hypertension; Blood pressure; Complications; Epidemiology; Diabetes mellitus; Risk factors; Incidence; Iran

1. Introduction

Patients with type 2 diabetes are at higher risk for many long-term complications, including early mortality and cardiovascular disease. The relationship between diabetes complications and hypertension is well established and consistent and has been examined in many different populations in developed nations [1–13]. Hypertension is associated with increased risk of nephropathy [1–3], retinopathy [4–6], and cardiovascular disease mortality and morbidity in diabetic patients [7–9]. Epidemiological studies of the impact of hypertension in type 2 diabetes in developing countries are scarce. Accurate information regarding the incidence of hypertension and associated risk factors in people with diabetes is important in the prevention or delaying of its development and of the cardiovascular impairment caused by this complication in these countries.

Diabetes mellitus and hypertension are often associated with each other, and both are risk factors for cardiovascular disease. Hypertension and type 2 diabetes mellitus are common causes of morbidity and mortality and are serious problems in Iran but to our knowledge, there have been no longitudinal studies describing the incidence or risk factors of hypertension in diabetic patients.

The objective of this report was to estimate the incidence of and risk factors of hypertension in diabetic patients using routinely collected data from a clinical information system for diabetes at Isfahan Endocrinology and Metabolism Research Centre, Iran.

2. Patients and methods

2.1. Data collection

Details of the recruitment and examination procedures of the Isfahan Endocrinology and Metabolism Research Centre out patient clinics have been published previously [14,15]. In brief, clinical data are collected for all consecutive patients at the first attendance and at review consultations (usually annually) using standard encounter forms. These include an examination of ocular fundus, lens, limbs, blood pressure and construction of a problem list by the clinician, measurement of fasting blood glucose, glycosylated haemoglobin (HbA_1), urine protein, triglyceride, cholesterol and serum creatinine, and reporting of smoking as part of a completed questionnaire on demography, family history, and smoking by the patient. A registry clerk enters data from these forms into the computer after the clinic.

Blood pressure was measured by standardised protocols, and hypertension was defined at least in two consecutive measurements within 2 months, based on the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [16]. According to this protocol, systolic and/or diastolic blood pressure $\geq$130 and $\geq$80 mmHg and/or the current use of anti-hypertensive medication in diabetes diagnosed as hypertension. However, according to the blood pressure classification of JNC7, systolic 120–139 and/or diastolic blood pressure 80–89 was classified as prehypertension in non-diabetic and systolic and/or diastolic blood pressure $\geq$130/80 mmHg as hypertension in diabetic individuals. The JNC7 recommendations are consistent with guidelines from the American Diabetes Association recommendations [17] which has also recommended that blood pressure in diabetic patients be controlled to level of 130/80 mmHg or lower.

Many patients have hypertension at diagnosis or develop it shortly afterwards. Since many patients were referred some years after diagnosis we have no means of knowing the relationship between the onset of diabetes and the development of hypertension among those with this complication at the time of referral. Also, the onset of type 2 diabetes may precede diagnosis by some years. This study was therefore

confined to those who were clinically free of hypertension at initial registration, recording the rate of development of hypertension over subsequent years.

2.2. Patients

Between 1992 and 2004, a total of 9897 type 2 diabetes were registered in the system. However, this study uses data only for 3202 (1315 male and 1887 female) type 2 diabetic patients who were free of hypertension at registration and had at least one subsequent review and for whom complete data were available. Baseline characteristics of those selected and not selected are shown in Table 1. Compared to non-participants, those who participated were younger at registration and diagnosis of diabetes, have lower systolic and diastolic blood pressure, duration of diabetes, body mass index (BMI), triglyceride, cholesterol and have lower proportion of proteinuria but have higher insulin-treated diabetes and slightly higher fasting blood glucose and HbA_1. The sample had similar distributions in creatinine, smoking and gender as those not selected. The 3202 patients had mean (standard deviation (S.D.)) duration of diabetes 6.5 (6.7) years and mean age of 48.3 (10.6) years at initial registration. The average time of follow-up was 2.9 (2.5) years (range 1–11 years).

