Antihypertensive Treatment and Resistant Hypertension in Patients With Type 1 Diabetes by Stages of Diabetic Nephropathy

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OBJECTIVE

To assess blood pressure (BP) control, antihypertensive treatment, and prevalence of resistant hypertension (RH) in patients with type 1 diabetes stratified by stage of diabetic nephropathy.

RESEARCH DESIGN AND METHODS

This cross-sectional study included a nationally representative cohort of patients with type 1 diabetes (*N* = 3,678) from the Finnish Diabetic Nephropathy Study (FinnDiane). The data were linked to the Drug Prescription Register to obtain purchases of antihypertensive drugs 6 months prior to the baseline visit. The treatment targets were based on the American Diabetes Association guidelines. RH was defined as failure to reach BP target despite the use of three or more antihypertensive drugs of different classes (one of which was a diuretic).

RESULTS

In patients with normal albumin excretion rate, 14.1% were on antihypertensive treatment and 74.6% of them had uncontrolled BP despite treatment. The corresponding figures were 60.5 and 71.2% for the microalbuminuric patients, 90.3 and 80.0% for the macroalbuminuric patients, 88.6 and 88.1% for dialysis, and 91.2 and 90.4% for kidney-transplanted patients. The prevalence of RH was 1.2% in the normoalbuminuric, 4.7% in the microalbuminuric, 28.1% in the macroalbuminuric, 36.6% in the dialysis, and 26.3% in the kidney transplant groups. Age (odds ratio 1.04 [95% CI 1.02–1.05]), estimated glomerular filtration rate (0.97 [0.96–0.97]), waist-to-hip ratio (1.44 [1.15–1.80]), triglycerides (1.19 [1.01–1.40]), microalbuminuria (2.58 [1.43–4.67]), and macroalbuminuria (5.61 [3.20–9.84]) were independently associated with RH.

CONCLUSIONS

The prevalence of uncontrolled hypertension and RH increases with advanced diabetic nephropathy. These data suggest that there is an urgent need for improvement of antihypertensive treatment.

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High blood pressure (BP) is a risk factor for coronary artery disease, heart failure, and stroke, as well as for chronic kidney disease. Furthermore, hypertension has been estimated to affect ~30% of patients with type 1 diabetes (1,2) and both parallels and precedes the worsening of kidney disease in these patients (3–5). In order to prevent micro- and macrovascular complications, the American Diabetes Association (ADA) has annually published clinical practice guidelines for the management of diabetes, including targets and strategies for BP control in patients with diabetes (6–8).

Despitestrong evidence that intensive treatment of elevated BP reduces the risk of cardiovascular disease and microvascular complications, as well as improves the prognosis of patients with diabetic nephropathy (especially with the use of ACE inhibitors [ACEIs] and angiotensin II antagonists [angiotensin receptor blockers, ARBs]) (1,9–11), treatment targets and recommendations seem difficult to meet in clinical practice (12–15). This suggests that the patients might either show poor adherence to the treatment and lifestyle changes or have a suboptimal drug regimen. It is evident that most patients with hypertension might require multiple-drug therapy to reach treatment goals (16). However, certain subgroups of the patients have been considered to have resistant hypertension (RH). RH is defined as office BP that remains above target even after using a minimum of three antihypertensive drugs at maximal tolerated doses, from different classes, one of which is a diuretic. Also, patients with controlled BP using four or more antihypertensive drugs are considered resistant to treatment (17).

The true prevalence of RH is unknown, but clinical trials suggest a share between 10 and 30% of the hypertensive patients in the general population (18). In the U.S., on the basis of the National Health and Nutrition Examination Survey (NHANES), 8.9% of all U.S. adults with hypertension had RH, and among the antihypertensive drug–treated patients, the figure was 12.8% (19). They also reported that adults with RH were more likely to be men, older, obese, and black and to have reduced renal function, albuminuria, diabetes, heart failure, and stroke. A Spanish study estimated that 12.2% of the treated hypertensive population had RH (20). They also showed that RH was associated with a longer duration of hypertension, obesity, abdominal obesity, left ventricular hypertrophy, reduced estimated glomerular filtration rate (eGFR), and microalbuminuria.

Previous studies have assessed BP control and treatment as well as the prevalence of RH in the general hypertensive population (19,21). Only a few studies have considered BP control and treatment in patients with type 1 diabetes (2,15,22). Typically these studies have been limited to a small number of participants, which has not allowed stratifying of the patients according to the nephropathy status. The rate of RH is therefore unknown in patients with type 1 diabetes in general and with respect to different stages of diabetic nephropathy. Therefore, we estimated to what extent patients with type 1 diabetes meet the BP targets proposed by the ADA guidelines. We also evaluated the use of antihypertensive medication and the prevalence of RH in the patients stratified by stage of diabetic nephropathy.

