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The increased risk of coronary heart disease associated with nephrotic syndrome

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The increased risk of coronary heart disease associated with nephrotic syndrome. Patients with nephrotic syndrome (NS) are believed to be at increased risk of atherosclerosis and coronary heart disease (CHD), although existing evidence for this association has not been persuasive. The risk of CHD among 142 persons with NS documented by proteinuria ≥ 3.5 g daily was compared with that among 142 matched controls randomly selected from the membership of a large Northern California health plan. Controls were matched for sex, year of birth, and presence in the health plan when the referent case was diagnosed. No diabetics were included in this study. Mean follow-up for nonfatal CHD events was 5.6 years for NS subjects and 11.2 years for controls. Among the NS subjects myocardial infarction (MI) developed in 11, and there were 58 deaths, seven because of CHD. Among the controls, there were four MIs and 10 deaths, three because of CHD. In matched-pair analysis, there were 11 MIs among NS subjects and none among controls [P = 0.001, lower bound of 95% confidence interval for relative risk (CI), 2.8]. In an unmatched analysis adjusted for hypertension and smoking at diagnosis of NS, the relative risk of MI was 5.5 (95% CI 1.6 to 18.3) and the relative risk of coronary death was 2.8 (95% CI 0.7 to 11.3). Omitting data of NS subjects with minimal change disease and systemic lupus erythematosus yielded similar results. These data suggest that persons with NS are at increased risk of CHD.

The nephrotic syndrome (NS) is characterized by heavy proteinuria and a variable tendency toward hypoalbuminemia, hyperlipidemia, and edema [1]. Patients with NS are assumed to be at increased risk for atherosclerosis and coronary heart disease (CHD), probably because of NS-associated hyperlipidemia. The most frequent of these abnormalities is hypercholesterolemia and, as the disease progresses in some patients, hypertriglyceridemia [2–5]. Although hyperlipidemia can lead to atherosclerosis, CHD has not been proven to be more common in persons diagnosed with NS than in the general population. Several case studies suggested increased risk of CHD among patients with NS [6, 7], but other studies [8–11] showed no increased risk of CHD among NS patients. These studies were criticized for having small sample sizes, ill-defined comparison groups [12, 13], or incomplete documentation of CHD among subjects [13].

Among the major challenges in studying the association between NS and CHD are: need for a large number of NS patients and an appropriate control group, need to adjust for potentially confounding factors (such as hypertension), and difficulty of obtaining sufficiently long-term follow-up. We used the computer-stored files and hospital records of a large prepaid health plan to investigate incidence of CHD among patients diagnosed with NS.

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Methods

The Kaiser Permanente Medical Care Program of Northern California (KPMCP) is a prepaid health plan that had about 1.8 million members in 1980. Comprehensive health services have been offered by the program since the late 1940s. Age and sex composition of the membership is similar to that of the United States Census population in the area, and the membership is representative of diverse racial, occupational, educational, and income groups [14, 15].

NS subject selection

Patients with clinically diagnosed NS were identified from the hospital discharge records of all Kaiser Foundation Hospitals in Northern California by using computer-stored files dating from 1976 to 1981 and manual review of hospital discharge logs dating from before 1976 (581 *ICDA*, 8th ed.) [16] (581.0-.9, *ICD-9-CM* 9th ed.) [17]. The criterion for confirming the diagnosis of NS was proteinuria of ≥3.5 g daily. The presence of hypoalbuminemia (serum albumin <3.0 mg/dl), hypercholesterolemia, and hypertriglyceridemia were also recorded but were not considered essential for the diagnosis [1]. Patients who had ever been diagnosed with diabetes mellitus and those younger than 15 years at NS diagnosis were excluded. We identified 155 persons diagnosed with NS between 1961 and 1981 who were alive on 1/1/71. Thirteen of these had evidence of CHD before diagnosis and were excluded from the main analyses.

Control subject selection

From computer-stored files of the general health plan membership, which were only available from 1971 onward, we selected one control subject for each NS subject. Control subjects were randomly selected from all eligible members who matched research subjects by sex and by age (within 5 years) and who were members of the health plan at NS diagnosis. We excluded potential control subjects whose medical records showed any evidence of kidney disease or diabetes.

Data collection

We reviewed the entire inpatient and outpatient record of each subject for the following demographic information: type and date of diagnosis of kidney disease; whether kidney biopsy was done; serum creatinine determinations; quantification of urinary protein excretion and cholesterol levels; date of onset and mode of treatment of end-stage renal disease (ESRD) when it occurred; smoking history; presence and date of onset of hypertension; and evidence of CHD. Hypertension was defined as three or more blood pressure recordings of ≥155/95 mm Hg.

