Hormone Replacement Therapy and Its Relationship to Lipid and Glucose Metabolism in Diabetic and Nondiabetic Postmenopausal Women

Results from the Third National Health and Nutrition Examination Survey (NHANES III)

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OBJECTIVE — Among postmenopausal women, those with diabetes experience more cardiovascular diseases than those without diabetes. We examine the relationship of hormone replacement therapy (HRT) with indicators of lipid and glucose metabolism using a national sample of diabetic and nondiabetic postmenopausal women.

RESEARCH DESIGN AND METHODS — We used data from the Third National Health and Nutrition Examination Survey, conducted from 1988 to 1994. A total of 2,786 postmenopausal women aged 40–74 years participated in an oral glucose tolerance test, had blood drawn for lipid assessment, and responded to HRT questions.

RESULTS — Our results show that postmenopausal women with diabetes had increased dyslipidemia compared with nondiabetic women. Among diabetic women, current users of HRT had significant different lipid and glucose control levels than never users of HRT for the following variables: total cholesterol (225 vs. 241 mg/dl), non-HDL (169 vs. 188 mg/dl), apoA (171 vs. 147 mg/dl), fibrinogen (306 vs. 342 mg/dl), glucose (112 vs. 154 mg/dl), insulin (16.81 vs. 22.6 uU/ml), and GHb (6.03 vs. 7.13 mg/dl).

CONCLUSIONS — Diabetic and nondiabetic postmenopausal women currently taking HRT had better lipoprotein profile than never or previous users of HRT. Diabetic women currently taking HRT had better glycemic control than never or previous users of HRT.

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Some studies have found the use of hormone replacement therapy (HRT) to be associated with a better cardiovascular health profile in healthy postmenopausal women, whereas others have found no benefits (1–6). Epidemiological research on the potential benefits of HRT use in postmenopausal women with diabetes is also inconclusive (7–11). Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Most cases of diabetes fall into two categories: type 1 and type 2 diabetes. In type 1 diabetes, the cause is an absolute deficiency of insulin secretion. In type 2 diabetes, the most common form of diabetes, the cause is a combination of resistance to insulin action and inadequate compensatory insulin secretory response. Risk factors for diabetes include age, family history, obesity, and physical inactivity. Moreover, diabetic individuals are also at higher risk for coronary heart disease, dyslipidemia, hypertension, retinopathy, and renal disorders (7,8,10,12–14).

Postmenopausal women experience more type 2 diabetes and cardiovascular diseases than their premenopausal counterparts. One hypothesis concerning the increased prevalence of type 2 diabetes and cardiovascular diseases in postmenopausal women is that it may be related to age-related changes in sex-steroid hormones. Although sex hormones do not appear to play a primary role in the etiology of type 2 diabetes, they may be related to other metabolic factors. After menopause there is an increase in dyslipidemia, especially reduced levels of HDL. In addition to HDL changes, menopause is also accompanied by changes in apolipoprotein (apo)A and apoB, fibrinogen, and hyperinsulinemia (1–3,5,8).

HRT may be effective in lowering the risk of cardiovascular disease in healthy menopausal women, and although postmenopausal HRT is recommended to prevent disease and prolong life, little data are available to examine the association between HRT and emerging hyperlipidemic indicators separately for diabetic

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Abbreviations: apo, apolipoprotein; HRT, hormone replacement therapy; Lp(a), lipoprotein(a); NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial by Buse and Raftery, p. 1876

subjects and nondiabetic postmenopausal women. In this study, we examined the relationship of HRT use with dyslipidemic indicators in a national sample of diabetic and nondiabetic postmenopausal women 40–74 years of age.