RESEARCH DESIGN AND METHODS

The present cross-sectional study is part of the nationwide multicenter Finnish Diabetic Nephropathy Study (FinnDiane) with the aim of identifying genetic, clinical, and environmental risk factors for the development of diabetes complications in patients with type 1 diabetes. A more detailed description of the study has been reported elsewhere (23). In brief, all adult patients with type 1 diabetes from >80 hospitals and primary healthcare centers across Finland were asked to participate. Type 1 diabetes was defined by age at onset of diabetes <40 years, C-peptide ≤0.3 nmol/L, and insulin treatment initiated within 1 year of diagnosis, if C-peptide was not measured. Written informed consent was obtained from each patient. The local ethics committees have approved the study protocol, and the study has been carried out in accordance with the Declaration of Helsinki.

At baseline, patients underwent a thorough clinical investigation that took place in conjunction with a regular visit. Details of the clinical characteristics of the patients were obtained from medical records by the attending physician using a standardized questionnaire. The measurement of height, weight, and waist and hip circumferences was performed. BP was measured twice with 2-min intervals in the sitting position after 10 min rest using a mercury sphygmomanometer or an automated standardized BP device. The mean of these two measurements was used in the analysis. Baseline data were collected between the years 1995 and 2008. About 60% of the patients had the baseline visit in 2000 or before. Therefore, we used two different ADA BP targets: <130/85 mmHg, which was the target until 2000 (6), and <130/80 mmHg, which was the target between 2001 and 2012 (7). Patients were divided into groups based on whether their BP had reached the target or not and whether the antihypertensive drug was in use or not. In the current study, uncontrolled hypertension was defined as failure to achieve target BP, based on these two different ADA guidelines, despite use of antihypertensive medication. RH was defined as failure to achieve the goal BP (<130/85 mmHg) even after using a minimum of three antihypertensive drugs, from different classes, one of which was a diuretic.

In addition, fasting blood samples were drawn and analyzed for HbA_{1c}, lipids, and serum creatinine. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (24). On the basis of eGFR (mL/min/1.73 m^2) level, patients were classified into five groups according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines: stage 1 eGFR ≥90, stage 2 eGFR 60–89, stage 3 eGFR 30–59, stage 4 eGFR 15–29, and stage 5 eGFR <15. Patients who were on dialysis were classified into stage 5. As a measure of insulin sensitivity, we used an equation for the estimated glucose disposal rate (25) modified for the use of HbA_{1c} instead of HbA_1 (23). Moreover, urinary

sodium excretion rate was measured in a single 24-h urine collection. The nephropathy status was defined on the basis of the urinary albumin excretion rate (AER) in at least two out of three overnight or 24-h urine collections.

A total of 3,678 patients with complete data on systolic and diastolic BP and nephropathy status were identified from the FinnDiane database. The patients were classified into five nephropathy status groups: normoalbuminuria (AER <20 μg/min or <30 mg/24 h; *n* = 2,370), microalbuminuria (AER 20–200 μg/min or 30–300 mg/24 h; *n* = 488), and macroalbuminuria (AER >200 μg/min or >300 mg/24 h; *n* = 526). The fourth and the fifth groups consisted of the patients with end-stage renal disease (ESRD), defined as dialysis or kidney transplantation (*n* = 294). Of the patients, 123 (41.8%) were on dialysis and 171 (58.2%) had received a kidney transplant.

The FinnDiane data were linked to the Drug Prescription Register (DPR) in order to obtain information on all purchases of outpatient prescription medications, including antihypertensive drugs. The Social Insurance Institution of Finland has maintained the DPR since 1994. The DPR contains information of all prescribed, purchased, and reimbursed medications in outpatient care. The data obtained from this register include the patient's unique identification number (assigned to every resident of Finland) and the Anatomic Therapeutic Chemical (ATC) classification code of the product, based on the 2012 ATC Index version. Patients can buy their drugs for a 3-month period at a time. Therefore, all purchases of antihypertensive drugs 6 months prior to the baseline visit were obtained from the DPR. Antihypertensive drugs were divided into eight classes: ACEIs (C09A and C09B), angiotensin II antagonists (C09C and C09D), diuretics (C03, C07BB, C09BA, and C09DA), β-blocking agents (C07), calcium channel blockers (C08, C07FB, C09BB, and C09DB), imidazoline receptor blockers (moxonidine and clonidine; C02AC), prazosin (C02CA01), and minoxidil (C02DC01). Patients taking a combination of antihypertensive pills were counted as taking separate classes for each drug.