Presence of CHD was determined by: (1) occurrence of myocardial infarction (MI); (2) a physician's diagnosis of angina pectoris or coronary insufficiency; (3) an abnormal electrocardiogram (ECG), read as "probable or definite ischemia" according to the Minnesota Code [18]; or (4) death secondary to CHD. All ECGs were read by an investigator who was blind to the NS status of the subject. The clinical diagnosis of MI was confirmed by abnormal ECG tracing and enzyme elevation.

We obtained information on date and cause of death from the medical record. Deaths were also independently confirmed by linking the files of research and control subjects to the California Mortality Linkage System (CAMLIS), a State of California registry of deaths since 1960 [19]. A final assessment of the cause of death was made on the basis of medical records, death certificates, and available autopsy records by an investigator who was blind to the NS status of the subjects.

Analysis

For analysis, we defined the follow-up period for nonfatal CHD events as the period from date of initial NS diagnosis (and the equivalent date for corresponding control subjects) to date of outcome (such as MI, ESRD, death), date of the last contact recorded in the medical record (up to 2/16/87), or termination of KPMCP membership, whichever came first. For fatal CHD events, we began follow-up on 1/1/71, because subjects were selected from the computer-stored 1971 membership file and, thus, by definition, had to be alive on that date. Follow-up ended at death or on 6/30/86, the date covered by the death search. More control subjects than NS subjects were reviewed later in the study period, which contributed to the longer total follow-up for control subjects than for NS subjects. We considered deaths of NS subjects in whom ESRD developed during follow-up to be "renal deaths," and follow-up was ended on the date of first dialysis.

For CHD outcomes, we first did a survival analysis using a matched-pair design in which follow-up for both members of each pair stopped at the end of follow-up for either the NS subject or the control subject. To estimate relative risk (RR), we calculated the ratio of events among NS subjects to events among control subjects. We determined statistical significance using a binomial test and calculated binomial confidence intervals. We next calculated rates of CHD outcomes per person-years of follow-up and then examined the risk of CHD events using proportional hazards models and adjusting for the presence of hypertension from five years before through the year of diagnosis and for current smoking status at diagnosis.

Table 1. Comparison of subjects with nephrotic syndrome (NS) and corresponding control subjects

	NS subjects		Control subjects	
	No.	Variable	No.	Variable
Number				
Mean age at diagnosis *years*	142	43.7	142	43.0
Percentage male	142	62.7	142	62.7
Mean follow-up *years*	142	5.6	142	11.2
Mean mortality follow-up *years*	142	7.8	142	10.9
Current smokers at diagnosis %	117	43.6	104	46.2
History of hypertension at diagnosis[a] %	141	29.8	142	9.2
Mean cholesterol level (mg/dl) ± SE at diagnosis[a,b]	109	371 ± 13	27	220 ± 8
Maximum cholesterol level[b] (mg/dl) ± SE at diagnosis	109	412 ± 16	27	222 ± 8

[a] History of hypertension (≥ 155/95 on 3 occasions) from 5 years before through the year of NS diagnosis and corresponding dates for matched comparison group.

[b] Cholesterol value recorded from one year before to six months after date of NS diagnosis and on corresponding dates for matched comparison group.

Results

NS and control subjects were closely matched for age and sex (Table 1). Six NS subjects and corresponding control subjects were younger than 18 years of age; the youngest was 15 years of age. Far more NS than control subjects had an outcome event during follow-up; the mean follow-up for nonfatal CHD events was 5.6 years for NS subjects and 7.8 years for mortality. Follow-up for the mortality analysis was longer because some deaths occurred after subjects left the KPMCP. Although the proportion of smokers was similar in each group, hypertension at the time of NS diagnosis was more frequent in NS subjects ($P \leq 0.001$). For subjects whose cholesterol level was recorded around the time of NS diagnosis, the mean and maximum cholesterol levels recorded within one year before to six months after the diagnosis were significantly ($P \leq 0.001$) higher for NS subjects than for controls. All but one of these 109 NS subjects had cholesterol levels >220 mg/dl (5.69 mmol/liter) during this 1½ year period. An additional 16 NS subjects had recorded serum cholesterol levels >220 mg/dl (5.69 mmol/liter) at other times during the follow-up period. The other 17 had either lower levels [4] or no recorded values. When compared with the 125 NS subjects with recorded values >220 mg/dl (5.69 mmol/liter), these 17 were more likely to be female and younger and to have shorter follow-up and more nonfatal CHD events. None of these differences was statistically significant. Among 135 NS subjects with a recorded serum albumin level, 107 (79.3%) had recorded values <3 mg/dl. Triglyceride values were not recorded frequently enough to provide useful data.

