White Coat Hypertension in NIDDM Patients With and Without Incipient and Overt Diabetic Nephropathy

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OBJECTIVE — Early data have suggested a high prevalence of white coat hypertension (~50%) in NIDDM patients. To study this phenomenon further, we determined the prevalence of white coat hypertension in NIDDM patients with normo- or microalbuminuria or with diabetic nephropathy.

RESEARCH DESIGN AND METHODS — Three groups of hypertensive NIDDM patients (repeated clinic blood pressure >140/90 mmHg or antihypertensive treatment) attending the Steno Diabetes Center were investigated in a cross-sectional study. Group 1 had normoalbuminuria (a urinary albumin excretion [UAE] rate <30 mg/24 h, n = 30, age 61 ± 7 [mean ± SD] years, 20 men), group 2 had microalbuminuria (UAE rate 30–300 mg/24 h, n = 51, age 55 ± 7 years, 35 men), and group 3 had diabetic nephropathy (UAE rate >300 mg/24h, n = 47, 62 ± 7 years, 36 men). If given, all previous antihypertensive medication was withdrawn at least 2 weeks before the study (48%). The prevalence of white coat hypertension (clinic hypertension with normal blood pressure values at home) was determined by comparison of clinic blood pressure (Hawksley Random sphygmomanometer) and the ambulatory daytime (7:00 A.M. to 11:00 P.M.) blood pressure (A&D TM2420). By applying established criteria, white coat hypertension was confirmed if daytime blood pressure was <135/85 mmHg.

RESULTS — The clinic blood pressure was 155/86 (SE 3/2) mmHg, 156/89 (2/1) mmHg, and 171/90 (3/2) mmHg in group 1, 2, and 3, respectively ($P < 0.05$ comparing group 3 with groups 1 and 2). The prevalence of white coat hypertension was significantly higher in group 1 as compared with groups 2 and 3, 23% (95% CI 10–42) vs. 8% (2–19) and 9% (2–20) ($P < 0.05$), with no difference between the latter two groups.

CONCLUSIONS — The prevalence of white coat hypertension in normoalbuminuric NIDDM patients resembles that observed in nondiabetic subjects with essential hypertension, whereas the prevalence is significantly lower in NIDDM patients with incipient or overt diabetic nephropathy, suggesting a difference between primary and secondary hypertension.

Arterial hypertension (mean of repeated blood pressure measurements ≥140/90 mmHg) is present in 71–93% of NIDDM patients, applying the criteria of The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1). The prevalence increases with increasing levels of urinary albumin excretion (UAE) rate (1). The treatment of hypertension is often everlasting, costly, and has side effects, and consequently should only be given to patients at risk of developing hypertensive target organ damage. The development of noninvasive ambulatory blood pressure monitoring techniques has provided a method for measuring blood pressure over more prolonged periods of time and across a wider variety of circumstances than is possible with clinic measurements. These techniques have demonstrated a subgroup of patients with a persistently raised clinic blood pressure together with a normal ambulatory blood pressure, so-called white coat hypertension (2). The prevalence of white coat hypertension is ~20–25% in essential hypertension (3). In striking contrast, two small studies have reported that the prevalence of white coat hypertension in hypertensive NIDDM patients is as high as 51–62% (4,5). Therefore, the aim of our study was to determine the prevalence of white coat hypertension in NIDDM patients with or without incipient or overt nephropathy.

RESEARCH DESIGN AND METHODS

— The patients included in the present study were selected from two previously reported studies (6,7). The 30 normoalbuminuric NIDDM patients and the 47 NIDDM patients with diabetic nephropathy included in the present study were selected from a previously reported case-control study describing diurnal blood pressure rhythm (6). Two weeks before this study, antihypertensive treatment was withdrawn. Patients from this study were included in the present study if they had received antihypertensive treatment before the investigations or if they were hypertensive (mean of repeated blood pressure measurements ≥140/90 mmHg) without antihypertensive medication. The 50 microalbuminuric NIDDM patients included in the present study were selected from another study evaluating hyperfiltration in 158 microalbuminuric NIDDM patients (7). In that study, antihypertensive treatment was not withdrawn at the time of investigation. Of the 158 patients studied, 54 patients (34%) received antihypertensive treatment and 58 of the remaining 104 patients were hypertensive (mean of repeated blood pressure measurements ≥140/90 mmHg). A 24-h ambulatory blood pressure was recorded successfully in 50 of these patients and they were included in the present study.