Risk factors for the development of hypertension were assessed using the following data from the patient's registration consultation: gender, age at diagnosis (the age at the time the diagnosis was first recorded by a physician on the participant's chart), age (the age at the time of the initial examination),

Table 1
Group means and proportions comparison of selected baseline characteristics between participants and non-participants type 2 diabetic patients

Characteristics	Participants		Non-participants		Differences (95% CI)
	No.	Mean (S.D.)	No.	Mean (S.D.)	
Age at registration (year)	3181	48.3 (10.6)	6556	53.9 (10.6)	−5.6 (−6.1, −5.1)**
Duration of diabetes (year)	3172	5.4 (5.5)	6576	6.9 (6.8)	−1.5 (−1.8, −1.2)**
Age at diagnosis (year)	3150	42.9 (10.4)	6481	47.0 (10.7)	−4.1 (−4.6, −3.7)**
BMI (kg/m^2)	3141	26.8 (4.4)	6449	27.9 (4.6)	−1.1 (−1.3, −0.9)**
Systolic BP (mmHg)	3203	110.3 (9.8)	5283	136.6 (21.5)	−26.3. (−27.0, −25.5)**
Diastolic BP (mmHg)	3203	70.6 (8.6)	4977	81.7 (12.0)	−11.1 (−11.6, −10.6)**
Fasting blood glucose (mg/dl)	2930	208.8 (76.2)	5473	202.5 (73.8)	6.3 (3.0, 9.7)**
HbA_1 (%)	2249	10.3 (2.4)	3563	10.1 (2.3)	0.2 (0.08, 0.3)*
Triglyceride (mg/dl)	2830	221.2 (143.3)	5233	238.8 (158.9)	−17.6 (−24.6, −10.6)**
Cholesterol (mg/dl)	2851	221.2 (54.4)	5256	228.6 (53.8)	−7.4 (−9.8, −4.9)**
Creatinine (μM/l)	2024	0.96 (0.9)	3788	1.0 (0.9)	−0.04 (−0.09, 0.01)

Characteristics	No. (%)	No. (%)	Differences (95% CI)
Gender			
Male	1315 (41.1)	2822 (42.5)	−1.4 (−3.5, 0.7)
Female	1887 (58.9)	3823 (57.5)	–
Smoking			
Never-smoker	2432 (84.7)	5135 (85.8)	−1.2 (−2.8, 0.4)
Current-smoker	441 (15.3)	847 (14.2)	–
Proteinuria			
Pressent	410 (27.6)	773 (33.8)	−6.2 (−9.2, −3.2)**
Absent	1076 (72.4)	1514 (66.2)	–
Therapeutic regimen			
Insulin	677 (21.1)	899 (13.5)	7.6 (6.0, 9.3)**
Non-insulin	2526 (78.9)	5753 (86.5)	–

Note: Total of each variable may vary because of missing value. CI: confidence interval.
* $P < 0.01$.
** $P < 0.001$ for the difference in the mean and proportion of the variables between participants and non-participants.

duration of diabetes (the time between diagnosis and the initial registration), BMI (weight/height^2 [kg/m^2]), smoking status (never, current), haemoglobin A_1 (HbA_1) (measured by ion-exchange chromatography; as an indicator of diabetic control), fasting blood glucose (measured by glucose oxidaze method; Clinical Chemistry Analyser Liasys, Italy), proteinuria (measured by precipitation with 3% sulfosalicylic acid and determination of turbidity by measuring absorbance at a wavelength of 550 nm with a spectrophotometer), serum creatinine, triglyceride, cholesterol (measured using conventional laboratory techniques) and blood pressure (systolic and diastolic) at registration. Diabetes treatment (insulin, oral agent, and diet alone) used in the analysis was that recorded at the last clinic visit. The physician defined the type of diabetes using the problem list.