Statistical Analysis

The data are expressed as mean ± SD for normally distributed variables, median with interquartile range for nonnormally distributed values, and percentage. Differences between groups for normally distributed variables were tested by using ANOVA and nonparametric data with Kruskal-Wallis tests. Frequencies were tested with Pearson χ^2 test. A multivariate logistic regression analysis was performed using a stepwise selection procedure to test which variables were independently associated with RH before the development of ESRD (dialysis and kidney transplantation patients were excluded). Variables showing a *P* value <0.05 in the univariate analyses were incorporated in the multivariate model. The predictors studied were sex, age, HbA_{1c}, insulin dose, laser treatment, triglycerides, HDL cholesterol, presence of coronary heart disease, nephropathy status, waist-to-hip ratio, eGFR, and 24-h urinary sodium excretion rate. Because of collinearity with age (*r* = 0.72), duration of diabetes was not used in the analyses. High collinearity was also observed between BMI and waist circumference (*r* = 0.77) as well as between BMI and hip circumference (*r* = 0.78), and therefore BMI was not included in either of the final models. Measurements of 24-h urinary sodium excretion rate were available in a subset of patients with normo-, micro-, and macroalbuminuria (*n* = 2,203), and thus a separate model was applied for these patients. Results are presented as odds ratios with 95% CIs.

RESULTS

Altogether, 3,678 patients with type 1 diabetes were studied, 51% of whom were men. The mean age was 38.0 ± 12.0 and mean duration of diabetes 22.1 ± 12.3 years. The characteristics of the patients with respect to nephropathy status are presented in Table 1. The patients with advanced diabetic nephropathy had higher BP, worse dyslipidemia, poorer glycemic control, and more insulin resistance and macrovascular complications. BMI values were lower in the dialysis patients, probably due to renal cachexia. Also, the proportion of smokers was lower in the dialysis and transplanted patients.

BP Control

Of all patients, 60.9% did not reach the BP target <130/85 mmHg, and the proportion was 70.3% with the target of <130/80 mmHg. Characteristics of the patients who reached the target and who did not are shown in Supplementary Table 1. The patients who were not on target had higher age and longer duration of diabetes and were more likely to be men. They also had poorer glycemic and lipid control as well as more micro- and macrovascular complications.

Based on the BP target <130/85 mmHg, more than half of the patients in the normoalbuminuria group did not reach the BP target, and the share increased along with the worsening of nephropathy; two-thirds of the patients in the microalbuminuria group and four-fifths in the macroalbuminuria group were not on target, while even 90% of the dialysis and kidney transplant patients did not reach the target (Fig. 1*A*). Based on the stricter BP target of <130/80 mmHg, the numbers were obviously worse, but the trend was the same (Fig. 1*B*). An additional analysis where the patients were classified into five groups on the basis of eGFR shows a similar trend along with the worsening of renal function (Supplementary Fig. 1*A* and *B*).

Antihypertensive Treatment

About 37% of the FinnDiane patients had antihypertensive treatment, but again the numbers varied greatly between the nephropathy groups. Whereas 14.1% of the patients with normal AER had antihypertensive treatment, the proportions were 60.5% in the microalbuminuric, 90.3% in the macroalbuminuric, 88.6% in the dialysis, and 91.2% in the kidney transplant patients. However, in all groups, only a minority of the patients had BP values on target with the antihypertensive drug treatment they were prescribed (Fig. 1*A* and *B*).

Number of Antihypertensive Drugs Taken

No differences were observed in the numbers of antihypertensive drugs taken between the normo- and

Table 1—Baseline characteristics of patients with type 1 diabetes by stages of diabetic nephropathy (*N* = 3,678)