All patients collected at least three 24-h urine collections. Patients previously receiving antihypertensive treatment performed the collections while they were without antihypertensive medication. Normoalbuminuria was confirmed if the UAE rate was

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UAE, urinary albumin excretion.

<30 mg/24 h and microalbuminuria if the UAE rate was 30–300 mg/24 h. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent UAE rate >300 mg/24 h, presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract disease (8). In patients (n = 15) with a persistent UAE rate >300 mg/24 h who did not fulfill the above-mentioned criteria, a kidney biopsy was performed to establish the presence of diabetic glomerulosclerosis. The patients were considered to have NIDDM if they were treated with diet alone, or in combination with an oral hypoglycemic agent, or if they were treated with insulin and had an onset of diabetes after the age of 40 years and a BMI index above normal (≥25 kg/m² in women, ≥27 kg/m² in men) at the time of diagnosis (9). All insulin-treated patients had a glucagon test performed, and NIDDM was diagnosed if a stimulated plasma C-peptide value was ≥0.60 pmol/ml (10). The glucagon/C-peptide test was carried out at 8:00 A.M. after an overnight fast. Blood samples for plasma C-peptide determination were obtained before and 6 min after an intravenous bolus injection of 1 mg glucagon (Novo Nordisk, Bagsværd, Denmark), as described previously (10). All microalbuminuric NIDDM patients had a glucagon/C-peptide test performed (as part of the original study protocol [7]). All subjects included in the study were Caucasian, and all gave informed consent to participate in the study. The study was approved by the Regional Ethics Committee.

Study protocol

The 24-h ambulatory blood pressure measurements were performed on each patient in their home. A 24-h ambulatory blood pressure was measured with the Takeda TM 2420 (A & D, Tokyo, Japan) device version 6 and 7 (11–13). A cuff size of 20–31 cm was used in patients with an upper arm circumference <32 cm, and a cuff size of 28–36 cm was used in patients with an upper arm circumference >32 cm. Patients were instructed not to move their arm during the ongoing measurement. Once yearly, the devices were tested on the bench by the local A & D agent. All devices had a variation of less than ±3 mmHg for both systolic and diastolic blood pressure, as compared with a mercury sphygmomanometer before and after the study. Recordings of 24-h ambulatory blood pressure during ordinary life conditions on two occasions 2–4 months apart in 63 diabetic patients revealed that the coefficient of variation for systolic/diastolic daytime blood pressure was 10/7%. Values were averaged for each hour before calculating the daytime blood pressure. No editing was performed in the recorded blood pressure values. Any 24-h blood pressure measurement was accepted if at least 50% of the programmed pressures were measured successfully for each hour during the whole 24-h monitoring interval. Clinic blood pressure was measured (three measurements) with a random zero sphygmomanometer (Hawksley, Lancing, West Sussex, U.K.) and expressed as the mean value. Blood pressure was determined between 8:00 A.M. and 12:00 P.M. according to the recommendations of the British Society of Hypertension, and the first and fifth Korotkoff sounds for systolic and diastolic blood pressure were applied (14). Cuff size 25 × 12 cm was used in lean patients and 30 × 15 cm in obese patients. The white coat effect was calculated as the difference between the clinic blood pressure and the daytime (7:00 A.M. to 11:00 P.M.) ambulatory blood pressure (3). White coat hypertension was diagnosed according to criteria established by European and American scientists if the daytime arterial blood pressure was <135/85 mmHg (15–17). Usual arterial blood pressure was determined as the average of at least three measurements in the sitting position using a mercury sphygmomanometer in the outpatient clinic during the year before the study. Glomerular filtration rate was measured after a single intravenous injection of 3.7 MBq chromium-51–labeled edetic acid at 8:00 A.M. by determining the radioactivity in venous blood samples taken from the other arm 180, 200, 220, and 240 min after injection (18).