2.3. Analysis

Statistical methods used included the Student's *t*-test, Chi-square test, and stepwise Cox's Proportional Hazards Model, which takes varying periods of follow-up and time-dependent changes of covariate values into account, to test associations between baseline variables and hypertension outcomes [18–21]. Two types of statistical analyses are presented in this report: Crude relative risks based on incidence rates and adjusted relative risk determined by a forward stepwise Cox's Proportional Hazard Model using the SPSS for Windows computer package which simultaneously adjusts for other covariates. For this analysis, follow-up time, age, age at diagnosis, duration of diabetes, fasting blood glucose, HbA_1, systolic and diastolic blood pressure, BMI, cholesterol, triglyceride and creatinine were included as continuous variables. Gender, proteinuria and cigarette smoking (never and current) were entered as dichotomous variables. Therapeutic regimen (diet, oral agent and insulin) was included as trichotomous variable. Likelihood ratio tests were selected for testing the significance of the coefficients. The likelihood ratio test made at each step determined if the last variable that entered the regression added significantly to the variables already selected. The forward stepwise procedures with 0.05 entry and removal criteria resulted in a ranking of the variables according to their relative importance. Adjustment for age was examined in separate models. Incidence of hypertension was expressed per 100 person-years of observation in subjects who were not hypertensive at registration. The numerator was the number of patients who had hypertension diagnosed between 1992 and 2004, and the denominator was person-times. The period of risk began on the date of first registration for patients entering the study after this date; it extended to the date of diagnosis of hypertension, date of last contact with registry, or close of the study. Patients who registered during the study period began to accumulate person-time from the date of registration. To save space and confusion, confidence intervals around the relative risks have been given, although significant P values ($P < 0.05$) have been reported. Relative risks and 95% confidence interval (CI) for incidence rates were estimated from the Cox regression analysis and 95% CIs for mean and proportion differences by confidence interval analysis software [22]. Because age and duration of diabetes are correlated ($r = 0.40$, $P < 0.001$), adjustment for one effectively adjusts for the other. To save space, only age-adjusted data are presented.

3. Results

3.1. Incidence of hypertension

Of the 3202 patients, 1952 (61.0%) (746 men and 1206 women) developed hypertension in a total of 9403 (3629 men and 5774 women) person-years of follow-up. The other 1250 diabetic patients had not developed hypertension by the end of this study period. Overall incidence of subsequent hypertension was 20.8 per 100 person-years (95% CI: 19.9, 21.6). There was a statistically increasing incidence of hypertension with increasing age ($P < 0.001$). Incidence rates were similar in women (20.9 (95% CI: 19.8, 21.9) per 100 person-years) and men (20.6 (95% CI: 19.2, 21.9). Of the 677 patients who had insulin-treated but were free of hypertension at initial registration, 473 subsequently developed hypertension, giving an incidence of 18.1 (95% CI: 16.6, 19.6) per 100 person-years. This was lower than the incidence rates seen for non-insulin-treated, 21.8 per 100 person-years (95% CI: 20.8, 22.8).

Table 2
Group means and proportions for selected variables between 1935 participants who did and 1267 who did not developed hypertension

