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DDT Metabolite and Androgens in African-American Farmers

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Background. The ubiquitous dichlorodiphenyltrichloroethane (DDT) metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) is an androgen receptor antagonist. Data on potential antiandrogenic activity of DDE in humans are limited. **Methods.** The relations between concentrations of plasma DDE and several serum androgens (total testosterone, bioavailable testosterone, 5 α -dihydrotestosterone, and free androgen index) were examined in 137 North Carolina black male farmers, using multiple linear regression.

Results. Participants ranged in age from 30 to 88 years (mean = 62 years). Most had farmed for about 30 years and 27% reported having used DDT. The median DDE level was 7.7 μ g per liter (1213 μ g per kg lipid), slightly higher than in other recent studies. Overall, concentrations of DDE and androgens

were unrelated. Total testosterone decreased 2% (95% confidence limits [CL] = -9%, 5%) per increase in interquartile distance of lipid-adjusted DDE. The percentage change in other hormones was similarly negligible. However, among those whose DDE level was in the top tenth percentile, compared with all others, total testosterone and free androgen index were lower by 23% (CL = -40%, 1%) and 22% (CL = -41%, 4%) respectively. Plasma androgen levels decreased with age, a relation that has previously been studied only in whites.

Conclusions. Studies of more highly exposed populations may be needed to evaluate effects, if any, of DDE. (EPIDEMIOLOGY 2002;13:454-458)

Key words: anti-androgen, androgens, hypogonadism, blacks, farmers, pesticide exposure, DDT, DDE.

The major metabolite of dichlorodiphenyltrichloroethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), is a persistent environmental contaminant that is ubiquitous among people worldwide. DDE was recently found to bind with the androgen receptor in male rats¹ and to inhibit the binding of androgen to the androgen receptor, androgen-induced transcriptional activity, and androgen action.¹⁻⁴ Kelce and Wilson⁵ suggested that DDE levels in humans can exceed the levels that inhibit human androgen receptor transcriptional activation *in vitro*. If DDE acts as

an androgen receptor antagonist in humans, it could affect normal sexual differentiation and fertility in males⁵ or induce a compensatory increase of testosterone.⁶ Blocking the androgen receptor causes a decrease in androgenic effects that would be detected by the hypothalamus, leading to a compensatory increase in levels of gonadotropins and thus androgens.⁷ Flutamide is an antiandrogen that, like DDE, acts by blocking androgen binding with its receptor. Administration of flutamide to human males causes androgen levels to increase.^{8,9} We hypothesized that DDE would have a similar effect on androgens, so that in a cross-sectional study DDE and androgen levels would be directly associated.

In this study, we examined the relationship between concurrent concentrations of plasma DDE and several serum androgens in a group of black male farmers and farm workers in North Carolina. Farmers and farm workers are likely to be more highly exposed to pesticides than is the general population.¹⁰ Furthermore, blacks have been found to have higher DDE concentrations than whites.^{11,12} Thus, North Carolina black farmers and farm workers were potentially more highly exposed to DDT than other groups in the United States.

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Methods

The Agricultural Health Study is an ongoing prospective study of licensed pesticide applicators from Iowa and North Carolina.¹³ To include more African Americans, in 1995–1996 we recruited additional participants at 118 predominantly black churches in five rural North Carolina counties. Eligibility criteria included being a resident of North Carolina, not having been previously recruited for the Agricultural Health Study, and having had at least 2 years of adult farming experience or a spouse with such. About 2,300 potentially eligible men and women completed a brief screening questionnaire, and 1,602 were found to be eligible. Of these, 1,186 (74%) completed a telephone interview about their farm experiences and health status. A total of 389 (33%) black men and 797 (67%) black women completed the interview, reflecting the predominance of women among the church attendees.

We recontacted the 389 men in 1999 and asked them to complete a follow-up telephone questionnaire. The follow-up interview included more detailed questions on previous farming and years of pesticide and DDT exposure. Fifty-five men did not complete the follow-up interview as a result of poor health ($N = 20$), death ($N = 30$), or lack of telephone service at the place of residence ($N = 5$). Of the remaining 334 men, 275 (82%) completed the questionnaire, 33 (10%) refused, and 26 (8%) could not be traced.

We attempted to collect a blood sample from interviewed men who lived in four contiguous northeastern counties. We excluded 27 of the 228 eligible men from a blood draw because they were currently taking anticoagulant medication or they had had a seizure in the past. Of the 201 remaining men, 141 (70%) attended one of 12 examination sessions. Blood samples could not be collected from three attendees because of very high blood pressure or other medical reasons. Thus, we obtained blood samples from 138 men.