	Normoalbuminuria (*n* = 2,370)	Microalbuminuria (*n* = 488)	*P*	Macroalbuminuria (*n* = 526)	*P*	Dialysis (*n* = 123)	*P*	Kidney transplantation (*n* = 171)	*P*
Men (%)	47.4	57.4	<0.0001	59.5	<0.0001	56.9	0.04	57.9	0.008
Age (years)	36.1 ± 12.0	38.6 ± 12.1	<0.0001	41.4 ± 10.0	<0.0001	46.7 ± 9.2	<0.0001	45.0 ± 7.9	<0.0001
Age at onset of diabetes (years)	16 (11–25)	11 (7–17)	<0.0001	11 (7–16)	<0.0001	12 (7–17)	<0.0001	12 (7–15)	<0.0001
Duration of diabetes (years)	18.6 ± 12.1	25.5 ± 10.6	<0.0001	28.8 ± 7.9	<0.0001	33.4 ± 8.7	<0.0001	32.8 ± 8.0	<0.0001
Systolic BP (mmHg)	129 ± 16	136 ± 17	<0.0001	145 ± 20	<0.0001	152 ± 25	<0.0001	155 ± 25	<0.0001
Diastolic BP (mmHg)	78 ± 9	81 ± 10	<0.0001	83 ± 10	<0.0001	83 ± 13	<0.0001	85 ± 12	<0.0001
BMI (kg/m^2)	24.8 ± 3.3	25.6 ± 3.6	<0.0001	25.8 ± 3.9	<0.0001	23.5 ± 3.7	0.0002	24.6 ± 4.0	0.6
Waist circumference (cm)	83.7 ± 10.3	87.5 ± 11.2	<0.0001	89.6 ± 12.6	<0.0001	88.6 ± 12.4	<0.0001	90.1 ± 13.5	<0.0001
HbA_{1c} (% [mmol/mol])	8.2 ± 1.4 [66 ± 16]	8.8 ± 1.5 [73 ± 16]	<0.0001	9.0 ± 1.6 [75 ± 17]	<0.0001	8.5 ± 1.6 [69 ± 17]	0.04	8.5 ± 1.5 [70 ± 16]	0.02
Insulin dose (IU/kg)	0.71 ± 0.24	0.75 ± 0.25	0.0003	0.68 ± 0.22	0.02	0.77 ± 0.52	0.02	0.75 ± 0.28	0.08
Total cholesterol (mmol/L)	4.78 ± 0.89	4.99 ± 0.90	0.0001	5.37 ± 1.08	<0.0001	5.11 ± 1.39	0.02	5.27 ± 1.16	<0.0001
Triglycerides (mmol/L)	0.93 (0.72–1.28)	1.06 (0.81–1.53)	<0.0001	1.40 (1.03–2.06)	<0.0001	1.40 (0.99–2.00)	<0.0001	1.44 (0.98–1.88)	<0.0001
HDL cholesterol (mmol/L)	1.37 ± 0.38	1.32 ± 0.39	<0.0001	1.20 ± 0.37	<0.0001	1.13 ± 0.46	<0.0001	1.32 ± 0.42	0.09
LDL cholesterol (mmol/L)	2.92 ± 0.81	3.08 ± 0.83	0.0002	3.39 ± 0.90	<0.0001	3.44 ± 1.15	<0.0001	3.38 ± 1.08	<0.0001
24-h urine sodium excretion rate (mmol/24 h)	147.4 ± 65.2	156.3 ± 68.8	0.03	148.7 ± 63.8	0.7	NA	NA	NA	NA
eGDR (mg • kg^{-1} • min^{-1})	7.5 ± 2.1	5.4 ± 2.0	<0.0001	4.4 ± 1.7	<0.0001	4.3 ± 1.6	<0.0001	4.1 ± 1.5	<0.0001
eGFR† (mL/min/1.73 m^2)	95 (82–108)	89 (74–103)	<0.0001	55 (32–79)	<0.0001	NA	NA	NA	NA
Coronary heart disease (%)	2.7	5.2	0.004	10.5	<0.0001	28.1	<0.0001	22.9	<0.0001
Acute myocardial infarction (%)	1.1	3.9	<0.0001	6.3	<0.0001	18.7	<0.0001	13.5	<0.0001
Stroke (%)	0.8	0.6	1.0	4.9	<0.0001	16.4	<0.0001	14.2	<0.0001
Laser treatment (%)	14.3	47.5	<0.0001	79.8	<0.0001	95.8	<0.0001	97.6	<0.0001
Current smoking (%)	22.4	30.5	0.0001	29.5	0.0006	13.1	0.02	17.8	0.2

Data are mean ± SD, median (interquartile range), or %. *P* values represent comparisons with normoalbuminuria group. eGDR, estimated glucose disposal rate. †Estimated using the CKD-EPI equation.