Membranous nephropathy was diagnosed in about 28% of research subjects (Table 2). Men predominated in all etiologic groups except the systemic lupus erythematosus (SLE) group. The category of glomerulonephritis (GN) included eight NS cases with mesangial proliferative GN diagnosed at biopsy, seven cases of membranoproliferative GN, and one case each of rapidly progressive GN and IgA nephropathy. The category

Table 2. Distribution of renal diagnoses and frequency of biopsies of NS subjects

Renal diagnosis	No. %	No. % who had biopsy	% Male	Mean age at diagnosis
Membranous nephropathy	40 (28.2)	40 (100.0)	75.0	46.0
Minimal change disease	17 (12.0)	17 (100.0)	58.8	43.4
Glomerulonephritis	30 (21.1)	21 (70.0)	56.7	40.1
Focal glomerulonephritis	9 (6.3)	9 (100.0)	66.7	45.0
Systemic lupus erythematosus	11 (7.7)	6 (54.6)	18.2	46.7
Amyloidosis	4 (2.8)	2 (50.0)	75.0	55.3
Multiple myeloma	4 (2.8)	1 (25.0)	50.0	50.5
Other	6 (4.2)	2 (33.3)	50.0	42.8
Unknown	21 (14.8)	1 (4.8)	76.2	42.4
Total	142 (100.0)	99 (69.7)	62.7	43.7

Table 3. Causes of death among NS subjects and their matched controls

Cause of death	NS subjects	Controls
Renal disease	32	1
CHD	7	3
Cancer	3	4
Pneumonia/respiratory disease	4	0
Stroke	2	1
Aortic aneurysm	1	0
Intestinal ischemia	1	0
Collagen vascular disease	2	0
Amyloidosis	2	0
Hypertensive disease	1	0
Trauma	1	0
Arrhythmia without CHD	1	0
Congestive heart failure	0	1
Other	1	0
Total	58	10

labeled "other" included two cases of primary hypertensive disease (1 biopsied), two cases of gold-associated nephropathy, and one case each of hereditary nephritis and pregnancy-associated nephropathy. Seventy percent of all diagnoses were confirmed by kidney biopsy.

At the end of the period of observation, 84 (59.2%) of the 142 NS subjects were alive, 29 (20.4%) had died, and ESRD had developed with hemodialysis begun in 29 (20.4%); all the deaths were confirmed by death certificate. Of the 142 control subjects, 10 (7.0%) died; death certificates were available for all but one, in which autopsy data were available. Causes of death are detailed in Table 3.

Hemodialysis was initiated in 29 of the 32 NS subjects in whom ESRD developed. Although the date of first dialysis for ESRD was used as the end of follow-up, we tallied outcomes after ESRD. At the end of the study, 14 persons had died, and death certificates were available for all of them. The cause of death was listed in nine cases as chronic renal failure, and in one case each as SLE, amyloidosis, ruptured aortic aneurysm, pericarditis, and multiple myeloma. No CHD deaths were recorded on the death certificates.

In the matched-pair analysis, 11 MIs occurred among NS subjects and none occurred among control subjects ($P = 0.001$; Table 4). Adding other nonfatal CHD outcomes to MIs still showed a highly significant difference ($P = 0.003$). The difference in overall mortality was marked; there were seven coronary deaths among NS subjects compared with two in the control group ($P = 0.180$). As reflected in the analysis based on person-years of follow-up, which takes the full period of follow-up into consideration, 11 MIs occurred among persons with NS and four occurred among control subjects (Table 5). Proportional hazards models revealed a relative risk of 5.8, which decreased slightly, to 5.5 (95% CI 1.6 to 18.3), when adjusted for hypertension and smoking. When we combined MIs with other nonfatal CHD outcomes, the adjusted RR was 2.3 (95% CI 1.0 to 5.2). CHD was not diagnosed in either NS or control subjects younger than 18 years of age. The adjusted RR of coronary death was 2.8 (95% CI 0.7 to 11.3), but the risk of dying of any cause, including renal disease, was seven times greater for NS subjects than for control subjects.