Fasting blood for DDE analysis was collected in a metal-free Vacutainer containing EDTA (lavender top) and was kept cool until later the same day when the plasma was frozen in glass at -20°C until analyzed. The serum from blood collected in a red-topped Vacutainer was refrigerated until analyzed for lipids within 48 hours. Samples for hormone analysis were refrigerated until later on the day of collection, when they were frozen at -80°C until analyzed.

The study was reviewed and approved by the Institutional Review Boards at the National Institute of Environmental Health Sciences and the National Institutes of Health. Participants gave verbal informed consent for the telephone interview and provided written informed consent for the blood draw.

Organochlorine Analysis

DDE was extracted from 2 ml of plasma using solid-phase extraction (C_{18}) by the Centre de Toxicologie du Québec. After a washing step, DDE was eluted with isooctane. The extract was then analyzed by gas chromatography with electron capture detection. Identification and quantification of DDE was confirmed by mass spectrometry. DDE ^{13}C was used as an internal standard. The limits of quantification and detection for total DDE were 0.5 and 0.2 μg per liter, respectively. All study samples were above the detection limit for DDE. A serum DDE 5 μg per liter standard and a serum DDE 25 μg per liter standard were analyzed with each batch. The corresponding between-batch coefficient of variation (CV) for the standards was 5.2% and 8.3%, respectively ($N = 24$ batches); recovery averaged 97%.

Lipid and Hormone Analysis

Standard enzymatic assays for total cholesterol and triglycerides were performed at the Duke University CARL Clinical Laboratory, where androgens were also measured. Total testosterone (TT) was determined using a chemiluminescent competitive immunoassay (Immulate 2000 Immunoassay System, Diagnostic Products Corp, Los Angeles, CA). Sex hormone binding globulin (SHBG) was quantified using a chemiluminescent immunometric assay (Immulate Immunoassay System, Diagnostic Products Corp). Bioavailable testosterone (BT) was measured using a competitive enzyme immunoassay (American Laboratory Products Company, Windham, NH). 5α -Dihydrotestosterone (DHT) was measured using a direct enzyme-linked immunosorbent assay (American Laboratory Products Company). The mean between-batch CV% was 5.2% for TT, 2.6% for SHBG, 10.3% for BT, and 9.3% for DHT.

Additional Covariates

A trained technician measured height, weight, and waist and hip circumferences of participants at the time blood was drawn. This information was used to calculate body mass index (BMI , kg/m^2) and waist-to-hip ratio (WHR).

Statistical Analysis

To express the DDE plasma concentrations on a lipid basis, total lipids (TL) were estimated as follows¹⁴: $\text{TL} = 2.27$ (total cholesterol) + triglycerides + 0.623. We calculated the free androgen index using the following formula¹⁵: free androgen index = $(\text{TT} [\text{nmol}/\text{L}] \times 100) / (\text{SHBG} [\text{nmol}/\text{L}])$. Because of the skewed distributions of plasma DDE, lipid-adjusted DDE, and serum hormone concentrations, the values were log_e transformed before testing for trend across age categories. Also, the Spearman correlation coefficient between lipid-adjusted DDE and BMI (and WHR) was calculated.

TABLE 1. Median and Interquartile Range for Plasma DDE and Serum Hormone Concentrations by Age Group in Black Male Farmers Participating in the Agricultural Health Study—Special Recruitment Study, 1999

	Age Group (Years)									
	<45 (N = 17)		45–54 (N = 28)		55–64 (N = 27)		65–74 (N = 37)		≥75 (N = 28)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Plasma DDE										
DDE ($\mu\text{g/l}$)*	8.0	1.8–14.1	5.6	3.3–9.4	6.2	3.2–13.6	8.7	4.0–16.9	11.9	5.5–19.5
Lipid-adjusted DDE ($\mu\text{g/kg}$)*	1,154	267–2,131	946	473–1,401	877	487–1,811	1,370	574–2,231	1,876	826–3,243
Serum hormones										
Total testosterone (ng/dl)†	544	421–661	475	390–596	454	355–538	440	342–514	396	300–505
Bioavailable testosterone (pg/ml)†	5.8	5.2–8.1	5.2	4.0–6.4	6.0	3.6–7.7	3.7	2.7–5.3	3.2	2.2–4.5
5 α -dihydrotestosterone (pg/ml)†	986	777–1,127	794	622–917	833	704–953	671	539–852	560	496–799
SHBG (nmol/l)*	25.8	19.3–31.8	29.2	19.0–40.3	29.4	25.6–42.7	32.9	27.4–45.6	41.8	33.6–56.4
Free androgen index†	69.6	61.8–77.4	57.4	49.0–71.5	51.4	38.0–62.6	40.8	34.5–48.6	35.6	28.8–40.5