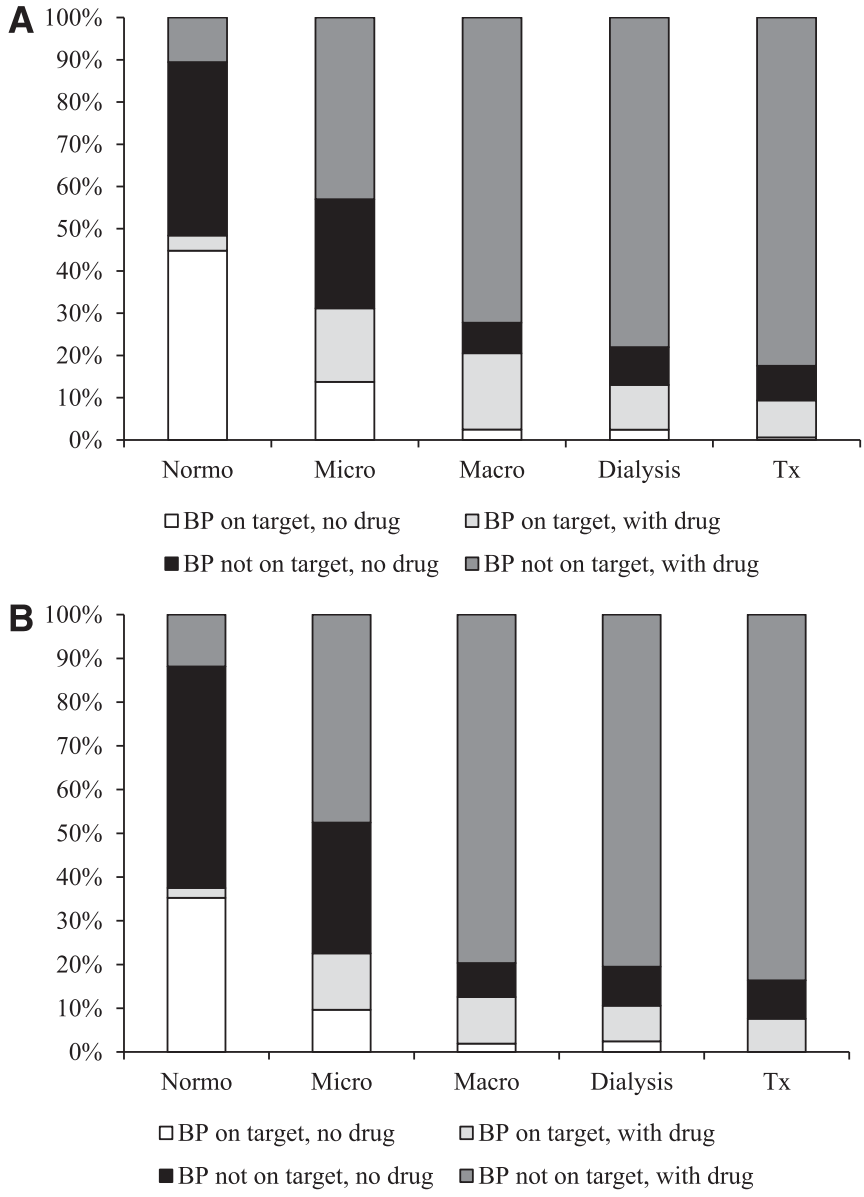

Figure 1—BP control based on the ADA BP target <130/85 (*A*) and <130/80 (*B*) in patients with type 1 diabetes by stages of diabetic nephropathy. Macro, macroalbuminuria; micro, microalbuminuria; normo, normoalbuminuria; Tx, kidney transplantation.

microalbuminuria groups (1.5 ± 0.8, P = 0.3), whereas the numbers were higher in the macroalbuminuria (2.2 ± 1.1, $P <$ 0.0001), dialysis (2.5 ± 1.1, $P < 0.0001$), and transplanted (2.3 ± 1.1, $P <$ 0.0001) groups. The mean numbers of antihypertensive drugs varied within the nephropathy groups between those who had BP on target and those who did not (Table 2). However, only in the micro- (P = 0.02) and macroalbuminuria (P = 0.003) groups were the mean numbers of the drugs higher if the BP was not on target, compared with those who had reached the targets. Notably, among the patients with normoalbuminuria who had not reached the BP target, 58% and, of the patients with microalbuminuria, 61% were taking only one antihypertensive drug. In contrast, more than half of the dialysis and 40% of the macroalbuminuric and transplanted patients, who had not reached the targets, had at least three drugs in their regimen. Moreover, one-fifth of the dialysis, 15% of the macroalbuminuric, and 10% of the transplanted patients had at least four antihypertensive drugs in use without reaching the target (Table 2). Almost all patients treated with antihypertensive drugs in the normo-, micro-, and macroalbuminuria groups (76% of normo-, 93% of micro-, and 89% of macrolbuminuric patients) had ACEIs or ARBs in the regimen. The proportions were lower in the ESRD groups: 42% of the dialysis and 29% of the transplanted patients were taking these drugs.

Prevalence of RH

In general, the prevalence of RH was 7.9% for all patients with type 1 diabetes

Table 2—Antihypertensive treatment (number and classes of drugs) according to the ADA BP target in patients with type 1 diabetes by stages of diabetic nephropathy