HbA_{1c} was measured by high-performance liquid chromatography (Bio Rad DIAMAT, Richmond, CA) (normal range 4.3–6.2%). Serum creatinine was measured by a reaction rate kinetic technique eliminating pseudo-creatinines (19). Urinary albumin concentration was measured using an enzyme immunoassay and expressed as the median of three 24-h collections (20). Smokers were defined as subjects smoking more than one cigarette daily.

Statistical analysis

Clinical data are given as means ± SD or median (range). All other normally distributed values are given as means ± SE. Frequencies are given as percentage and 95% CI.

In a comparison of the non-normally distributed variables, the Kruskal-Wallis test of variance was used to test for differences among the three groups. If differences were found, the Mann-Whitney test was used for comparisons between two groups. For all other normally distributed variables, analysis of variance was performed to test for differences among the three groups. If differences were found, the Student's t test was used for comparison between two groups. Correction for multiple analysis was not performed because statistical analysis was planned before calculations were made. The χ^2 test was used for evaluating frequencies.

A P value (two-tailed) <0.05 was considered statistically significant. For correlation analysis, Pearson's correlation coefficient was calculated. All calculations were made with a commercially available program, Statgraphic (STSC, Rockville, MD).

RESULTS — Table 1 shows pertinent clinical data in the three groups. The microalbuminuric patients were younger and had a shorter known duration of diabetes as compared with the normoalbuminuric and nephropathic groups, with no differences between the latter two groups. The three groups were well matched with regard to BMI.

The ambulatory daytime blood pressure is plotted against the clinic blood pressure in Fig. 1. Applying the established definition of white coat hypertension on our data, the prevalence of white coat hypertension was 23% (95% CI 10–42), 8% (2–19), and 9% (2–20) in the NIDDM patients with normoalbuminuria, microalbuminuria, and nephropathy, respectively ($P < 0.05$ comparing normal with elevated levels of UAE rate). Only one normoalbuminuric NIDDM patient who previously had received antihypertensive medication was normotensive in the clinic and hypertensive outside the clinic and classified as pseudonormotensive. The vast majority (88% [95% CI 81–93]) of the NIDDM patients in our study were truly hypertensive.

The white coat effect (clinic blood pressure ÷ daytime blood pressure) was significant for the systolic blood pressure in the NIDDM patients with normoalbuminuria (13 mmHg [95% CI 5-20], $P < 0.001$) and in NIDDM patients with nephropathy (9 mmHg [95% CI 2–16], $P < 0.02$), whereas no significant white coat effect was seen in the NIDDM patients with microalbuminuria (Fig. 2 and Table 2). No white coat

Table 1—*Clinical data in NIDDM patients with normal or elevated UAE rate*

	NIDDM patients with normoalbuminuria	NIDDM patients with microalbuminuria	NIDDM patients with nephropathy	*P* value
Sex (M/F)	20/10	34/16	36/11	NS
Age (years)	62 ± 7	55 ± 7	62 ± 7	* †
Known diabetes duration (years)	14 ± 8	8 ± 7	14 ± 8	* †
BMI (kg/m^2)	29.5 ± 5.2	29.7 ± 3.7	29.9 ± 4.6	NS
HbA_{1c} (%)	8.2 ± 1.4	8.7 ± 1.7	8.6 ± 2.0	NS
Treatment (%) (diet/oral hypoglycemic agent/insulin)	23/50/23	28/58/14	12/48/40	‡
Retinopathy (none/simplex/proliferative)	33/57/10	72/26/2	9/64/27	§ ‖
UAE rate (mg/24 h)	10 (2–29)	80 (32–292)	1225 (270–6058)	
Glomerular filtration rate (ml · min^{-1} · 1.73 m^{-2})	95 ± 18	120 ± 22	70 ± 32	* † ¶
Previous antihypertensive treatment (%)	53	0	90	* † #
Prevalence of smokers (%)	47	34	45	NS

Data are means ± SD or median (range). *$P < 0.0001$ comparing NIDDM patients with normoalbuminuria and microalbuminuria; †$P < 0.0001$ comparing NIDDM patients with microalbuminuria and nephropathy, ‡$P < 0.01$ comparing NIDDM patients with microalbuminuria and nephropathy; §$P < 0.001$ comparing NIDDM patients with normoalbuminuria and microalbuminuria, ‖$P < 0.02$ comparing NIDDM patients with normoalbuminuria and nephropathy, ¶$P < 0.0001$ comparing NIDDM patients with normoalbuminuria and nephropathy, #$P < 0.0002$ comparing NIDDM patients with normoalbuminuria and nephropathy.

effect was seen for the diastolic blood pressure in any of the three groups.