DDE = 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; SHBG = sex hormone binding globulin; IQR = Interquartile range (25th–75th percentile). Units of $\mu\text{g/l}$ and $\mu\text{g/kg}$ are equivalent to parts per billion on a wet basis and lipid basis, respectively. The free androgen index (FAI) was calculated using the following formula¹⁵: $\text{FAI} = (\text{TT} [\text{nmol/l}] \times 100) / (\text{SHBG} [\text{nmol/l}])$, where TT = total testosterone. Plasma DDE and serum hormone values were log_e transformed before testing for trend across age categories.

* Increase was linear with age; $P < 0.02$, with 1 degree of freedom, age ordinal.

† Decrease was linear with age; $P < 0.01$ with 1 degree of freedom, age ordinal.

Models of log_e-transformed values of each serum hormone concentration were fitted with coefficients for untransformed DDE concentration (lipid basis), age at blood draw, and BMI (or WHR, where noted). To increase interpretability, we also present the model results on hormone-DDE associations as the percentage change in interquartile distance of DDE, with the change expressed using hormone values in their natural scale. To evaluate linearity, we examined models of hormone levels with DDE levels categorized by quartile or dichotomized at the 90th percentile (*vs* all other values) of the distribution.

One subject had an unusually high plasma DDE concentration of 232 μg per liter. The sample was reextracted and reassayed and the concentration on repeat analysis was 231 μg per liter. As this concentration was an outlier, the observation was excluded from our reported statistical analysis. Including this participant did not alter the findings.

Results

The average age at blood draw among the 137 men was 62 years (standard deviation [SD] = 13 years; range 30–88). The average BMI was 28.7 kg/m^2 (SD = 4.7), and the average WHR was 0.95 (SD = 0.06). Fifty-five per cent of the men had farmed for 25 years or more, 74% reported ever having used any pesticides, and 27% reported ever-use of DDT. The average number of years of any pesticide use was 12.3, and the average for DDT use for agricultural purposes was 2.2 years. The median DDE level (7.7 μg per liter) was slightly higher than the level observed among other recently studied groups of North Carolinians; Millikan *et al.*¹⁶ reported a median DDE level of 5.7 μg per liter, and Vine *et al.*¹⁷ reported a median of 2 μg per liter.

Plasma DDE and lipid-adjusted DDE concentrations increased linearly with age (Table 1). The Spearman correlation coefficient between lipid-adjusted plasma DDE and BMI was 0.11 (95% confidence limits [CL] = –0.06, 0.28), and that between DDE and WHR was 0.19 (CL = 0.03, 0.36).

Serum TT, BT, 5 α -dihydrotestosterone (DHT), and free androgen index decreased linearly with age, whereas sex hormone binding globulin (SHBG) increased linearly with age (Table 1). All of these associations were consistent with expectations.^{12,18–22} Four men had total testosterone levels less than 200 ng per deciliter, a value used clinically to define hypogonadism.²³ All were 65 years of age or older. Thus, among men age 65 years or older, the prevalence of hypogonadism was 6%.

Multivariate regression models of log_e TT, BT, and DHT concentrations, and free androgen index showed that after adjusting for age and BMI, lipid-adjusted plasma DDE was not associated with any androgen (Table 2). Adjust-

TABLE 2. Multiple Linear Regression Analysis Between Serum Androgens and Variables of Interest in the Agricultural Health Study—Special Recruitment Study (N = 137)

Variable	β	SE	r^*	R^2	Percentage Change in Hormone†	95% CL†
Log total testosterone (ng/dl)				0.225		
Age (years)	-0.011	0.0032	-0.23			
Body mass index (kg/m ²)	-0.046	0.0086	-0.37			
Lipid-adjusted DDE ($\mu\text{g/kg}$)	-0.000014	0.000023	-0.12		-2.1%	-8.9%, 5.1%
Log bioavailable testosterone (pg/ml)				0.183		
Age (years)	-0.021	0.0045	-0.37			
Body mass index (kg/m ²)	-0.032	0.012	-0.16			
Lipid-adjusted DDE ($\mu\text{g/kg}$)	-0.000012	0.000032	-0.14		-1.8%	-11.1%, 8.4%
Log 5 α -dihydrotestosterone (pg/ml)				0.074		
Age (years)	-0.011	0.0035	-0.24			
Body mass index (kg/m ²)	-0.014	0.0094	-0.093			
Lipid-adjusted DDE ($\mu\text{g/kg}$)	0.0000030	0.000025	-0.060		0.5%	-7.1%, 8.7%
Log free androgen index				0.252		
Age (years)	-0.022	0.0035	-0.49			
Body mass index (kg/m ²)	-0.011	0.0094	-0.021			
Lipid-adjusted DDE ($\mu\text{g/kg}$)	-0.0000082	0.000025	-0.16		-1.3%	-8.7%, 6.8%