Because of concern about both the lower risk of CHD in patients diagnosed with minimal change disease and the independent risk of CHD in patients with SLE, we repeated the analysis and excluded the 29 NS subjects with these diagnoses and the corresponding control subjects. The RR estimates were substantially the same by both matched and unmatched analyses.

Table 4. CHD and NS by matched-pair analysis

CHD outcome	NS subjects	Control subjects	P values (two-tailed test)	Relative risk	95% Confidence interval
MI	11	0	0.0010	—	2.8
MI + AP + CI	13	3	0.0213	4.3	1.3–19
MI + AP + CI + ECG	17	3	0.0026	5.7	1.7–24
Deaths (all)	56	5	<0.0001	11.2	4.3–32
Deaths (CHD)	7	2	0.1797	3.5	0.8–19

Abbreviations are: AP, angina pectoris; CHD, coronary heart disease; CI, coronary insufficiency; ECG, abnormal ECG (probable ischemia); MI, myocardial infarction.

Table 5. CHD and NS by person-year analysis

	NS subjects		Control subjects		Relative risk		95% Confidence interval
	No.	Rate/1000 py	No.	Rate/1000 py	Unadjusted	Adjusted[a]	
MI	11	14.9	4	2.6	5.8	5.5	1.6–18.3
MI + AP + CI	14	19.2	8	5.4	3.2	2.7	1.1–7.0
MI + AP + CI + ECG	18	25.2	13	8.9	3.1	2.3	1.0–5.2
Deaths (all)	58	52.2	10	6.5	7.7	7.2	3.6–14.2
Deaths (CHD)	7	6.3	3	1.9	3.1	2.8	0.7–11.3

Abbreviations are: AP, angina pectoris; CHD, coronary heart disease; CI, coronary insufficiency; ECG, abnormal ECG (probable ischemia); MI, myocardial infarction; py, person-years.

[a] Adjusted for current smoking and hypertension at diagnosis of NS

Discussion

This study provides evidence that NS is associated with an increased risk of CHD. We estimate that the risk of myocardial

infarction is between five and six times higher for persons with NS than for those without NS and that all CHD events and deaths from CHD are between two and three times higher than they are in the general population of the same age and sex. We relied on a clinical diagnosis of angina or coronary insufficiency in three NS subjects and four controls who did not have an MI. We did require that ECG abnormalities for probable or definite ischemia be based on a blind ECG reading and the use of the Minnesota Codes [18]. If we had considered other sequelae of atherosclerotic cardiovascular diseases in our definition of CHD outcomes, our risk estimates would have been somewhat higher. Furthermore, we did not include in our analysis data from 13 NS subjects who had evidence of CHD before NS diagnosis. If some of this disease was in fact associated with NS which had not been diagnosed, the results would have been still more striking. Excluding persons with minimal change disease or other diagnoses with known independent higher risk of CHD did not substantially alter the level of risk.

The few previous attempts to describe how NS and CHD are related produced inconsistent results and generated disagreement among authorities about whether NS increases CHD risk. Of at least four published reports [6, 7, 9, 11] and data presented in two letters [8, 10], three small studies and one large study found no increased risk of CHD. However, all these reports had methodologic shortcomings or depended on a small number of subjects and were therefore of limited reliability. The two studies which showed an increased risk were based on a small series of only 15 [6] and 17 [7] subjects from tertiary referral centers, and they used large and relatively undefined populations for comparison [20]. The estimates from Berlyne and Mallick [6] that risk is increased 85 times and from Alexander, Schapel and Edwards [7] that CHD will develop in 53% of NS patients were much higher than our current modestly elevated estimate and were substantially less reliable because they depended on small numbers of subjects. The studies that showed no increased risk included slightly more cases (N = 18 to 49) [8–11] but had insufficient follow-up and reflected the possible blunting effect of including a high proportion of patients with minimal change disease [5]. Moreover, these studies either had no control group or failed to control for the potential confounding effects of smoking and hypertension. The single large study by Wass et al [11], although roughly the same size as our current study, found that 27% of subjects had minimal change disease. The inconsistent results of these studies have led two leading authorities to support opposing arguments about the association between NS and CHD [12, 20].