RESEARCH DESIGN AND METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. NHANES III is designed to produce nationally representative data regarding the civilian, noninstitutionalized U.S. population aged 2 months and older. NHANES III was conducted between 1988 and 1994, and consisted of a home interview and a detailed clinical examination performed in a mobile examination center. Subjects signed a consent form, and approval was obtained from a human subjects committee in the U.S. Department of Health and Human Service. Self-reported information provided the basis for the identification of race ethnicity and allowed for the oversampling of Mexican-Americans and non-Hispanic blacks. A total of 18,885 adults 20 years of age or older responded to the household adult and family questionnaires. Body measurements and blood chemistries were obtained during a subsequent visit to the mobile examination center (15–18). For this study, postmenopausal women 40–74 years of age were selected, and our findings are only applicable to the analytic sample studied.

Reproductive health

A trained interviewer collected information on reproductive health, use of HRT, time on HRT, and mode of administration of HRT. Some of the questions asked by the interviewer were as follows: Have you had a period in the past 12 months? How old were you when you had your last period? Have you had a hysterectomy? Has your uterus/womb been removed? How old were you when you had your (hysterectomy/uterus/womb removed)? Have you had one or both of your ovaries removed? Postmenopause was defined as a woman who has not had a menstrual period in the past 12 months. We only report data on postmenopausal women.

The interviewer also asked about past and current use of female hormone pills, including birth control pills and estrogen pills. Some of the questions asked were: Have you ever taken estrogen or female hormone pills by mouth other than oral contraceptive pills? Have you ever taken or used estrogen or female hormones in the form of vaginal cream, suppository, or injection? Have you ever used female hormones in the form of patches that are placed on the skin? Not counting any time when you stopped using the female hormone patches, for how many years altogether have you used them?

Current users of HRT were those who answered yes to the use of estrogen or female hormones in the form of pills, vaginal cream, suppository, injection, or patches and who were also currently using HRT. Previous users of HRT were women who answered "yes" to any of the above questions, but who were not currently using HRT. Never users of HRT refers to women who answer no to all of the above questions about usage of HRT.

Oral glucose tolerance test

During NHANES III, an oral glucose tolerance test (OGTT) was conducted on participants aged 40–74 years who attended the mobile examination part of the survey. Participants were randomly assigned to receive an OGTT in the morning after an overnight fast. Almost half of the OGTT examinees received the morning OGTT after an overnight fast. This subsample most closely conformed to the World Health Organization criteria for OGTTs to identify diabetes (12,19,20). Therefore, those who attended the morning subsample of the NHANES III were used to estimate the prevalence of diabetes as recommended by National Center for Health Statistics guidelines. People who reported a medical history of diabetes but who were not using insulin therapy were asked to conform to the fasting instructions for their examination session and were eligible for an OGTT if the age criteria were satisfied.

Participants aged 40–74 years who used insulin were excluded from the OGTT. A first venipuncture was obtained on these individuals, but the glucose challenge and second venipuncture were canceled. In these cases, NHANES III data report values for fasting glucose, but the results for the second glucose values from the second venipuncture are blank-filled to indicate a medical exclusion. Those who answered "yes" to the hemophilia question or who received chemotherapy within the past 4 weeks were also excluded from venipuncture. Examinees who reported that they used insulin therapy on their examination day were also excluded from the OGTT. If an examinee was between the ages of 40 and 74 years and received the OGTT, two timed venipunctures were performed.

Diabetes

The Expert Committee on Diagnosis and Classification of Diabetes (12) recommends that for epidemiological studies, estimates of diabetes prevalence and incidence should be based on a fasting plasma glucose of 126 mg/dl. This recommendation is made in the interest of standardization and also to facilitate field work. However, the committee concedes that this approach can lead to slightly underestimate prevalence that would be obtained from the combined use of fasting plasma glucose and OGTT (19–21). For this study, the prevalence of diabetes is defined as fasting (at least 8 h) plasma glucose ≥126 mg/dl, plasma glucose values ≥200 mg/dl after a 2-h postload glucose (OGTT), currently taking antihyperglycemic medication (such as insulin), or a (self-reported) medical history of diabetes.