In the normoalbuminuric NIDDM patients, no significant differences were found comparing patients with (n = 16) or without (n = 14) previous antihypertensive treatment regarding the following parameters: clinic blood pressure of 160/86 (4/6) vs. 150/84 (3/2) mmHg, daytime blood pressure of 144/86 (4/2) vs. 139/85 (5/2) mmHg, and systolic white coat effect of 16 (95% CI 5–27) vs. 10 (−1 to 21) mmHg or the prevalence of white coat hypertension of 21% (95% CI 5–51) vs. 25% (7–52), respectively.

CONCLUSIONS — We report a cross-sectional study demonstrating the prevalence of white coat hypertension (normal ambulatory blood pressure and persistently elevated clinic blood pressure) to be 23% (95% CI 10–42), 8% (2–19), and 9% (2–20) in NIDDM patients with normoalbuminuria, microalbuminuria, or diabetic nephropathy, respectively. The prevalence of white coat hypertension in the normoalbuminuric NIDDM patients is comparable to that observed in nondiabetic subjects with essential hypertension, as reviewed by Pickering (3), and higher than in NIDDM patients with elevated UAE rates. Furthermore, the white coat effect was present only in systolic blood pressure.

Theoretically, the results of our study might have been influenced by differences in antihypertensive treatment in the three investigated groups. However, it is controversial whether antihypertensive treatment has any influence on the white coat effect, as reviewed by Pickering (3). In addition, the prevalence of white coat hypertension has been shown to be ~25% in both newly diagnosed untreated Danish hypertensive patients and in hypertensive patients who had antihypertensive medication withdrawn (21). Furthermore, no significant differences were demonstrated in clinic or daytime blood pressure, in the systolic white coat effect, or in prevalence of white coat hypertension comparing normoalbuminuric NIDDM patients with or without previous antihypertensive treatment in our study.

A short duration of hypertension is associated with a high prevalence of white coat hypertension (22). The duration of hypertension was not known in our patients. Because none of our microalbuminuric NIDDM patients received any antihypertensive treatment, this might indicate a shorter duration of hypertension as compared with the normoalbuminuric and nephropathic patients, where the prevalence of previous antihypertensive treatment was 53 and 90%, respectively. If the duration of hypertension was shorter in the microalbuminuric patients as compared with the other patients studied, we would have overestimated the prevalence of white coat hypertension in the microalbuminuric patients, thus rein-

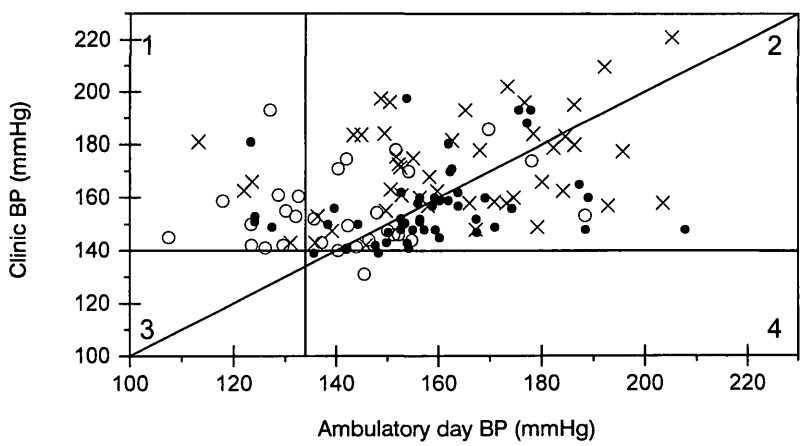

Figure 1—*Plot of daytime (7:00 A.M. to 11:00 P.M.) systolic ambulatory blood pressure against clinic blood pressure. The four quadrants are separated by cutoff points for "normal" clinic (140 mmHg) and ambulatory daytime (134 mmHg) blood pressures. (○), NIDDM patients with normoalbuminuria; (●), NIDDM patients with microalbuminuria; (×), NIDDM patients with diabetic nephropathy. Quadrant 1, white coat hypertension; 2, sustained (true) hypertension; 3, true normotension; 4, pseudonormotension. Diagonal line is the line of identity. The white coat effect is the distance of each point from the line of identity.*