DDE = 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; SE = standard error; $\mu\text{g/kg}$ = parts per billion. The free androgen index (FAI) was calculated using the following formula¹⁵: $\text{FAI} = (\text{TT} [\text{nmol/l}] \times 100) / (\text{SHBG} [\text{nmol/l}])$, where TT = total testosterone.

* Partial r values are shown.

† Percentage change in hormone per increase in interquartile distance for lipid-adjusted DDE ($\mu\text{g/kg}$) and its 95% confidence limits.

ment for WHR instead of BMI gave similar results (not shown). In the model of free androgen index, the coefficient for the interaction between age and DDE level was -3.5×10^{-6} (CL = -7.4×10^{-6} , 0.5×10^{-6}), suggesting that at older ages, DDE may be associated with a lower free androgen index. For example, the model predicted that the free androgen index for an 85-year-old man with a plasma DDE level of 5,000 $\mu\text{g/kg}$ would be 18% lower than if his DDE level were 1,000 $\mu\text{g/kg}$.

When the multivariate regression analysis was repeated using quartiles of lipid-adjusted plasma DDE, the results were consistent with a linear relation between DDE and each of the log_e hormone concentrations. On the other hand, total testosterone was 23% lower (CL = -40%, 1%) among those whose DDE level was in the top tenth percentile, compared with all others. Those in the top tenth percentile also differed in level of free testosterone (-18%; CL = -43, 17), 5 α -dihydrotestosterone (-0.5%; CL = -25, 33), and free androgen index (-22%; CL = -41, 4) (not shown in table).

Discussion

Among the North Carolina black male farmers and farm workers in our study, overall androgen levels were unrelated to DDE levels overall. The absence of an association between lower levels of DDE and androgen level among adult males has recently been reported.²⁴ Twenty-four young men from a malaria area of Mexico had a mean serum DDE level of ~600 μg per liter.²⁵ DDE was inversely related to the ratio of bioavailable to total testosterone and positively related to SHBG level in these young men. We found neither relation in our data. Although neither association observed in the Mexico

study was in the direction we hypothesized (that DDE, acting as an androgen receptor antagonist, might lead to a compensatory increase in androgens), each was consistent with some disruption of androgen metabolism by DDE. DDE was also associated with decreased semen volume and sperm count in the men from Mexico, providing further support for some disruption of androgen metabolism by DDE. Our data suggested that higher levels of DDE were associated with lower levels of total testosterone and free androgen index. Overall, the available data suggest that if DDE alters androgen levels in adult males, this may occur only at higher exposure levels. Among U.S. agricultural workers exposed to DDT before it was banned, serum levels of DDT and DDE combined were directly related to levels of several enzymes in serum that reflect liver function.²⁶ That observation lends credibility to the possibility that effects on liver function, such as enzyme induction, could be responsible for lower androgen levels.

In our data, DDE level was inversely associated with free androgen index among older men. As with the associations in the Mexican men, this finding was not in the hypothesized direction. The relation of DDE with the ratio of bioavailable to total testosterone was not similarly modified by age. Without confirmation in other data, the importance of the effect modification by age is questionable.

DDE concentrations tend to remain fairly constant over time and a single measure for estimating exposure is highly reliable.²⁷ Among 99 men with stable weight, the correlation among serum total testosterone levels measured 1 year apart was 0.61, suggesting that a single androgen level is fairly reliable.²⁸ Nonetheless, our ability to measure an association of DDE with androgen levels was hampered by the limited sample size, and

possibly by selection bias. Plasma DDE and serum hormone concentrations were available for only 138 of the 275 men. Those who did and did not provide a blood sample differed in level of education and a few farming-related characteristics. Whether the relation of DDE to androgen levels differs between the study group and the larger group of eligible men is unknown, although such a difference seems unlikely.

The age-related decline in testosterone levels among males is well documented for whites but not for other racial/ethnic groups.²³ Our data provide further information on the population distribution of androgen levels in African-American men and suggest that the decline with age observed in whites also occurs in African Americans. Whether the prevalence of hypogonadism in our population was unusual could not be determined because of the absence of data on the prevalence of low total testosterone levels among other populations with defined age distributions and because of uncertainties about the comparability of low testosterone levels measured in different laboratories.

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