Lipids

Assessment of lipid levels was conducted using the following variables: total serum cholesterol levels, HDL cholesterol, non-HDL cholesterol (calculated by subtracting HDL from total cholesterol levels), triglyceride level, and the ratio of total cholesterol to HDL. LDL in NHANES III was calculated and not measured, thus, participants with triglycerides >300 mg/dl do not have LDL levels reported. Because diabetic subjects had significantly greater triglyceride levels than nondiabetic subjects, we decided not to report LDL levels but to use non-HDL. During phase 1 (1988–1991), levels of apoA and apoB were measured as part of the lipid profile, whereas in phase 2 (1991–1994) measurements of lipoprotein(a) [Lp(a)] were ascertained instead (16,22).

Table 1—*Descriptive characteristics of postmenopausal women according to diabetes status*

	All		Diabetic		Nondiabetic	
	Sample size*	%	Sample size*	%	Sample size*	%
Age-groups (years)	2,786	100	830	30	1,956	70
40–49	374	13	59	7	315	16
50–59	805	29	191	23	614	31
60–69	1,088	39	381	46	707	36
70–74	519	19	199	24	320	16
Race/ethnicity						
Non-Hispanic white	1,309	47	315	38	994	51
Non-Hispanic black	739	27	219	26	520	27
Mexican-Americans	629	23	268	32	361	18
Other race/ethnicity	109	4	28	3	81	4
Education						
Less than high school	1,322	48	488	59	834	43
High school	879	32	226	27	653	33
More than high school	585	21	116	14	469	24
Body weight categories (kg/m^2)						
Underweight (BMI <18.5)	73	3	13	2	60	3
Normal weight (BMI 18.5–24.9)	768	28	151	18	617	32
Overweight (BMI 25–29.9)	948	34	280	34	668	34
Obesity (BMI 30+)	997	36	386	47	611	31
Smoking status						
Current smokers	592	21	125	15	467	24
Previous smokers	667	24	224	27	443	23
Never smokers	1,527	55	481	58	1,046	53
HRT						
Currently using HRT	388	14	84	10	304	16
Previously used HRT	700	26	184	23	516	27
Never used HRT	1,639	60	542	67	1,097	57

*Unweighted sample sizes.

Statistical analysis

Statistical analyses were carried out using SAS, SUDAAN, and STATA statistical software. All analyses incorporated the sampling weights and the complex sample design unless otherwise specified. Prevalence estimates and 95% CIs were calculated taking into account the design effect of a multistage stratified complex sample design. Differences between groups are determined based on the prevalence estimates and their 95% CIs. Multivariate adjustments for other confounders (e.g., age, BMI, race/ethnicity, smoking, and education) were made using the general linear model procedure and the least square means option in SAS callable SUDAAN, and 95% CIs were obtained using the survey procedure to calculate means in the STATA software.

RESULTS — Table 1 describes selected characteristics according to diabetes status. The percent of women with less than a high-school education was greater among diabetic women (59%) than among nondiabetic women (43%). The percent of current smokers was higher among nondiabetic menopausal women (24%) than among diabetic women (15%). Obesity was more prevalent among diabetic (47%) than nondiabetic (31%) women. Current use of HRT was 60% lower among diabetic women than among nondiabetic women (10 and 16%, respectively). The most common form of HRT administration among women who reported ever taking HRT were pills (90%).