Table 2—*Clinic blood pressure and daytime blood pressure in NIDDM patients with normal or elevated UAE rate*

	NIDDM patients with normoalbuminuria	NIDDM patients with microalbuminuria	NIDDM patients with nephropathy	*P* value
Clinic blood pressure (mmHg)	155/85 ± 3/2	156/89 ± 2/1	171/90 ± 3/2	*,†,NS
SDaytime blood pressure (mmHg)	142/85 ± 3/2	157/88 ± 2/1	162/89 ± 3/2	*,‡,NS

Data are means ± SE. *$P < 0.0001$ comparing NIDDM patients with normoalbuminuria and nephropathy, †$P < 0.0001$ comparing NIDDM patients with microalbuminuria and nephropathy, ‡$P < 0.0001$ comparing NIDDM patients with normoalbuminuria and microalbuminuria.

forcing the statement that the prevalence of white coat hypertension decreases in NIDDM patients as elevated UAE rate appears. Based on the above-mentioned data, it does not appear that our results are caused by the presence or absence of previous antihypertensive treatment.

The phenomenon of white coat hypertension is founded on the white coat effect, which is generally defined as the difference between the average clinic blood pressure and the daytime ambulatory blood pressure. White coat hypertension is a measure of blood pressure level, whereas the white coat effect is a measure of change. A large white coat effect is by no means confined to patients with white coat hypertension. Several factors are known to increase the white coat effect, such as older age, higher blood pressure level, African-American race, female sex, lack of rest, and silence in conjunction with the blood pressure measurement and performance of blood pressure measurement by a doctor as compared with a nurse, as reviewed by Pickering (3). In contrast, lifestyle factors, such as smoking and alcohol intake, are not associated with white coat hypertension (22).

The broad definition of white coat hypertension is a persistently elevated clinic blood pressure and a normal ambulatory blood pressure. The precise definition is inevitably arbitrary, like any other category of hypertension. The normal levels of ambulatory daytime blood pressure have been reported as a wide range of values in small studies, but already in 1990, a consensus report (23), based on a meta-analysis of the previously published studies (24), recommended that the normal value for ambulatory daytime blood pressure should be <135/85 mmHg. Recently, this level has been confirmed by European (16) and American (15) scientists. Now the general accepted definition of white coat hypertension is as follows: persistently elevated clinic blood pressure ≥140/90 mmHg and a normal daytime ambulatory blood pressure <135/85 mmHg (15–17).

The prevalence of white coat hypertension has been reported to be as high as 51–62% in NIDDM patients (4,5). In 29 microalbuminuric NIDDM patients free of antihypertensive medication, Burgess et al. (4) reported the prevalence of white coat hypertension to be 62%. Clinic hypertension was defined as a mean blood pressure ≥100 mmHg, and white coat hypertension was considered to be present if the mean ambulatory blood pressure (8:00 A.M. to 12:00 A.M.) was lower than the mean clinic blood pressure. Applying this inclusion criterion and the definition of white coat hypertension on our study population reveals a prevalence of white coat hypertension of 63% (95% CI 54–72), which is in accordance with the 62% (42–79) reported by Burgess et al. (4) ($P = 0.92$).