	Normoalbuminuria (n = 335)		Microalbuminuria (n = 295)		Macroalbuminuria (n = 475)		Dialysis (n = 109)		Kidney transplantation (n = 156)	
BP target <130/85	On target	Not on target	On target	Not on target	On target	Not on target	On target	Not on target	On target	Not on target
n (%)	85 (25.4)	250 (74.6)	85 (17.4)	210 (43.1)	95 (18.1)	380 (72.2)	13 (10.6)	96 (78.1)	15 (8.7)	141 (82.5)
Number of antihypertensive drugs, mean ± SD	1.4 ± 0.7	1.6 ± 0.8	1.3 ± 0.5	1.6 ± 0.8†	1.8 ± 0.9	2.3 ± 1.1‡	2.1 ± 1.0	2.6 ± 1.1	2.3 ± 1.2	2.3 ± 1.0
1 drug	61 (71.8)	144 (57.6)	67 (78.8)	127 (60.5)	44 (46.3)	114 (30.0)	4 (30.8)	20 (20.8)	3 (20.0)	33 (23.4)
2 drugs	15 (17.7)	74 (29.6)	14 (16.5)	57 (27.1)	28 (29.5)	108 (28.4)	5 (38.5)	24 (25.0)	8 (53.3)	51 (36.2)
3 drugs	8 (9.4)	24 (9.6)	4 (4.7)	19 (9.1)	17 (17.9)	103 (27.1)	3 (23.1)	31 (32.3)	2 (13.3)	44 (31.2)
≥4 drugs	1 (1.2)	8 (3.2)	None	7 (3.3)	6 (6.3)	55 (14.5)	1 (7.7)	21 (21.9)	2 (13.3)	13 (9.2)
Antihypertensive drug										
ACEI	53 (62.4)	160 (64.0)	71 (83.5)	161 (76.7)	86 (90.5)	268 (70.5)	5 (38.5)	29 (30.2)	1 (6.7)	26 (18.4)
ARB	12 (14.1)	32 (12.8)	9 (10.6)	32 (15.2)	2 (2.1)	67 (17.6)	None	13 (13.5)	3 (20.0)	15 (10.6)
Diuretic	18 (21.2)	66 (26.4)	11 (12.9)	51 (24.3)	38 (40.0)	196 (51.6)	7 (53.8)	65 (67.7)	8 (53.3)	71 (50.4)
β-Blockers	23 (27.1)	80 (32.0)	14 (16.5)	41 (19.5)	23 (24.2)	147 (38.7)	10 (76.9)	71 (74.0)	11 (73.3)	104 (73.8)
CCB	13 (15.3)	57 (22.8)	2 (2.4)	40 (19.0	26 (27.4)	171 (45.0)	4 (30.8)	62 (64.6)	10 (66.7)	94 (66.7)
Other	None	1 (0.4)	None	1 (0.5)	None	17 (4.5)	1 (7.7)	7 (7.3)	1 (6.7)	13 (9.2)
RH§										
≥3 drugs	NA	29 (8.7)	NA	23 (7.8)	NA	148 (31.2)	NA	45 (41.3)	NA	45 (28.8)
≥4 drugs	1 (1.2)	NA	0	NA	6 (6.3)	NA	1 (7.7)	NA	0	NA

Data are n (%) unless otherwise indicated. CCB, calcium channel blocker. Other indicates imidazoline receptor blockers (moxonidine and clonidine), prazosin, and/or minoxidil. †$P < 0.01$. ‡$P < 0.001$, on target vs. not on target within the nephropathy groups. §The failure to achieve target BP (<130/85 mmHg) using a minimum of three antihypertensive drugs, from different classes, one of which was a diuretic, and who achieve target BP, but require four or more antihypertensive drugs.

(n = 3,678) and 21.2% for the antihypertensive drug–treated patients (n = 1,370). The proportion was higher in men than in women (10.0 vs. 5.7%, $P <$ 0.0001). Notably, eight patients reached the BP target but required four or more antihypertensive drugs. If those patients are also considered as resistant to treatment, the prevalence of RH increases to 8.1% for all and 21.8% for drug-treated patients. When the patients were stratified by nephropathy status, the figures changed; in the normoalbuminuria group, the prevalence of RH was 1.2% of all and 8.7% of the drug treated patients. The corresponding numbers were 4.7 and 7.8% for the microalbuminuric patients, 28.1 and 31.2% for the macroalbuminuric patients, 36.6 and 41.3% for the patients on dialysis, and 26.3 and 28.8% for the kidney-transplanted patients, respectively (Table 2). The prevalence of RH also increased along with the worsening of renal function. The share was 1.4% for all and 7.4% for drug-treated patients at KDOQI stage 1. The corresponding numbers were 3.8 and 10.0% for the patients at stage 2, 26.6 and 30.0% for the patients at stage 3, 54.8 and 56.0% for the patients at stage 4, and 48.0 and 52.1% for those at stage 5, when kidney transplantation patients were excluded.

Factors Related to RH

In a multivariate logistic regression analysis, higher age, lower eGFR, higher waist-to-hip ratio, higher triglycerides, as well as microalbuminuria and macroalbuminuria, when normoalbuminuria was the reference category, were independently associated with RH (Table 3). A separate analysis also showed that dietary sodium intake, based on urinary sodium excretion rate, was independently associated with RH.