We found a poorer lipid profile and, as expected, glucose metabolism among diabetic women compared with their nondiabetic counterparts. The differences in lipid and glucose profile between dia-

Table 2—*Indicators of lipid and glucose metabolism according to HRT in diabetic postmenopausal women aged 40–74 years: NHANES III, 1988–1994*

	HRT use status in diabetes					
	Current		Previous		Never	
	Sample size*	Mean (95% CI)	Sample size*	Mean (95% CI)	Sample size*	Mean (95% CI)
Total cholesterol (mg/dl)	83	225 (217–233)	178	247 (238–256)	524	241 (235–246)
HDL (mg/dl)	82	56 (50–62)	175	52 (49–56)	516	51 (48–53)
Non-HDL (mg/dl)	82	169 (158–180)	175	192 (182–201)	516	188 (182–194)
Total cholesterol–to–HDL ratio	82	4.40 (3.85–4.94)	175	5.09 (4.69–5.49)	516	5.15 (4.89–5.39)
Triglycerides (mg/dl)	83	219 (167–270)	177	249 (194–304)	524	224 (201–246)
Lp(a) (mg/dl)	54	22 (10–33)	92	24 (15–32)	289	22 (17–27)
ApoA (mg/dl)	29	171 (158–185)	84	151 (142–161)	232	147 (143–150)
ApoB (mg/dl)	29	117 (109–125)	85	135 (127–143)	234	125 (120–130)
Fibrinogen (mg/dl)	82	306 (285–327)	172	336 (309–363)	515	342 (331–353)
C-reactive protein (mg/dl)	82	0.97 (0.58–1.35)	177	0.66 (0.48–0.83)	522	0.84 (0.70–0.98)
Fasting glucose (mg/dl)	83	112 (104–120)	180	151 (137–166)	528	154 (141–166)
Fasting insulin (μU/ml)	82	16.7 (13.4–20.1)	178	20.6 (16.5–24.7)	523	22.6 (19.4–25.8)
GHb (mg/dl)	84	6.03 (5.70–6.35)	180	6.91 (6.46–7.36)	525	7.13 (6.81–7.44)

*Unweighted sample sizes.

Table 3—*Indicators of lipid and glucose metabolism according to HRT in nondiabetic postmenopausal women aged 40–74 years: NHANES III, 1988–1994*

	HRT use status in nondiabetic women					
	Current		Previous		Never	
	Sample size*	Mean (95% CI)	Sample size*	Mean (95% CI)	Sample size*	Mean (95% CI)
Total cholesterol (mg/dl)	293	224 (218–230)	491	231 (227–235)	1,031	227 (223–231)
HDL (mg/dl)	292	64 (61–67)	488	57 (55–59)	1,027	55 (53–56)
Non-HDL (mg/dl)	292	160 (153–167)	487	174 (170–178)	1,027	172 (168–176)
Total cholesterol–to–HDL ratio	292	3.78 (3.55–3.99)	487	4.40 (4.21–4.58)	1,027	4.54 (4.31–4.76)
Triglycerides (mg/dl)	293	155 (142–167)	491	150 (139–160)	1,028	139 (132–147)
Lp(a) (mg/dl)	164	24 (19–29)	265	26 (20–31)	527	25 (20–29)
ApoA (mg/dl)	128	174 (168–181)	227	158 (153–162)	498	152 (148–156)
ApoB (mg/dl)	129	109 (103–115)	227	115 (110–120)	500	116 (113–118)
Fibrinogen (mg/dl)	292	297 (283–310)	488	301 (292–310)	1,019	320 (310–330)
C-reactive protein (mg/dl)	292	0.60 (0.50–0.68)	492	0.46 (0.37–0.54)	1,023	0.45 (0.40–0.51)
Fasting glucose (mg/dl)	300	92 (91–93)	501	94 (93–96)	1,047	96 (95–96)
Fasting insulin (μU/ml)	297	8.59 (7.7–9.4)	497	10.30 (9.0–11.6)	1,043	10.38 (9.7–11.0)
GHb (mg/dl)	298	5.3 (5.21–5.33)	501	5.37 (5.32–5.42)	1,045	5.42 (5.36–5.48)

*Unweighted sample sizes.

betic and nondiabetic subjects did not change drastically after adjusting for age, race/ethnicity, BMI, smoking, and educational attainment (data not shown). Of note, fibrinogen and C-reactive protein were also higher in diabetic subjects (336 and 0.81 mg/dl) than among nondiabetic women (310 and 0.48 mg/dl, respectively).