Variables	Hypertension		No hypertension		Difference (95% CI) @
	No.	Mean (S.D.)	No.	Mean (S.D.)	
Age at registration (year)	1935	49.0 (10.5)	1246	47.2 (10.6)	1.8 (1.1, 2.6)***
Duration of diabetes (year)	1930	5.5 (5.4)	1242	5.3 (5.6)	0.2 (−0.2, 0.6)
Age at diagnosis (year)	1913	43.6 (10.4)	1237	41.9 (10.3)	1.7 (0.9, 2.4)***
BMI (kg/m^2)	1919	27.2 (4.4)	1222	26.1 (4.3)	1.1 (0.8, 1.4)***
Systolic BP (mmHg)	1952	111.4 (9.4)	1251	108.7 (10.2)	2.7 (2.1, 3.4)***
Diastolic BP (mmHg)	1952	71.7 (8.4)	1251	68.7 (8.5)	3.0 (2.4, 3.6)***
Fasting blood glucose (mg/dl)	1754	206.4 (75.7)	1176	212.2 (76.9)	−5.8 (−11.4, −0.1)*
HbA_1 (%)	1585	10.2 (2.3)	664	10.4 (2.5)	−0.2 (−0.4, 0.2)
Triglyceride (mg/dl)	1719	227.6 (150.5)	1111	211.3 (130.7)	16.3 (5.5, 27.1)**
Cholesterol (mg/dl)	1724	224.3 (53.9)	1127	216.5 (55.0)	7.8 (3.7, 11.9)***
Creatinine (μM/l)	1416	0.94 (0.8)	608	1.00 (1.1)	−0.06 (−0.2, 0.03)

Variables	No. (%)	No. (%)	Difference 95% CI@
Gender			
Female	1206 (61.8)	681 (54.5)	7.3 (3.8, 10.8)***
Male	746 (38.2)	569 (45.5)	–
Smoking			
Never-smoker	1536 (87.4)	896 (80.4)	7.0 (4.2, 9.8)***
Current-smoker	222 (12.6)	219 (19.6)	–
Proteinuria			
Absent	649 (68.8)	427 (78.8)	−10.1 (−14.6, −5.5)***
Present	295 (31.1)	115 (21.2)	–
Therapeutic regimen			
Non-insulin	1479 (75.8)	1047 (83.7)	−7.9 (−10.7, −5.1)***
Insulin	473 (24.2)	204 (16.3)	–

Note: Total of each variable may vary because of missing value. CI: confidence interval. The symbol @ indicates the difference in the mean or percentage of the variables between hypertension and no hypertension.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

3.2. Risk factors

Table 2 shows the group means (S.D.) and proportions for those participants who did and did not develop hypertension. Those who developed hypertension had higher systolic (111.4 mmHg versus 108.7 mmHg; $P < 0.001$) and diastolic (71.7 mmHg versus 68.7 mmHg; $P < 0.001$) blood pressure, lower fasting blood glucose (206.4 mg/dl versus 212.2 mg/dl; $P < 0.05$), higher body mass index (27.2 versus 26.1; $P < 0.001$) and were diagnosed with diabetes at older ages (43.6 years versus 41.9 years; $P < 0.001$) and were older at registration (49.0 versus 47.2; $P < 0.001$). They had higher triglyceride (227.6 mg/dl versus 211.3 mg/dl; $P < 0.01$) and cholesterol level (224.3 mg/dl versus 216.5 mg/dl; $P < 0.001$). A lower proportion of those who developed hypertension were non-insulin-treated (75.8% versus 83.7%; $P < 0.001$), but higher proportion used insulin (24.2% versus 16.3%; $P < 0.001$), had proteinuria (31.1 versus 21.2; $P < 0.001$), lower proportion of current smoker (12.6% versus 19.6%; $P < 0.01$) and male gender (38.2 versus 45.5; $P < 0.001$).

To determine the influence of potential factors on hypertension, univariate analysis was first performed (Table 3). Crude relative risk showed that those who had hypertension were more likely to be older at registration and diagnosis of diabetes, lower fasting blood glucose and HbA_1, with higher BMI, and non-smokers. Age-adjusted Cox regression coefficient