CONCLUSIONS

The current study shows that the prevalence of RH in patients with type 1 diabetes increases alongside the worsening of diabetic nephropathy. Whereas less than one-tenth of the antihypertensive drug–treated patients with normo- or microalbuminuria met the criteria for RH, the proportions were substantially higher among the patients

Table 3—Variables independently associated with RH

	Odds ratio	95% CI	*P* value
Model 1 (*n* = 3,384)			
Age (years)	1.04	1.02–1.05	<0.0001
eGFR (mL/min/1.73 m^2)	0.97	0.96–0.97	<0.0001
Normoalbuminuria	1.0	—	—
Microalbuminuria	2.58	1.43–4.67	0.002
Macroalbuminuria	5.61	3.20–9.84	<0.0001
Waist-to-hip ratio (per one-tenth increase)	1.44	1.15–1.80	<0.0001
Triglycerides (mmol/L)	1.19	1.01–1.40	0.04
Model 2 (*n* = 2,203)			
Age (years)	1.04	1.02–1.07	<0.0001
eGFR (mL/min/1.73 m^2)	0.96	0.95–0.98	<0.0001
Normoalbuminuria	1.0	—	—
Microalbuminuria	2.86	1.37–5.95	0.005
Macroalbuminuria	6.93	3.54–13.54	<0.0001
Triglycerides (mmol/L)	1.22	1.01–1.49	0.04
24-h sodium excretion rate (mmol/24 h; per 10 units increase)	1.05	1.02–1.09	0.002

Stepwise multivariate logistic regression analysis. Predictors in the model include sex, age, HbA_{1c}, insulin dose, laser treatment, triglycerides, HDL cholesterol, presence of coronary heart disease, nephropathy status, waist-to-hip ratio, eGFR, and 24-h urinary sodium excretion rate. Dialysis and kidney transplantation patients were excluded.

with overt nephropathy: one-third of the patients with macroalbuminuria or a transplanted kidney and even 40% of the patients on dialysis. However, the additional analysis shows that the prevalence of RH for the drug-treated patients was even higher (56%) in patients at the predialysis stage (eGFR 15–29). The findings are consistent with other studies that have demonstrated that chronic kidney disease is a strong predictor of failure to achieve BP targets despite the use of three or more different types of antihypertensive drugs in the general hypertensive population (26).

The prevalence of RH was 21.2% of the patients treated with antihypertensive drugs. Previous studies have indicated a prevalence of RH of 13% among patients being treated for hypertension (19–21,27). In fact, in these studies, patients with controlled BP requiring four or more antihypertensive drugs were classified as having RH. Although these patients also benefit from special diagnostic and therapeutic considerations, they may not be truly resistant to therapy. Therefore, we did not classify them as having RH. Thus, the prevalence seems to be even higher among the drug-treated type 1 diabetic patients. These figures can only partly be explained by the use of a lower treatment target for BP, as recommended for patients with diabetes (6), since even when we used the BP target recommended for hypertensive patients (<140/90 mmHg), our data still showed a higher prevalence of RH (17%). To our knowledge, this is the first study that has estimated the prevalence of RH in a large, nationwide, representative cohort of patients with type 1 diabetes in general as well as by stages of diabetic nephropathy.

Several risk factors for RH have been reported in the general population, including advanced age, male sex, diabetes, obesity, excessive dietary sodium intake, abdominal obesity, and renal and cardiac damage (17,19,20). In accordance with previous studies, we also observed that RH was associated with increased age, advanced kidney damage (both reduced eGFR and increased albuminuria), and higher waist-to-hip ratio, a marker of abdominal obesity. We also found an association between RH and triglycerides, suggesting that insulin resistance may be involved. It is of note that in addition to elevated BP, abdominal obesity and triglycerides are both components of the metabolic syndrome (28), with insulin resistance being the common factor behind the cluster of these metabolic abnormalities (29).

Excessive dietary sodium intake contributes to the development of RH by directly increasing BP and by blunting the BP-lowering effects of the antihypertensive drugs in the general hypertensive population (17). Therefore, we also estimated the average dietary salt intake, based on the 24-h urinary sodium excretion, and found an independent association between dietary sodium intake and RH. In our cohort (ESRD patients were not included), the mean daily salt intake was higher in the patients with RH ($P = 0.03$), exceeding 9.4 g/day (162.3 ± 64.2 mmol/24 h), compared with 8.6 g/day (148.3 ± 65.6 mmol/24 h) in those who did not fulfill the definition of RH.