In the absence of firm epidemiologic evidence, those who believe that the association exists have relied on the biologic plausibility of an increased risk of CHD in NS patients. Fifty percent or more NS patients are known to have elevated serum cholesterol or low-density lipoprotein (LDL) levels, or both [5], and hypercholesterolemia is recognized as a major risk factor for MI and other forms of cardiovascular disease [21]. In patients with NS, hyperlipidemia could accelerate progression of atherosclerosis and increase platelet aggregation. Frequent hypertension and use of steroids in therapy can further increase CHD risk. Given this line of evidence, reinforced by increased safety and effectiveness of modern antihyperlipidemic medications, authorities now advocate pharmacologic treatment of the hyperlipidemia of NS [4, 5, 22–25].

Our data did not allow us to elucidate the particular characteristics of NS which may be responsible for the increased risks we observed. Our primary analysis was directed at determining whether CHD incidence and mortality were elevated among persons with NS when compared with those for the general population. We did not intend to determine what specific aspect of NS (that is, hypercholesterolemia, hypertriglyceridemia, or hypertension) conferred the most risk because our retrospective medical record review data were inadequate for key variables like cholesterol levels. However, because one of the most likely features of NS which could contribute to increased CHD risk is hyperlipidemia, we believed it appropriate to exclude the cholesterol level from the model. Thus, the risk we report can be interpreted as the additional CHD risk posed by having NS after adjusting for effects of age, sex, hypertension, and smoking. We cannot determine what residual risk might exist after controlling for hyperlipidemia. Even if we had lipid level data for all subjects, hyperlipidemia and NS are so closely associated that it would not be possible to determine their separate effects on CHD risk.

One reason that direct evidence of an association between NS and CHD has been difficult to establish is that appropriate studies are difficult to perform [26]. Among other things, large numbers of patients are needed and must be available for reasonably long follow-up. We previously estimated the annual incidence of hospitalization for NS in our population at only 2.6/100,000 members [14]. In our study, we searched for all patients hospitalized with NS from 1971 through 1981 in a large, well-defined population that grew from 1 million to about 1.8 million during that period. The search was facilitated by computer-stored diagnoses since 1976 and hospital discharge logs dating back to the early 1950s. The membership we studied received primary through tertiary care within the comprehensive health plan. Any selection bias in the group of NS subjects studied was thus minimal compared with that of studies from referral centers. We selected a contemporaneous control group, matched for age and sex, from the same membership population. Control subjects had access to the same medical care system as persons with NS. We accumulated a mean 5.6 years of follow-up for CHD morbidity while subjects were in the health plan and a mean 12.1 years for the mortality follow-up. We were further able to obtain data on possible confounding factors such as hypertension and smoking in most subjects.

The limitations of our study were primarily a feature of the retrospective nature of the data collected from medical records. Medical care was not delivered nor were laboratory evaluations done in any standard fashion. Because few control subjects had serious diagnosed diseases, the possibility of finding evidence of angina, ECG abnormalities, and coronary insufficiency may have been more rare for them than for persons with NS. However, we do not believe that acute MI or deaths were less likely to have been recognized in control subjects than in research subjects. Additionally, our cholesterol level data were insufficient to analyze the risk by specific lipid levels or by duration of hyperlipidemia. Finally, in our analysis of nonfatal CHD events, we began follow-up at the date of NS diagnosis, even though 40 (28%) occurred before 1/1/71, which was the date after which we could identify persons with the disease from our computer-stored records. This circumstance means that the nature of nonfatal CHD events occurring before 1/1/71

among persons who died before that date may have differed from those occurring after that date. Nevertheless, no bias exists between NS subjects and their controls because both were analytically treated alike. Furthermore, even if certain CHD events were not recorded, they would probably have been more numerous among the NS subjects than among the controls and would only have increased the relative risks we have reported.

As in the large study by Wass et al [11], we excluded from follow-up NS subjects who had reached ESRD and in whom either dialysis was initiated or transplants were done. Despite concern that this approach [5] may not identify a possible increased risk of CHD after terminal failure [27], our study found that of the 14 deaths among the 29 patients with ESRD treated by hemodialysis, none was clearly secondary to CHD.

Some investigators have argued that the decision to treat the hyperlipidemia of NS rests on two types of evidence: (1) that the risk of CHD is increased in NS patients and, (2) that the necessary medications are reasonably safe and effective [28]. Other factors, such as the substantial comorbidity among NS patients reflected in the high overall mortality observed in this group and the complexity of existing therapeutic regimens, must also be considered. Our study suggests that at least the current assumption about increased CHD risk among persons with NS is valid. Further work will be needed to evaluate the factors that contribute to this increased risk.

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