Table 3
Incidence rates of hypertension by baseline variables

Variables	At risk (no.)	Cases (no.)	Person-year	Incidence per 100 person-year	Crude relative risk (95% CI)	Age-adjusted relative risk (95% CI)[†]
Gender						
Female	1887	1206	5774	20.9	1.0	1.0
Male	1315	746	3629	20.6	0.98 (0.91, 1.07)	1.05 (1.01, 1.09)**
Age at registration (year)						
<40	625	339	1783	19.0	1.0	–
40–49	1159	689	3471	19.9	1.04 (0.93, 1.17)	–
50–59	871	559	2651	21.1	1.11 (0.98, 1.25)	–
60–69	426	285	1241	23.0	1.21 (1.05, 1.39)***	–
≥70	100	63	233	27.0	1.42 (1.13, 1.79)***	–
Age at diagnosis (year)						
<30	248	144	759	19.0	1.0	1.0
30–59	2691	1625	8006	20.3	1.06 (0.92, 1.25)	0.96 (0.90, 1.02)
≥60	211	144	549	26.2	1.36 (1.13, 1.69)***	1.14 (1.00, 1.29)*
Duration of diabetes (year)						
<5	1810	1082	5167	20.9	1.0	1.0
5–7	573	355	1736	20.4	0.98 (0.88, 1.09)	1.00 (1.00, 1.07)
8–11	386	230	1193	19.3	0.92 (0.81, 1.05)	0.97 (0.89, 1.05)
≥12	403	263	1243	21.2	1.01 (0.90, 1.14)	0.97 (0.89, 1.06)
Fasting blood glucose (mg/dl)						
<120	267	166	721	23.0	1.0	1.0
120–139	274	181	874	20.7	0.90 (0.75, 1.08)	0.95 (0.86, 1.04)
140–200	951	566	2981	19.0	0.83 (0.71, 0.96)*	0.96 (0.90, 1.03)
≥200	1438	841	4329	19.4	0.84 (0.73, 0.98)*	1.00 (0.94, 1.06)
HbA_1 (%)						
<9	802	571	2430	23.5	1.0	1.0
9.0–10.9	734	533	2585	20.6	0.88 (0.79, 0.97)*	1.02 (0.95, 1.11)
11–12.9	404	275	1442	19.1	0.81 (0.71, 0.92)**	1.01 (0.92, 1.11)
13–14.9	209	143	838	17.1	0.73 (0.62, 0.86)*	0.90 (0.80, 1.01)
≥15	100	63	400	15.8	0.67 (0.53, 0.85)*	0.89 (0.75, 1.04)
BMI (kg/m^2)						
<27	1740	979	5190	18.9	1.0	1.0
27–33	1214	808	3514	23.0	1.22 (1.12, 1.32)**	1.00 (0.94, 1.07)
≥34	187	132	536	24.6	1.31 (1.11, 1.53)***	1.03 (0.93, 1.14)
Smoking						
Never-smoker	2432	1536	7401	20.8	1.0	1.0
Current-smoker	441	222	1267	17.5	0.84 (0.74, 0.96)*	1.02 (0.97, 1.08)
Proteinuria						
Absent	1076	649	3944	16.5	1.0	1.0
Present	410	295	1695	17.4	1.06 (0.93, 1.20)	0.95 (0.90, 1.00)
Creatinine (M/l)						
≤1.5	1955	1372	6525	21.0	1.0	1.0
>1.5	68	43	261	16.5	0.78 (0.59, 1.03)	0.94 (0.84, 1.06)
Therapeutic regimen						
Non-insulin	2526	1479	6792	21.8	1.0	1.0
Insulin	677	473	2612	18.1	0.93 (0.82, 1.05)	0.78 (0.73, 0.82)***

Total number of person-years and at risk is not the same for each variable because of missing values.
* $P < 0.5$.
** $P < 0.01$
*** $P < 0.001$.
† Relative risks (with 95% CI) calculated by Cox's Proportional Hazard Model [20].

among those free of hypertension at registration showed that significant risk factors for developing hypertension were male gender, older age, and non-insulin treatment. The insulin treatment reduced the risk of developing hypertension.

To determine the independent predictors of the incidence of hypertension a stepwise Cox's Proportional Hazard Model was performed. Male (relative risk 1.10 (95% CI: 1.01, 1.20)) was more likely and insulin-treated patients (relative risk 0.84 (95% CI: 0.74, 0.95)) were less likely to develop hypertension. No other variables were significant when other covariates were considered.