The study also confirmed previous findings that a large number of patients with type 1 diabetes do not achieve the recommended BP targets. Although the prevalence of RH increased with the severity of diabetic nephropathy, our data also suggest that patients with normo- and microalbuminuria might have a suboptimal drug regimen, since the majority of those who had not reached the BP target were taking only one antihypertensive drug. We further showed that uncontrolled and therapy-RH is a common clinical problem in patients with a transplanted kidney. Although almost all of these transplanted patients had antihypertensive treatment, <10% had BP at target and 26% did not reach the target despite concurrent use of three or more antihypertensive drugs. There is therefore an urgent need to improve antihypertensive treatment, not only in

patients with overt nephropathy but also in those who have elevated BP without complications or early signs of renal disease. Moreover, further emphasis should be placed on the transplanted patients, since it is well known that hypertension affects both graft and patient survival negatively (30).

The high prevalence of uncontrolled BP may partly be explained by poor adherence to antihypertensive treatment. A retrospective study showed that 40% of patients with newly diagnosed hypertension discontinue their treatment during the 1st year of treatment (31). A recent paper, however, suggested that poor adherence may be less common in patients with diabetes since only 20% of the respondents showed poor adherence to their antihypertensive medications (32). In general, patients with type 1 diabetes have regular visits at the outpatient clinic or see their general practitioner at 3–4-month intervals. Given the fact that many patients are not optimally controlled for their BP, the true implementation of the prescribed medication should be reviewed during every visit, and interventions to improve adherence to antihypertensive treatment should be incorporated into each visit.

Previous studies have shown that the prevalence of obesity has risen among the type 1 diabetic population (33). The metabolic syndrome, which is characterized by impaired glucose regulation, central obesity, dyslipidemia, and hypertension, is also common in patients with type 1 diabetes and increases with advanced diabetic nephropathy (23). Therefore, in the strategies to improve the therapeutic efficacy and adherence to the antihypertensive treatment, more attention should be paid to lifestyle modifications, such as weight loss, exercise, dietary changes, and reduction of alcohol use. Assessment of mood disturbances, like depression, should also be included in such strategies, since these factors do affect adherence and impose barriers to the management of the patients (34).

Our findings indicate that a more aggressive and individualized approach to tackle the hypertension problem is required (18,35,36). The first step is to confirm the presence of uncontrolled hypertension or RH by using the correct BP measurement technique, excluding the white coat effect, and assessing the patient's adherence to their treatment. Second, successful treatment requires the identification and reversal of harmful lifestyle factors, discontinuation or minimization of interfering substances, and screening for secondary causes of hypertension. Moreover, an efficient pharmacotherapy regimen should be tailored on an individual basis for each patient. Finally, when a specific secondary cause of hypertension is suspected or the BP remains elevated in spite of 6 months treatment, referral to an appropriate specialist should be considered.

There are some limitations in our study that need to be addressed. First, the BP readings were based on two office-based measurements at a single visit. Ambulatory BP (ABP) measurements may provide more accurate estimates of BP, including information on nocturnal BP, and thus have been shown to better distinguish between true and apparent RH (26). Consequently, previous studies have suggested that 20–30% of the patients with RH have in fact controlled BP, if ABP measures are used instead of office-based readings (27,37). However, masked hypertension, defined as a normal office BP and elevated ABP, may occur in 10% of the patients with type 1 diabetes (38). Notably, the prevalence of masked hypertension could be even higher in patients with albuminuria than in those with normal AER, since reduced nocturnal dipping of BP has been reported to be associated with microalbuminuria in patients with type 1 diabetes (39). Therefore, hypertension status may have been incorrectly assigned to some patients. As a consequence, our results might overestimate the true prevalence of RH because the white coat effect was not excluded, but also underestimate it because the masked effect was not assessed. However, it is important to acknowledge that office-based measurements reflect the current clinical practice and are routinely used in the management of patients with hypertension. Second, although the coverage and accuracy of the Finnish DPR is very high, medication doses and frequencies are not recorded in this register. Moreover, we were not able to assess the patient adherence to antihypertensive treatment. Nevertheless, the main strength of our study is the large sample size and well-characterized study population, regarding clinical factors, medical history, and classification of diabetes complications. The generalizability of the present results may be limited by the fact that the FinnDiane study is not, by strict definition, population based. However, a possible selection bias is unlikely as the geographical distribution of the patients was similar to the general distribution of people in Finland, and patient recruitment at the participating centers was random.

In summary, this study shows that the prevalence of uncontrolled hypertension and RH increases with more severe stages of diabetic nephropathy in patients with type 1 diabetes. Our data also point out that elevated BP and suboptimal drug regimen are common in patients who have normal AER or early signs of kidney disease. This highlights the fact that a more aggressive approach to improve BP control should be implemented, not only in patients with overt nephropathy and RH but also in those patients who have uncontrolled BP with or without early signs of diabetes complications.

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