Recently, Puig et al. (5) found a prevalence of white coat hypertension of 51% in 43 Spanish hypertensive NIDDM patients without renal insufficiency, defined as a creatinine clearance >30 ml/min. If given, antihypertensive medication was withdrawn 2 weeks before the study (58%). Clinic hypertension was defined as a diastolic blood pressure between 90 and 104 mmHg, and white coat hypertension was considered to be present if the diastolic 24-h ambulatory blood pressure was <85 mmHg. If we apply the inclusion criterion and the definition of white coat hypertension used by Puig et al. (5) on our NIDDM patients, we find the prevalence of white coat hypertension to be 35% (95% CI 32–50), which is not significantly different from the prevalence of 51% (35–67), as reported by Puig et al. (5) ($P = 0.11$).

It is obvious that when using the same criteria for the diagnosis of white coat hypertension, the prevalence of the phenomenon is comparable in our study and in the two previously reported studies by Puig et al. (5) and Burgess et al. (4). The high prevalence of white coat hypertension in the two previously reported studies is mainly the consequence of applying nonestablished criteria for the definition of white coat hypertension. This calls for a plea for consistency when applying criteria for the division of a continuous variable into a dichotomous variable.

White coat hypertension appears to be a low-risk condition. It has been demonstrated that the prognosis of white coat hypertensive patients is comparable to that of the normotensive population (25). Furthermore, white coat hypertension is associated with a relative absence of target organ

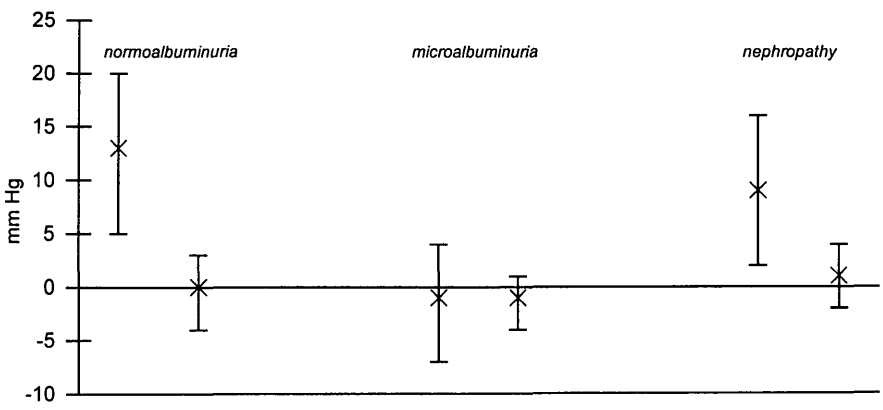

Figure 2—*The white coat effect (clinic blood pressure − daytime [7:00 A.M. to 11:00 P.M.] ambulatory blood pressure) for systolic and diastolic blood pressure in NIDDM patients with normoalbuminuria, microalbuminuria, or diabetic nephropathy. The values are means and 95% CI.*

damage and metabolic abnormalities characteristic of sustained hypertension, as reviewed by Pickering (3). Challenging this point of view, Glenn et al. (26) recently described functional cardiovascular abnormalities in white coat hypertensive patients without identifiable structural cardiovascular abnormalities in a cross-sectional study. The prognostic impact of these functional cardiovascular abnormalities awaits further investigation. The authors suggest that white coat hypertensive patients might benefit from antihypertensive treatment. This is not in accordance with the generally accepted view that pharmacological treatment of white coat hypertension is ineffective in reducing ambulatory blood pressure levels and therefore considered unnecessary, as reviewed by Pickering (3). The ineffectiveness of antihypertensive treatment on ambulatory blood pressure in white coat hypertensive patients has also been demonstrated in NIDDM patients by Puig et al. (5). No information on the long-term effect of antihypertensive treatment of white coat hypertension is available at the present time.

White coat hypertensive patients seem to have a high risk of developing persistent hypertension, as demonstrated by Bidlingmeyer et al. (27), who recently demonstrated that persistent hypertension developed over a 6-year period in 75% of patients with white coat hypertension. This development could not be predicted by the clinic blood pressure. Therefore, the patients with white coat hypertension should be followed regularly with ambulatory blood pressure measurements.

In conclusion, the prevalence of white coat hypertension in normoalbuminuric NIDDM patients resembles that observed in nondiabetic subjects with essential hypertension, whereas the prevalence is significantly lower in NIDDM patients with incipient or overt diabetic nephropathy, suggesting a difference between primary and secondary hypertension.

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