Tables 2 (diabetic subjects) and 3 (nondiabetic subjects) show indicators of lipid and glucose metabolism according to HRT status. Table 2 shows that among women with diabetes, serum cholesterol levels were significantly lower (225 mg/dl) among those currently taking HRT than among previous or never users of HRT (>240 mg/dl). Non-HDL levels were significantly lower among diabetic as well as nondiabetic women currently taking HRT (Tables 2 and 3). HDL levels were not significantly different among diabetic women on HRT and previous or never users of HRT (Table 2). In nondiabetic women, however, HDL levels were significantly higher in those taking HRT than in those who have never used HRT or who previously used HRT (Table 3). Similar divergent results were observed for the total cholesterol–to–HDL ratio. Thus, although HDL and total cholesterol–to–HDL ratios were significantly different among nondiabetic women currently taking HRT compared with previous HRT users or never HRT users, these results were not observed in diabetic women.

Diabetic women currently taking HRT had significantly lower fasting glucose levels (112 mg/dl) than previous or never HRT users (>150 mg/dl) (Table 2). Among diabetic and nondiabetic women, however, fasting insulin levels were not significantly different when compared across HRT use category (Tables 2 and 3). Never users of HRT had higher fibrinogen levels than current users for both diabetic and nondiabetic postmenopausal women (Tables 2 and 3). Adjustment for age, BMI, smoking, and education did not alter the above findings.

CONCLUSIONS — We examined lipid profiles and indicators of glucose metabolism in a nationally representative sample of postmenopausal diabetic and nondiabetic women from NHANES III. Although HDL was found to be significantly higher among nondiabetic women who were currently taking HRT than among never or previous users of HRT, this finding was not observed among diabetic women. Total cholesterol and non-HDL levels, however, were significantly lower among diabetic women currently on HRT than among never or previous users of HRT. Furthermore, these findings were not observed in nondiabetic women. This divergent result may be indicative of a different effect of HRT on lipid metabolism in diabetic compared with nondiabetic women.

Our findings confirm that glucose metabolism among diabetic women who were currently taking HRT as evidenced by lower fasting glucose, fasting insulin, and GHb is superior to those who were not on HRT. This may indicate that women who take HRT are also in better control of their diabetes and may be indicative of other favorable health behaviors among women who use HRT. Not only were fasting glucose and GHb lower among diabetic current users of HRT compared with never or previous users of HRT, but also among nondiabetic women users of HRT compared with nonusers.

Current users of HRT in both diabetic and nondiabetic postmenopausal women also had significantly higher levels of apoA levels than never users of HRT. ApoA is the major protein component of HDL and an important coenzyme for the enzyme lecithin:cholesterol acyltransferase, which attaches a free fatty acid on the cholesterol molecule, forming a cholesterol ester that will later remove cholesterol via the bile acids (23). Therefore, higher levels of apoA are considered to be beneficial. ApoB is an atherogenic component of the lipoproteins and is more closely linked to non-HDL cholesterol. ApoB levels in both diabetic and nondiabetic postmenopausal women appear to be lower in current users of HRT when compared with women who previously or never used HRT, but it only approached statistical significance because the 95% CIs overlapped slightly. Other researchers have found that HRT reduced apoB in postmenopausal women with type 2 dia-

betes (11,24). The difference may be due to the smaller sample size in our study or the cross-sectional design of our study (11).

We found no significant differences in Lp(a) among the groups studied. Lp(a) is a complex of an LDL-like particle and apoA. Elevations in Lp(a) have been associated with coronary heart disease and thrombotic stroke (25–27). The mechanism of this relationship is not known, but it is thought that because apoA and plasminogen are homologous, elevated levels of Lp(a) may interfere with fibronolysis and therefore promote thrombosis (2).