4. Discussion

In this follow-up study of 3202 diabetes clinic attenders, we found an overall incidence of hypertension of 20.8 per 100 person-years (1952 patients) over an average follow-up of 2.9 years. To the best of our knowledge, no other incidence rates for hypertension between Iranian diabetic and non-diabetics have been reported. The prevalence of hypertension in general population aged $\geq$19 years was 18% [23]. This incidence seems surprisingly high for patients with type 2 diabetes from a developing country like Iran. These data are consistent with the high prevalence of hypertension in the diabetic population [7]. Incidence rates in various studies from around the world show considerable variation. Estimates of incidence of hypertension will depend upon the definition of the hypertension used and the composition of the community examined by age and social class [12,24], making comparisons between studies of limited values. However, the estimates of the incidence of hypertension varied widely in other studies too as a result of variations in study design, detection methods, or the examination of patients at different stages in the natural history of diabetes and the study of selected populations of diabetic individuals. One study from Mexico among type 2 diabetes, which used a different definition of hypertension, found after the 5 years, 40% and at 15 years follow-up, 71% of diabetic patients had hypertension [25]. Another study from Tanzania found the 5-year incidence of hypertension of 25.4% among the subjects with type 2 diabetes [26]. In San Antonio Heart Study, USA, which used a different definition of hypertension, the 8-year incidence of hypertension was 16% in non-Hispanic White with type 2 diabetes mellitus [27]. In Wisconsin, USA, which defined hypertension as a mean systolic blood pressure of 160 mmHg or more and/or mean diastolic blood pressure of 95 mmHg or more, after 10 years of follow-up, observed incidence of hypertension among subjects younger than 30 years and taking insulin was 25.9% [28]. Our clinic-based incidence is higher than the values reported in San Antonio Heart Study [27], Wisconsin Epidemiological Study of Diabetic Retinopathy [28], Mexico [25] and Tanzania [26] studies. Higher rates in our study could have been due to a different definition of hypertension, and differences in medical care access and therapy might be one reason. However, it seems that the incidence of hypertension among Isfahanian diabetic patients was high.

Univariate analysis (Table 2), even when taking into account time (Table 3), shows an expected pattern of association for many variables with the development of hypertension. In multivariate analysis fewer remain independently associated. In this study, males had a slightly higher risk of developing hypertension in age-adjusted analysis. After adjusting for other confounders, gender was significant independent predictor. This finding is consistent with Klein et al. [28]. We cannot explain the mechanisms for this discrepancy between the genders. But duration of diabetes was not associated with the incidence of hypertension in type 2 diabetes after age-adjustment. It should be noted that age and duration of diabetes are correlated in this patients population ($r = 0.40$, $P < 0.001$), and thus, controlling for age effectively controls for duration. Therefore, it follows that duration-specific or -adjusted target values are also not indicated.

Consistent with prior studies in non-diabetic population [29], the present study found similarly increasing incidence of hypertension with increasing age in a diabetic population.

By multivariate analysis, we found that the incidence of hypertension was not similar in insulin-treated and non-insulin-treated type 2 diabetes. The incidence was lower in insulin-treated type 2 diabetic patients than in non-insulin treated. The association of insulin with blood pressure has been controversial [30]. Fasting insulin concentrations

predicted the development of hypertension in some studies [27,31–33]. Several mechanisms have been proposed for the effect of insulin on blood pressure, including effects on the sympathetic nervous system [34], proliferation of vascular smooth-muscle cells [35], ion transport [36], and increase renal sodium reabsorbtion [37]. However, conflicting data also exist. Laakso et al. [38] suggested that insulin may lead to vasodilation. Hall et al. [39] showed no increase in mean arterial blood pressure after 7 days of insulin infusion into dogs. Anderson et al. [40] suggested that short-term infusion raise cathecolamines but not blood pressure in normotensive men. However, the effect of chronic hyperinsulinemia is unknown.

Klein et al. [28] suggested that glycaemic control may be an effective approach for preventing the development of hypertension in type 1 diabetes. Haffner et al. [41] reported a strong positive relationship of hyperglycaemia and the 8 years incidence of hypertension in women but not men, with impaired glucose tolerance or type 2 diabetes. In univariate analysis, the level of hyperglycaemia, as measured by one glycosylated haemoglobin determination at baseline, was negatively associated with the development of hypertension. After age-adjustment, the level of hyperglycaemia was not found to be a predictor of incidence of hypertension. After adjustment for other covariates in the multivariate analysis, the level of glycated haemoglobin was non-significant. Because most of our patients did not have HbA_1 as an indicator of metabolic control and insufficient follow-up period, our study did not show poor metabolic control to be an important risk factor for hypertension. However, this warrants further study. Although these data have failed to confirm relationship between metabolic control and the incidence of hypertension, they in no way diminish the need for optimal glycaemic control for the prevention of type 2 diabetes complications, which has been well demonstrated both epidemiologically and interventionally.

Previous studies differ in relation to the importance of obesity as a risk factor. By multivariate analysis, however, we found no association between BMI and hypertension.

A number of previous studies in non-diabetic populations have found an association between cigarette smoking and the risk of hypertension [42], but this finding was by no mean universal [43]. In this study, smoking (classified in two simple categories of never, and current) was not associated with the incidence of hypertension after correcting for other covariates. This lack of association may reflect some pattern of survivorship. Those who smoked at registration and continued to do so may have died of a smoking related illness, including cardiovascular disease, neoplasia and other causes of death, before having opportunity to develop hypertension.

The Isfahan clinical information system for diabetes provides one of the largest clinic-based datasets of its kind in developing countries. Although we have not carried out any special studies of the validity or reliability of data for this analysis, a clerk was employed to check consistency and, where possible, to ensure completeness of data. Previous studies show that these patients are a representative sample of known diabetic patients of Isfahan [44,45]. Our experience with other parts of the dataset gives us some confidence that data quality is sufficient for this type of study and that our results provide useful additional evidence on the incidence of and risk factors for hypertension. The study was clinic, rather than population based, and so may not contain a clinical spectrum representative of diabetic patients in the community. Many patients requiring only oral or dietary treatment may never attend the clinic [46]. Clinic-based estimates of the incidence or prevalence of complications are most likely to be affected by referral patterns. Selection bias is less likely to affect incidence rates and associations between risk factors and complications [46] as investigated in this study. The study was performed according to the recommendations by the JNC7 [16]. According to JNC7 recommendations [16] we used systolic and/or diastolic blood pressure $\geq$130 and $\geq$80 mmHg is considered the most appropriate. The JNC7 recommendations are consistent with guidelines from the American Diabetes Association recommendations [17] which has also recommended that blood pressure in diabetic patients be controlled to level of 130/80 mmHg or lower.

Our diagnosis of hypertension is not based on a single examination but continuing examination during follow-up, using a problem list as the basis for further clinical decisions. Nevertheless, several observers made observations over the years, and problems of

observer error need to be considered. It seems reasonable to assume that observer error is independent of such variables as age, gender, duration of diabetes and type of treatment of the patient. If this is so, misclassification resulting from observer error will tend to reduce rather than increase the significance of differences between groups of patients. If therefore a significant difference is found between two otherwise comparable groups of patients, it is reasonable to infer that it is not due to observer error but must reflect a true difference. In this study, the mean follow-up period was short and the statistical power to detect small significant differences in our study was limited. Differences in baseline systolic and diastolic blood pressure, fasting blood glucose, HbA_1, age, triglyceride, cholesterol, proteinuria and therapeutic regimen between study participants and the entire population of registered type 2 diabetic patients could limit the generalizability of our findings.

In summary, with an estimated incidence of 20.8 per 100 person-years of observation, hypertension clearly poses a formidable health threat to Iranian diabetic patients. The results of this study highlight the need for vigorous blood pressure control in people with type 2 diabetes.

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