Fibrinogen is an important component in platelet aggregation and is also a risk indicator for cardiovascular disease, including coronary heart disease, stroke, and peripheral artery disease, and has been closely linked to smoking, hypertension, and total cholesterol (28). We found fibrinogen to be significantly lower among current HRT users than women who never used HRT for both diabetic and nondiabetic women. Similar findings were observed in a group of postmenopausal women aged 52–65 years (n = 300), where HRT usage was associated with significantly lower fibrinogen concentration (232 vs. 268 mg/dl) and decreased plasma viscosity (29). Results from this study, however, were not provided separately for diabetic and nondiabetic women.

C-reactive protein is an important inflammatory biomarker that has been suggested to have an intermediary role in the pathogenesis of cardiovascular disease in individuals with type 2 diabetes (14). Our results indeed confirm higher levels of C-reactive protein among postmenopausal diabetic women. Both diabetic and nondiabetic women currently using HRT had higher levels of C-reactive protein than previous or never users, but these only approached statistical significance.

We found lower fasting glucose and GHb among diabetic women currently using HRT than among never or previous users of HRT. This may be due to higher compliance in using glucose-controlling medication among diabetic women currently using HRT than among with previous or never users of HRT and is not necessarily an effect of HRT. However, several studies support our findings using prospective, observational, or randomized controlled trials (7,9,11). Also, the fact that we observed a similar finding in nondiabetic women confirms the possible hypoglycemic effect of HRT or the fact that women on HRT may have healthier habits. Adjustment for smoking, BMI, physical activity, education, and race/ethnicity did not alter the lower fasting glucose levels observed, especially among diabetic women (data not shown).

One of the strengths of this analysis is the inclusion of emerging cardiovascular disease risk factors such as Lp(a), fibrinogen, apoA, and apoB in a national sample of postmenopausal women according to HRT use. Some of these measurements were obtained during phase 1 (apoA and apoB), while another [Lp(a)] was collected during phase 2. One of the limitations of this study was that to further subdivide the analytic sample among diabetic and nondiabetic subjects by HRT use, we reduced the sample size considerably for some of these components, and because of these smaller sample sizes, we may have failed to see a difference when there was one. We did, however, observe statistically significantly different levels of apoA between current HRT users compared with never or previous HRT users in both diabetic and nondiabetic women.

A possible limitation of this analysis is that it is based on cross-sectional data. However, this is a descriptive epidemiological analysis based on a national representative sample of the civilian noninstitutionalized population of postmenopausal women 40–74 years of age who underwent a rigorous lipid and glucose metabolism assessment. Our findings serve to confirm previous smaller studies that have examined the relationship of HRT with glucose and lipid metabolism in diabetic and nondiabetic postmenopausal women.

Our definition of diabetes is not a clinical definition of diabetes, but rather an epidemiological definition based on clinical measurements, self-reported use of medications to control glucose levels, and previous diagnosis of diabetes by a health professional. The prevalence of diabetes in the U.S. among individuals aged 40–74 years falls between 12 and 14%. Since the prevalence of undiagnosed diabetes (5–7%) can be as great as the prevalence of diagnosed diabetes (7%), our definition of diabetes allowed us to more clearly separate postmenopausal women without diabetes from those with diabetes.

Although favorable lipid and glucose profiles were observed among HRT users, we caution that our findings are observational and may not be adequate to guide lipid-altering therapy in postmenopausal diabetic women. Nevertheless, our findings at the population level suggest that HRT use may be associated with increased apoA and lower fasting glucose, GHb, total cholesterol, and non-HDL in this group of diabetic postmenopausal women. To what extent these differences are explained by the fact that women who use HRT are more health conscious is not entirely clear. In our analyses we controlled for BMI, education, race/ethnicity, smoking, and age and the results did not change substantively. A large and more rigorous clinical trial is necessary to better assess if the potential cardiovascular risk–reducing benefits of HRT observed in nondiabetic women are applicable to women with diabetes.

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